EVIDENCE THAT ADRENAL OESTROGENS ARE NOT INVOLVED IN BENIGN BREAST DISEASE

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Summary: We have studied 30 women with symptomatic benign breast disease in order to test the hypothesis that in some it might be caused by an enzyme variant leading to excessive adrenal production of oestrone. Synthetic 1-24 ACTH (Synacthen) was given intramuscularly after overnight suppression with dexamethasone, during the early follicular phase of the menstrual cycle.

In no subjects did plasma oestrone levels show a consistent and significant response to ACTH despite the expected consistent rises in androstenedione and cortisol.

We conclude that it is unlikely that adrenal oestrogens play a significant role in the pathophysiology of even a minority of patients with benign breast disease.

INTRODUCTION

Although largely circumstantial, there is considerable evidence to indicate that oestrogens are intimately involved in the development of benign breast lesions (see Gollinger [1] for review).

In mice [2] oestrogen administration can produce hyperplasia of breast tissues similar to that seen in human benign breast disease. The breasts of men working with stilboestrol [3] have been reported to show duct and alveolar hyperplasia, and a study of women [4] with benign breast disease has demonstrated an excess in stilboestrol users compared with controls. The same workers, however, found no positive correlation between oral contraceptive use and benign breast disease (BBD), and a recent report [5] even suggests a lower incidence of BBD among oral contraceptive users.

A histological study [6] of unaffected breast tissue from patients with breast cancer treated with oestrogens showed proliferative changes as seen in BBD. In patients with carcinoma of the breast Bacigalupo and Schubert found an increased urinary oestrogen excretion among those with co-existent BBD.

There have been several studies [7, 8, 9] which report raised plasma oestradiol levels during the luteal phase of the menstrual cycle in patients with benign breast disease. Anti-oestrogens such as tamoxifen [10] and ethamoxytrihetol [11] have been reported to produce objective improvement in some patients with BBD. Progestogens have also been shown to be beneficial [12, 13], possibly by correcting an oestrogen-progesterone imbalance [9].

It has long been known that some adrenal tumours produce feminisation by excessive oestrogen secretion [14-18]. In postmenopausal and oophorectomised women the major source of circulating oestrogens (principally oestrone) is the adrenal [19]. This is believed to arise principally from peripheral aromatisation of androstenedione secreted by the adrenal in response to ACTH; some direct secretion of oestrone may also occur. It is therefore surprising to us that there has been no study of significant numbers of women with BBD to examine whether the adrenal might be a potential source of excess oestrogens. If this were the case it might be sufficient to interfere with

normal cyclic changes in the breast induced by oestrogens and progesterone of ovarian origin, and so induce BBD. The present study of 30 women with BBD of unknown aetiology examines this possibility, using ACTH stimulation from an acutely suppressed state.

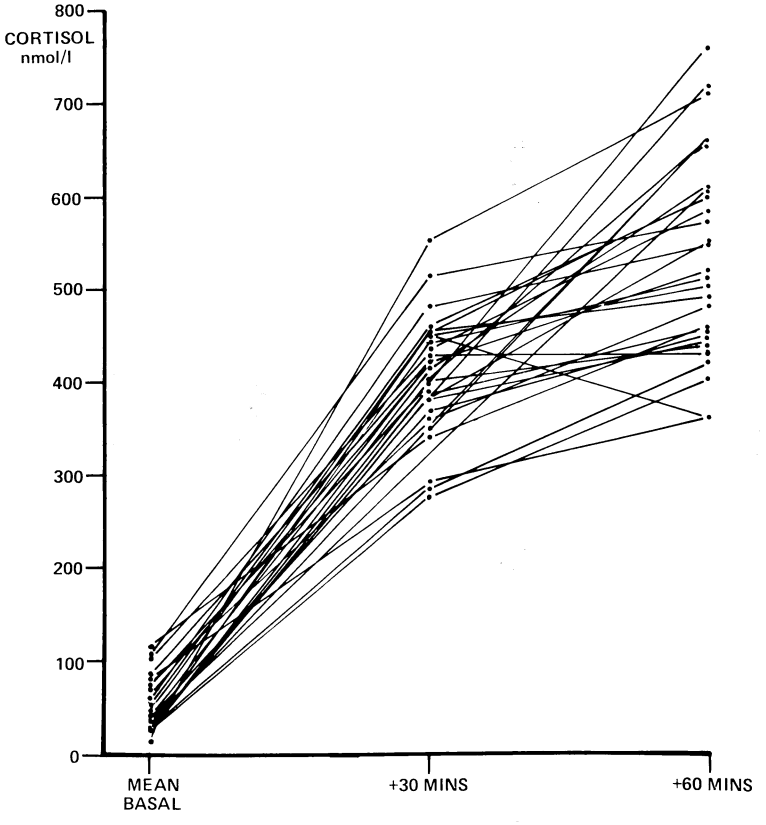

Fig. 1. — Plasma cortisol levels (nmol/l) following overnight dexamethasone suppression and 30 and 60 minutes after Synacthen.

