SHORT REPORTS

Incidence of thyroid disease associated with oral contraceptives

Cell-mediated immunosuppression in pregnancy and in women taking oral contraceptives has been described.^{1,2} Temporary remission of autoimmune thyroid disease with postpartum recurrence has also been reported associated with the gradual reduction of serum antithyroid antibody titres as the pregnancy progressed, followed by a postpartum increase reaching a peak three to four months after delivery.³

Study and results

Thyroid diseases were analysed as part of a continuing major prospective survey of oral contraceptives. The study began in 1968. About 23 000 women currently taking a contraceptive pill and a similar number of controls who had never taken an oral contraceptive were recruited by 1400 general practitioners over a period of 14 months. Observations of subsequent morbidity and other relevant data of this population formed the basis for our analyses. The design of the study and the interpretation of the findings have been described elsewhere.⁴

The main findings are shown in the table. Because of the close inter-relationship of thyroid disorders we analysed only the frequency of reporting of the first diagnosis during the study of any thyroid disease in one patient. Cases first diagnosed during pregnancy were excluded together with the associated periods of observations. Patients were categorised according to their contraceptive status at the time of diagnosis as (1) takers (those currently taking an oral contraceptive who had had no break in use longer than one cycle); (2) ex-takers (those who had formerly used oral contraceptives); and (3) controls (those who had never used oral contraceptives). All three clinical groups of thyroid disease were reported less frequently in takers than in controls. In patients with euthyroid swelling the rate in takers was 69% of that in controls, and the proportions for thyrotoxicosis and myxoedema were 71% and 57% respectively. Although these differences taken separately do not reach statistical significance, the frequency of reporting in takers was consistently materially less than in controls. When the subcategories are combined the risk ratio of 0.68 becomes highly significant ($P < 0.01$; 95% confidence limits 0.52 to 0.85). An important finding was that the rates for thyroid disease in ex-takers did not differ from controls. The frequency of reporting of thyroid disease showed no correlation with age, parity, cigarette consumption, or social class in any of the contraceptive categories, and reporting rates did not correlate with oestrogen or progestogen dosage or with the duration of use of oral contraceptives.

Comment

These results suggest that oral contraceptives exert a protective effect against thyroid disease. In our interim report⁴ we assessed the probable biases in a prospective study of this type. Selection bias was substantially avoided by excluding all women who had had the disease before recruitment. Other forms of bias generally operate in the one direction, giving an estimated 20% overreporting in the takers and a tendency to exaggerate adverse reactions to oral contraceptives and underassess beneficial effects. Our findings of a higher rate of reporting of thyroid disease in controls than takers is contrary to the expected effect of these biases. The finding that the frequency of thyroid disease in ex-takers is not materially different from the controls suggests that there is no residual protective effect against thyroid disease after the contraceptive has been stopped. Our observations suggest that the

effect of oral contraceptives on thyroid disease may be associated with preventing or retarding autoimmune processes. The reduced incidence of rheumatoid arthritis⁵ in oral contraceptive takers probably has a similar mechanism. In absolute terms the protective effect against thyroid disease would be as small as 1 in 1600 oral contraceptive users a year. The observation, however, may contribute to an understanding of the mechanism of action of oral contraceptives and the aetiology of thyroid disease.

¹ Barnes, E W, *et al*, *Lancet*, 1974, **1**, 898.
² Hill, C A St, Finn, R, and Denye, V, *British Medical Journal*, 1973, **3**, 513.
³ Amino, N, Kuro, R, and Tanizawa, O, *Clinical Experimental Immunology*, 1978, **31**, 30.
⁴ Royal College of General Practitioners, *Oral Contraceptives and Health*. London, Pitman Medical, 1974.
⁵ Royal College of General Practitioners Oral Contraception Study, *Lancet*, 1978, **1**, 569.

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Uneventful pregnancy after Wilms's tumour

Pregnancy after successful treatment for Wilms's tumour is rare; we found only one such case reported from California. We describe here another patient managed at the City of London Maternity Hospital who had had a Wilms's tumour in childhood.

Case report

This 18-year-old, single, West Indian Negro primigravida had her last menstrual period in May 1975 and was seen in the ante-natal clinic in January 1976 in the 36th week of gestation. She had had no previous ante-natal care.

