Using a standard brachial or femoral approach we inserted disposable catheters into the right (venous) and left (arterial) sides of the heart after the patients had been given lorazepam as premedication. Patients with chest pain also underwent maximum incremental atrial pacing with continuous monitoring by 12 lead electrocardiography.

During catheterisation all patients with coronary artery and mitral valve disease were insensitive to movement of the catheter. In contrast, six of the seven patients with syndrome X and all four patients with chest pain and normal coronary arteries, although unaware of arterial catheterisation, experienced spontaneous but shortlived chest pain similar to that of which they had previously complained when the venous catheter was moved within the proximal 3-5 cm of the superior vena cava and the entire right atrium. This pain was consistently and rapidly provoked by turning and forward and backward movements of the catheter. As the venous catheters were moved within the vascular sheaths the patients were not aware of movements of the catheter through the skin. The inferior vena cava, right ventricle, pulmonary artery, and coronary sinus were also not sensitive to movement of the catheter.

Injection of 10 ml saline into the right atrium briefly provoked anginal pain, but a second and third injection did not; incremental increases in the volume of saline injected did not provoke pain until 50 ml was injected, when six out of 11 patients felt pain. Throughout the procedure there were no changes in right atrial pressure or the electrocardiograms.

Comment

We observed that in patients with angiographically normal coronary arteries typical chest pain was reproduced consistently by direct right atrial stimulation and infusion of saline. The perception of pain is subjective, and this study lacked an unequivocal, objective end point. Electrocardiographic changes were not observed. The brief duration of right atrial stimulation and chest pain was possibly an insufficient stimulus to induce electrocardiographic changes, which, anyway, need not indicate myocardial ischaemia in patients with syndrome X.³

The mechanism of chest pain in coronary artery disease remains poorly understood. Both atria and ventricles have liberal sensory innervation, and myocardial ischaemia stimulates non-myelinated sympathetic nerves by way of the cardiac plexus to the sympathetic ganglia from C7 to T4. The nature of this stimulus is unknown. It may be acidosis or a raised intracellular potassium concentration, but sympathetic afferent fibres also possess some mechanosensitivity.⁵

The mechanism of chest pain in syndrome X is less clear. In some patients hyperventilation and oesophageal or psychological factors may be relevant. Syndrome X, however, is a particularly heterogeneous disorder, and some patients have abnormalities of coronary vasodilator reserve or myocardial metabolism.^{2,4} Our observation suggests a further mechanism whereby chest pain may arise from altered awareness of the changes in right atrial pressure and volume that occur during exercise.

1 Proudfit WL, Shirey EK, Somes FM. Selective cine coronary arteriography: correlation with clinical findings in 1000 patients. *Circulation* 1966;33:901-10.

2 Opher D, Mall G, Zebe H, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. *Circulation* 1984;69:1-7.

3 Poole-Wilson PA. Potassium and the heart. *Clin Endocrinol Metab* 1984;24:9:68.

4 Richardson PJ, Livesley B, Oram S. Angina pectoris with normal coronary arteries. Transvenous myocardial biopsy in diagnosis. *Lancet* 1974;ii:677-80.

5 Malliani A, Lombardi F. Consideration of the fundamental mechanisms eliciting cardiac pain. *Am Heart J* 1982;103:575-8.

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Hyperthyroidism after gonadotrophic ovarian stimulation

We report two cases of hyperthyroidism associated with pharmacological ovarian stimulation in patients with underlying autoimmune thyroiditis.

Case reports

Case 1—A 29 year old woman was admitted for in vitro fertilisation and embryo transfer because of her husband's infertility. Her history was unremarkable.

Tests of thyroid function yielded normal results: free triiodothyronine concentration was 3.9 pmol/l (normal 2.8-5.6 pmol/l), free thyroxine concentration 9.2 pmol/l (normal 6.6-14.0 pmol/l), and thyroid stimulating hormone concentration 1.4 mU/l (normal 0.1-6.0 mU/l). Antibodies to thyroglobulin and microsomal antibodies were present (1/10 and 1/25 600, respectively), and the concentration of immunoglobulins inhibiting binding of thyroid stimulating hormone was 6.5 U/l (normal <10 U/l). All hormonal determinations were performed with commercially available radioimmunoassay kits. From day 3 after the onset of menses follicular stimulation was initiated with clomiphene citrate 100 mg twice daily for five days and enhanced by menotrophin (Humegon, Organon) follicle stimulating hormone 75 IU and luteinising hormone 75 IU/phial twice daily from day 7. When the follicles were sufficiently mature ovulation was induced by one injection of two phials of human chorionic gonadotrophin (Pregnyl, Organon; 5000 U/phial). During this procedure the patient developed symptoms of hyperthyroidism: free triiodothyronine concentration was more than 28.7 pmol/l, free thyroxine concentration greater than 48.7 pmol/l, and thyroid stimulating hormone concentration less than 0.1 mU/l. The serum oestradiol concentration was 4767 pmol/l (ovulation occurs at oestradiol concentrations of 1830-11000 pmol/l). She was cured after 18 months of treatment with propylthiouracil 100 mg thrice daily.