PATIENTS AND METHODS

Thirty three women aged between 20 and 45 years with severe long standing benign breast disease were recruited from a large breast clinic. They all gave their informed consent. The patients were all menstruating regularly and not taking any drugs or hormone preparations, and were studied within 5 days of onset of menstruation.

Three women were excluded when their progesterone levels demonstrated that they had been tested in the luteal phase of the menstrual cycle.

At an initial visit blood was taken for the estimation of gonadotrophins, prolactin, thyroxine, tri-iodothyronine and TSH. The night before testing the patients took 1.5 mg dexamethasone orally at 11 pm. The following morning they were fasted and blood taken at 30 minute intervals over 2 hours, with the patient recumbent or seated quietly. After the first three samples Synacthen 250 µg was injected intramuscularly. Two further samples at half hour intervals were then obtained.

After leaving for 1 hour at room temperature, blood samples were contrifuged and the serum stored at −20 °C until assay.

Cortisol was analysed in all samples by radioimmunoassay after ether extraction, and an-

drostenedione and oestrone by radiommunoassay after ether extraction and celite column fractionisation (42, 43).

RESULTS

Three women had luteal phase levels of progesterone and were therefore excluded from further analysis. In the remaining thirty women prolactin, thyroxine, triiodothyronine, TSH and gonadotrophin levels were all within the normal range for the early follicular phase.

Figure 1 (cortisol) demonstrates that all patients had taken their dexamethasone and showed a normal cortisol rise in response to Synacthen. The rise from basal levels at 30 minutes and the rise from 30-60 minutes are both highly significant, $t=25.098$ and 23.078 respectively ($p<0.0001$) (Student's t test). Figure 2 demonstrates a significant increase in androstenedione at 30 minutes, $t=5.1821$ ($p<0.001$). The rise from 30-60 minutes is also significant, $t=3.2986$ ($p<0.005$).

Figure 3 demonstrates the large variation in basal levels of oestrone and the absence of any consistent rise following adrenal stimulation.

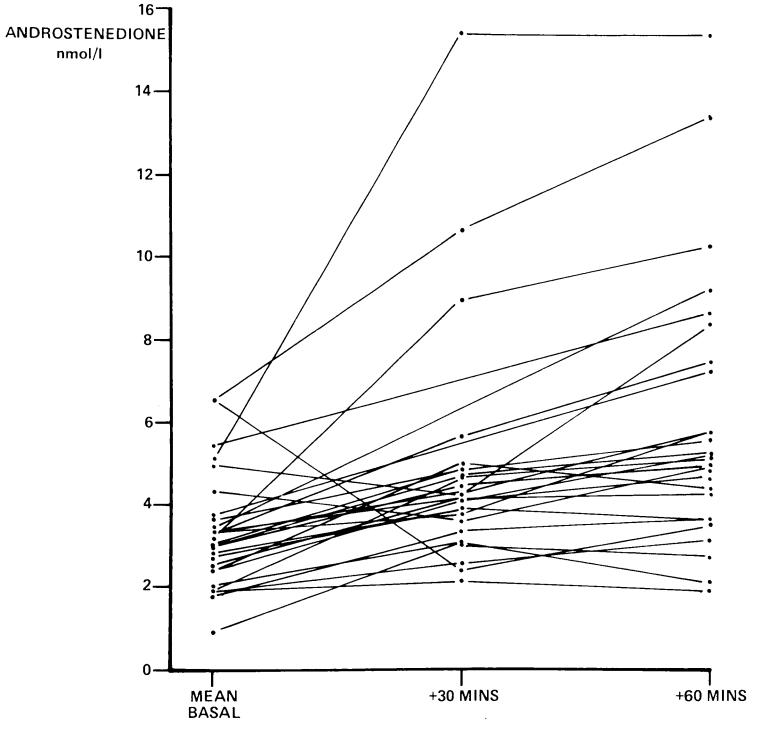

Fig. 2. — Plasma androstenedione levels (nmol/l) following overnight dexamethasone suppression and 30 and 60 minutes after Synacthen.