Her history showed that she had been treated for Wilms's tumour of her right kidney. In 1970, when she was 12, she was admitted to Queen Elizabeth Hospital for Children, London, with a mass on her right flank, and the right kidney was removed. A tumour weighing 1 kg was found, which was shown to be a nephroblastoma. There was no spread beyond the kidney and no obvious lymph node or renal vein metastases. After operation she was given a course of actinomycin D followed by cobalt teletherapy at St Bartholomew's Hospital. A mid-plane dose of 3500 rads was given over five weeks to the right renal bed and para-aortic nodes. No other chemotherapy was given, and she subsequently remained well.

On booking into our unit she appeared to be a well developed, healthy teenager. She was 167.6 cm tall, weighed 56.7 kg, and had blood pressure of 105/60 mm Hg and pulse rate of 76 beats/min. A nephrectomy scar was present. The size of her uterus corresponded to the period of amenorrhoea.

First diagnoses of any thyroid disease by oral contraceptive use (standardised for age, cigarette consumption, parity, and social class)

International classification of disease category	Takers		Ex-takers		Controls		Ratio of standardised rates	
	No observed	Standardised rate (TWY)	No observed	Standardised rate (TWY)	No observed	Standardised rate (TWY)	Takers: controls	Ex-takers: controls
240, 241, 245, 246 (Benign thyroid swelling (euthyroid))	45	0.68	33	0.80	106	0.98	0.69	0.81
242 (Thyrotoxicosis)	29	0.44	24	0.57	67	0.63	0.71	0.90
244 (Myxoedema)	11	0.17	15	0.35	32	0.30	0.57	1.17
Total thyroid disease (240, 241, 242, 244, 245, 246)	85	1.30	72	1.72	205	1.90	0.68†	0.91
Periods of observation (women-years)	66 787		40 609		107 551			

TWY = Thousand women-years.
† $P < 0.01$; 95% confidence limits 0.52 to 0.85.

Pelvic examination showed that it was normal and adequate for vaginal delivery. Her haemoglobin at the time of booking was 12 g/dl, group O, rhesus positive. Haemoglobin electrophoretic pattern was A+C. Serological test was negative. Urine analysis showed no abnormality.

The pregnancy progressed normally and she went into labour spontaneously at term. On 18 February 1976, after being in labour for 9 hours 45 minutes, she delivered a normal, healthy, infant weighing 2830 g with an Apgar score of 7. The puerperium was uneventful. Both mother and the baby were in a satisfactory condition.

Comment

Nephroblastoma is a malignant condition of infancy and childhood. The tumour is usually unilateral, though it may rarely be bilateral. The survival rate in this disease has improved in recent years,² but cytotoxic and radiation therapy usually affect fertility. In our patient such treatment did not affect fertility.

We thank Mr Elliot Philipp for permission to report this case.

¹ Wolff, J R, and Lebherz, T B, *American Journal of Obstetrics and Gynecology*, 1968, **100**, 1151.

² *British Medical Journal*, 1976, **1**, 1166.

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Congenital factor XIII deficiency in a neonate

Congenital factor XIII deficiency is rare. Only two cases have been described in the newborn.¹ The diagnosis is simple and important, since the condition is readily treated with prophylactic factor XIII concentrate. We present a further case.

Case report

A girl was born at term by normal delivery weighing 3.03 kg. There was no family history of a bleeding disorder or consanguinity. When 7 days old the cord stump separated and she started to bleed from her umbilicus. The bleeding slowly worsened, leading to her admission at 10 days. Examination showed a healthy looking infant, not shocked or anaemic. Venous blood oozed from the base of her umbilicus, overlying which was a friable clot. Local measures failed to stem the bleeding. Initial routine coagulation screening (Thrombotest, Normotest, prothrombin time, kaolin cephalin clotting time, and thrombin time) were all normal. Fibrin clot solubility tests showed a rapid solubility in 5M urea solution, so factor XIII deficiency was provisionally diagnosed. The bleeding arrested without recurrence during a transfusion of 80 ml stored bank blood.