Case 2—Graves' disease was diagnosed in 1983 in a 34 year old woman. She was successfully treated with methimazole. In 1986 she was admitted for in vitro fertilisation and embryo transfer, the indication being andrological. Tests of thyroid function yielded normal results: free triiodothyronine concentration was 6.6 pmol/l; free thyroxine concentration was 13.5 pmol/l; thyroid stimulating hormone concentration was 4.5 mU/l; microsomal antibodies were present (1/25 600); and the concentration of immunoglobulins inhibiting binding of thyroid stimulating hormone was 5 U/l. After a few days of treatment with menotrophin (Humegon) and before human chorionic gonadotrophin was given she developed symptoms of hyperthyroidism. Free triiodothyronine concentration was 9.7 pmol/l, free thyroxine concentration 29.9 pmol/l, and thyroid stimulating hormone concentration less than 0.1 mU/l. The serum oestradiol concentration was 4584 pmol/l. No antithyroid drugs were given apart from beta blockade; treatment with menotrophin was stopped. Three weeks later all signs of hyperthyroidism resolved and the results of thyroid function tests returned to normal.

Comment

Although hyperthyroidism may have developed by chance in these patients with underlying autoimmune thyroiditis, the close temporal relation between ovarian stimulation and the occurrence of hyperthyroidism, and the spontaneous resolution of symptoms in case 2 after follicular stimulation was stopped, suggest that other mechanisms may have been implicated.

As thyrotoxicosis that develops in the course of trophoblastic diseases has been postulated to be due to the stimulating effects of human chorionic gonadotrophin on the thyroid¹ and as temporary aggravation of Graves' disease during early pregnancy coincides with maximal serum concentrations of human chorionic gonadotrophin² might human chorionic gonadotrophin have been a possible causal factor in at least case 1? Hyperthyroidism in trophoblastic disease, however, seems to be mediated by thyroid stimulating, acidic isoelectric variants of human chorionic gonadotrophin, which are present only in low concentrations in the serum of pregnant women³; in vivo studies with crude human chorionic gonadotrophin failed to show appreciable stimulation of the thyroid in euthyroid men.⁴ Furthermore, our second patient developed hyperthyroidism during treatment with menotrophin before human chorionic gonadotrophin had been given. Though luteinising hormone (present in menotrophin) shows a close structural analogy with human chorionic gonadotrophin, it has, to our knowledge, never been shown to stimulate the thyroid. Therefore the hypothesis that human chorionic gonadotrophin (luteinising hormone) alone was the causal agent seems weak.

Factors other than human chorionic gonadotrophin such as an appropriate hormonal environment⁵ and pre-existing autoimmune thyroid disease may have a role. Thyroid antibodies were not measured in the cases of trophoblastic disease associated with hyperthyroidism reported by Nisula and Ketelslegers.¹ Pharmacological ovarian stimulation induces an important hormonal imbalance with high oestrogen concentrations. An eventual role for hyperoestrogenism in the pathogenesis of thyroid overactivity is difficult to assess as the interactions of oestrogen with the hypothalamopituitary-thyroid axis are complex and their exact nature poorly documented.

We postulate that the interplay of factors resulting from pharmacological ovarian stimulation and pre-existing autoimmune thyroid disease may have precipitated hyperthyroidism in our two patients.

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1 Nisula BC, Ketelslegers JM. Thyroid-stimulating activity and chorionic gonadotrophin. *J Clin Invest* 1974;54:494-9.

2 Amino N, Tanizawa O, Mori H, et al. Aggravation of thyrotoxicosis in early pregnancy and after delivery in Graves' disease. *J Clin Endocrinol Metab* 1982;55:108-12.

3 Mann K, Schneider N, Hoermann R. Thyrotropic activity of acidic isoelectrical variants of human gonadotrophin from trophoblastic diseases. *Endocrinology* 1986;118:1558-66.

- 4 Sowers JR, Hershmann JM, Carlson HE, *et al.* Effect of human chorionic gonadotrophin on thyroid function in euthyroid man. *J Clin Endocrinol Metab* 1978;47:895-8.
- 5 Norman RJ, Lowrings C, Oliver T, *et al.* Doubts about human chorionic gonadotrophin as a thyroid stimulator. *Lancet* 1985;i:1096.