DISCUSSION

We have previously found a subpopulation of normal subjects using this procedure who have an excessive adrenal response of progesterone secretion and 17α

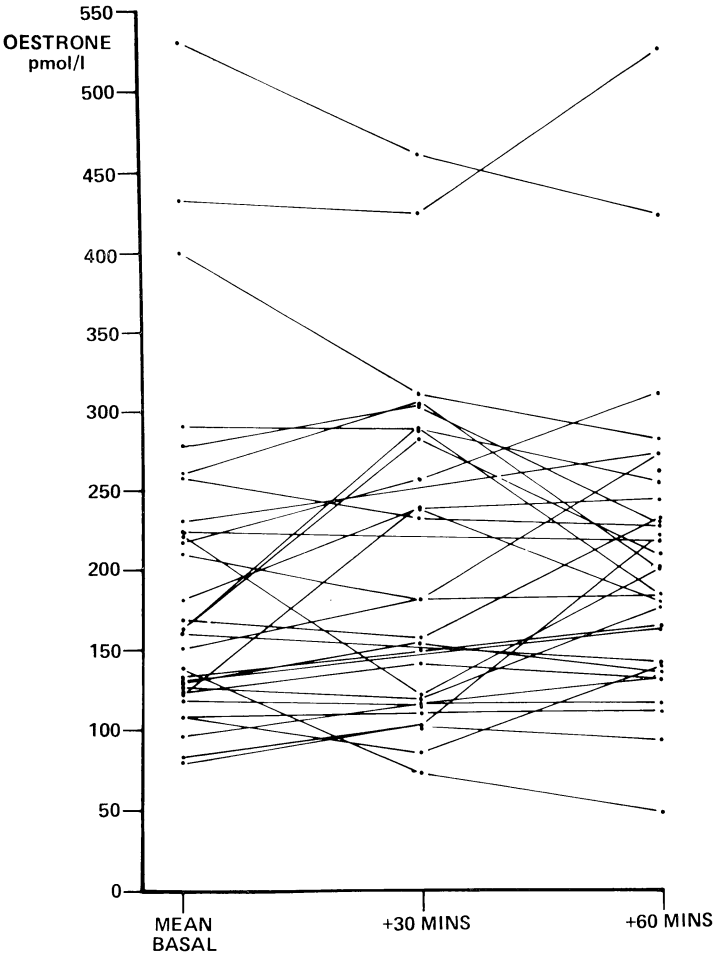

Fig. 3. — Plasma oestradiol levels (pmol/l) following overnight dexamethasone suppression and 30 and 60 minutes after Synacthen.

OH-progesterone, due apparently to an adrenal enzyme variant in 21-hydroxylase. However in the present study we were unable to find evidence of significant oestrone production from the adrenal in even a subpopulation of women with benign breast disease. We had speculated that in some individuals adrenal aromatase activity might be excessive but the lack of a significant response following overnight suppression with dexamethasone indicates that the ovary is by far the major source of plasma oestrone even in women with BBD.

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ANY PLACE FOR ANTENATAL DIAGNOSIS IN THE THIRD TRIMESTER OF PREGNANCY?

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Summary: The need for a means of antenatal diagnosis of chromosomal abnormalities in the last trimester of pregnancy to avoid unnecessary intervention for the sake of the fetus is illustrated by a case in which polyhydramnios and suspected fetal hydrocephalus were found by ultrasound at 36 weeks gestation. The mother decided against early caesarian section for possible neurosurgery for the fetus. Later, she delivered vaginally of a baby with multiple abnormalities and trisomy 18.

INTRODUCTION

The appearance of third trimester complications in an otherwise uneventful pregnancy often presents a management dilemma, as it is possible that the fetus may have a lethal chromosomal abnormality.

CASE SUMMARY

A 34 year old para 1 woman was referred at 36 weeks. Polyhydramnios and dilatation of the cerebral ventricles were detected by ultrasound 2 weeks before. Her last pregnancy was also complicated by polyhydramnios and delivery at 32 weeks of a stillborn female in China. On examination, no medical or infectious conditions were detected. The only fetal abnormality detected by a repeat ultrasound scan was asymmetric cerebral ventricular dilatation. The mother preferred vaginal delivery despite the possibility that immediate Caesarean section might give the fetus a better chance. Labour was induced and 3.5 litres of clear liquor were drained. A male baby weighing 1.49 kg was delivered after 4 1/2 hours and died three hours