Prophylactic treatment was started after one month with an infusion (4 ml/kg) of fresh frozen plasma (FFP). Regular intravenous injections (4 ml) of factor XIII concentrate (Hoechst) were started the following month at intervals determined by the results of preinjection clot solubility tests. Apart from a small epistaxis the day before the first factor XIII injection, no bleeding episodes occurred. The table shows results of the clot solubility studies. The diagnosis was confirmed by the absence of factor XIII subunit A on immunoelectrophoresis and the return to normal of the clot solubility with reappearance of subunit A after FFP and specific factor XIII concentrate injection.

Clot solubility studies in neonate with factor XIII deficiency

	5M Urea	2% Acetic acid	1% Monochloroacetic acid
Initial test	50 min	30 min	—
Normal control	>24 h	>24 h	—
PreFFP	120 min	10 min	10 min
PostFFP	>24 h	>24 h	>24 h
Preconcentrate	90 min	10 min	6 min
Postconcentrate	>24 h	>24 h	>24 h

Comment

Factor XIII deficiency was first described in 1960,² although the existence of a plasma factor responsible for fibrin stabilisation has been known since 1944. Since then about 100 cases have been reported.³ Factor XIII is composed of two subunits. Subunit A carries the enzymatic activity and subunit S is the support unit. Inheritance is autosomal recessive and heterozygotes may be identified by measuring subunits A and S.⁴ We have shown the carrier state in both parents of our patient. No other family members are homozygotes.

Apart from wound bleeding, typically delayed, and easy bruising, umbilical bleeding is the commonest manifestation occurring in over 80% of reported cases. Unlike the more common hereditary coagulation disorders, intracranial bleeding is a frequent (25%) complication. Prophylactic treatment, recommended because of this risk, is feasible since factor XIII has a relatively long half life of 12 days and is active in low concentrations (0.5-1.0% of normal). Factor XIII concentrate has superseded FFP in the management of congenital deficiency because of its higher activity (1 ml=60 ml FFP) and a lower risk of hypersensitivity and hepatitis. We believe our patient is the youngest to start prophylactic treatment with factor XIII concentrate.

In only two other reported cases has the diagnosis been made in the newborn, despite its common presentation at that time. Delay in diagnosis occurs for two main reasons. Firstly, the stability of factor XIII in stored bank blood has resulted in haemostasis during transfusion and failure to pursue investigation. Secondly, the diagnosis has not been considered. Indeed, a recent review on neonatal bleeding⁵ failed to mention factor XIII deficiency. If the diagnosis is considered laboratory confirmation by clot solubility studies is simple and rapid.

We thank Dr L G Evans-Jones for his help and encouragement in reporting his patient.

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² Duckert, F, Jung, E, and Shmerling, D H, *Thrombosis et Diathesis Haemorrhagica*, 1960, **5**, 179.

³ Losowsky, M S, and Miloszewski, K J A, *British Journal of Haematology*, 1977, **37**, 1.

⁴ Barbui, T, et al, *British Journal of Haematology*, 1978, **38**, 267.

⁵ *British Medical Journal*, 1977, **2**, 915.

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Salicylate hepatotoxicity in systemic lupus erythematosus: a common occurrence?

Acetylsalicylic acid (ASA) can induce abnormalities of liver function in patients with rheumatic fever, juvenile (and adult) rheumatoid arthritis, and systemic lupus erythematosus (SLE). How often this happens in SLE is not known, but it may be commoner than realised.¹ We report our experience of aspirin hepatotoxicity in SLE.

Patients and results

During the 18 months to June 1978, 74 patients were admitted for SLE and eight for mixed connective tissue disease (MCTD). All had high titres of either anti-ds DNA antibody (Farr assay) or anti-RNP antibody (by counter-immunoelectrophoresis). All patients had at least one sequential multiple analysis (SMA 12), which included serum albumin, globulin, bilirubin, alkaline phosphatase, and aspartate transaminase (serum AST; SGOT). Eight SLE and two MCTD patients had abnormal liver function tests. Three patients (SLE with lymphoma, SLE with pneumococcal pneumonia and raised bilirubin concentration, and MCTD with active myositis and raised serum AST and creatinine phosphokinase concentrations) were not taking salicylate. Of the other seven, five had started taking acetyl-