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Importance of negative result of cervical biopsy directed by colposcopy

Treatment is not recommended for patients with cervical intraepithelial neoplasia unless the lesion has been assessed colposcopically.¹ The aim of our study was to examine the accuracy of cervical punch biopsy directed by colposcopy in excluding disease.

Patients, methods, and results

We reviewed the records of all patients referred to the colposcopy clinic at Birmingham and Midland Hospital for Women from March 1984 to October 1985 for investigation of persistent cytological abnormalities of the cervix. At the initial visit patients were assessed by colposcopy and a cervical smear and punch biopsy specimen were taken. In 132 patients the initial biopsy did not confirm the presence of disease. These patients were reviewed at intervals of four months and further smears and biopsies performed as necessary. Four groups with the following characteristics were identified.

Group 1 (n=51)—A histological abnormality was seen in a subsequent punch biopsy specimen.

Group 2 (n=65)—Subsequent cervical smears showed no abnormality; the median follow up period was 14 months and the median number of follow up smears per patient was two. Initial smears showed no abnormality in 31 patients.

Group 3 (n=8)—The cytological abnormality continued. A further punch biopsy yielded negative results in five cases.

Group 4 (n=8)—These patients underwent cone biopsy because of persistent unexplained cytological abnormality (six) or a predicted glandular lesion of the cervix (two). In the patients with an unexplained abnormality histological

Comparison of cytological findings on day of initial punch biopsy in patients who did and did not have abnormality at subsequent examinations

Outcome	Cytological findings*					Total
	No abnormality	Atypical	IIa	IIb	IV	
Subsequent positive histological findings	12	5	12	12	14	55
Negative findings at follow up smear	31	6	17	9	2	65
Total	43	11	29	21	16	120

*Atypical=Cellular atypia not amounting to mild dyskaryosis. IIa=Mildly dyskaryotic cells suggesting cervical intraepithelial neoplasia Grade 1. IIb=Moderately dyskaryotic cells suggesting cervical intraepithelial neoplasia Grade 2. IV=Severely dyskaryotic cells or cells that appear malignant, suggesting cervical intraepithelial neoplasia Grade 3.

examination of the biopsy specimen showed cervical intraepithelial neoplasia grade III (one patient), adenocarcinoma in situ (one), adenocarcinoma in situ with cervical intraepithelial neoplasia grade III (one), and no abnormalities (three). In the two further patients histological examination showed mild cervical glandular atypia in one and no abnormalities in the other.

Comment

We found that 55 of 132 women in whom an initial punch biopsy gave a negative result had a cervical lesion on repeat biopsy. Absence of histological abnormalities at the initial screening may be due to a false positive result for the referral smear, a false negative result for the initial biopsy, or spontaneous regression of a cytological abnormality. A false positive result was unlikely as only patients with a history of persistent cytological abnormality were seen. False negative results of biopsy may result from inaccurate sampling of a small lesion or one located in the lower part of the endocervical canal or from the pathologist overlooking a lesion if the tissue has not been completely sectioned after initial histological assessment has given a negative result. A true negative biopsy result would occur if the lesion had regressed spontaneously before colposcopy.

Spontaneous regression of cytological abnormalities is well recognised^{2,3} and seems to have occurred in the 31 patients in group 2 in whom cytological and histological examination on the day of the initial assessment and subsequent cytological review did not show any abnormality. In these cases the colposcopist probably misinterpreted inflammation or immature metaplasia as intraepithelial neoplasia when selecting the area for biopsy. The 34 cases in group 2 in which cytological examination showed abnormalities on the day of the initial punch biopsy but subsequently yielded negative results are difficult to explain. This might occur if the biopsy removed the whole lesion but the pathologist did not detect it or if the colposcopist failed to obtain a specimen of the lesion, which then regressed spontaneously before the next smear was taken. The rate of false negative results would decrease if the colposcopist took multiple specimens, but we disagree with this policy because it would lead to an increase in morbidity and laboratory workload and almost certainly to a less critical colposcopic assessment.

The cervical smear taken on the day of initial colposcopy was of limited value in predicting the final outcome (table). We emphasise, therefore, the importance of follow up examinations in patients referred because of cytological abnormality in whom the initial biopsy directed by colposcopy does not confirm the presence of disease.

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- Jordan JA, Sharp F, Singer A, eds. *Pre-clinical neoplasia of the cervix. Proceedings of the ninth study group of the Royal College of Obstetricians and Gynaecologists*. London: Royal College of Obstetricians and Gynaecologists 1982:299.
- Nasiell K, Nasiell M, Vaclavinkova V. Behavior of moderate cervical dysplasia during long term follow-up. *Obstet Gynecol* 1983;61:609-14.
- Nasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasia during long term follow-up. *Obstet Gynecol* 1986;67:665-9.

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