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Serum Prolactin, Androgens, Oestradiol and Progesterone in Adolescent Girls with or without a Family History of Breast Cancer

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Abstract—*Serum levels of prolactin, progesterone, oestradiol, androstenedione and dehydroepiandrosterone sulphate have been measured in 52 adolescent girls with a family history of breast cancer and 90 girls without such a history. Using conventional statistical tests no significant differences were found in the endocrine status of the two groups.*

INTRODUCTION

THE RESULTS of MacMahon and his colleagues [1] showed that an early age at first child correlated with life-long diminution in risk of breast cancer, and a generalization derived from these data is that early endocrine events may be of critical importance in the aetiology of the disease.

Henderson and his colleagues [2] measured some aspects of endocrine function in American adolescent girls whose mothers had breast cancer and in girls with no familial breast cancer history. In their first study, plasma prolactin and oestradiol levels were marginally higher in the family history group than in the controls, but no significant differences were found when a second blood sample was subsequently obtained [3]. The point is of considerable importance: if risk is largely determined by endocrine status at, or shortly after puberty, then attempts to diminish incidence of breast cancer by endocrine manipulation might be too late if applied to adults. Accordingly, the experiment was repeated in an English population.

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MATERIALS AND METHODS

Subjects

The volunteers for the study were between 14 and 20 years of age. A history of endocrine therapy and oral contraceptive use was obtained (Table 1).

The control group consisted of volunteers up to the age of 18 from Kidbrook School. This is a comprehensive school of 2000 girls with no selection for pupil entry, and is situated within the Guy's hospital catchment area. Girls over 18 years of age were nursing staff.

Table 1. Comparability of control and family history groups

	Controls	Any family history	Mothers only
Number	90	52	35
Age at menarche	12.71 ± 1.23*	12.67 ± 1.23	12.91 ± 1.15
Height (cm)	163.4 ± 8.9	162.2 ± 7.4	162.6 ± 6.5
Weight (Kg)	58.83 ± 9.06	57.06 ± 8.17	56.11 ± 7.45
Follicular phase	26 (29%)	17 (33%)	11 (31%)
Luteal phase	29 (32%)	13 (25%)	8 (23%)
(anovulatory)	5 (17%)†	4 (31%)	2 (25%)
Unknown phase	24 (27%)	13 (23%)	8 (23%)
Contraceptive steroids	11 (12%)	9 (17%)	8 (23%)

*Mean ± 1 S.D.
†Percentage of subjects with anovulatory cycles in the luteal phase.

Girls with a family history were obtained by writing to the daughters of patients with breast cancer who had attended Guy's Hospital Breast Unit. Some of the volunteers in the control group were found to have a family history of breast cancer and were, therefore, excluded from this group. These girls, together with those whose mothers have the disease, have been statistically treated as a group of girls having any known family history of breast cancer. Of the 52 subjects with a known family history, 49 came from the Guy's Hospital catchment area.

There were no significant differences between the groups in terms of age, age at menarche, height or weight, which indicates that there is no gross disparity in socio-economic class (see Valaoras *et al.* [4]).

A 50 ml sample of blood was obtained from an ante-cubital vein, using a Vacutainer, between 18.30 and 20.00 hr. After clotting (1 hr), and centrifugation at 800 *g* for 20 min, the serum was separated and stored at −20°C. The reason for choosing this time was that Kwa *et al.* [5, 10] reported that women with an increased risk of breast cancer due to a family history of the disease have elevated plasma prolactin levels at this time.

Definition of phase of menstrual cycle

The volunteers were asked the date of their last menstrual periods and the length of their cycles. They were also given a calendar on which they noted the date of their next period following blood donation. For the purpose of this study the follicular phase was defined as days 2–13 (day 1 = first day of bleeding) of cycles of 23–39 days in length. This definition resulted in an average of 28% of the cycle having elapsed, and in no case had the cycle progressed further than 46% of the total length of the cycle at the time the blood sample was obtained.

The luteal phase was defined as days 16–35 of the cycle (since cycle lenghts ranged from 23–39 days), providing the next cycle occurred within the following 1–12 days after the blood was taken. The average cycle time elapsed was 83% and was never less than 57%. All other volunteers were classed as unknown (e.g. cycle lengths of < 22 days, > 40 days). Mid-cycle collections (days 14 and 15) were defined as unknown unless serum progesterone levels exceeded 3 ng/ml, in which case the cycle was classed as luteal. Girls, who by the definition above were in the luteal phase of the cycle, but who had less than 3 ng/ml of progesterone, were considered anovulatory (Table 1).

The classification of cycle phase was carried out by an independent statistician who was not informed whether the volunteers had or did not have a family history of breast cancer.

Serum hormone measurements

Oestradiol, androstenedione and dehydroepiandrosterone sulphate were measured by radioimmunoassay, and progesterone was measured by competitive protein binding using pregnant guinea pig serum. The details of all these assays have already been described elsewhere [6–9].

Serum prolactin was measured using a homologous radioimmunoassay at five dilutions of serum [10].

RESULTS

The mean levels of progesterone and oestradiol in controls and in the adolescent girls with a family history of breast cancer are shown in Table 2. It is quite clear that there are no significant differences between the groups (using the conventional *t*-test on the logarithms of the hormone values, or ranking tests). Although the progesterone values during the follicular phase are high, they are not unprecedentedly so. In serial samples, Black *et al.* reported levels of 2 ± 1.3 ng/ml during the proliferative phase of the menstrual cycle [11]. Martin *et al.* reported levels of 1.9 ± 1.1 ng/ml [12], and Hagerman and Williams, levels of 2.7 ng/ml [13] during this phase of the cycle Finally, Swain *et al.* found that women with benign breast disease had a mean level of 2.93 ng/ml, and this level was not statistically higher than that found in normal control women [14]. The progesterone levels in the luteal phase and the oestradiol levels throughout the cycle are within the normal ranges cited in the literature.

The plasma androgen levels are shown in Table 3 and, again, there are no significant differences between girls with or without a family history. The androstenedione levels are at the upper end of the ranges found by the following workers: Abrahams and Chakmakjian (1940 ± 390 pg/ml), Rivarola and Migeon (1970 ± 537 pg/ml); Bardin and Lipsett (1700 ± 400 pg/ml); and Moshang *et al.* (2220 ± 430 pg/ml) [15–18]. In a previous publication we reported a level of 1800 ± 840 pg/ml for British adolescent girls [19]. Prolactin levels in the control and family history groups are shown in Table 4. There are no significant differences.

There are few data on evening values for plasma prolactin. The levels found in the

Table 2. Serum progesterone and oestradiol in adolescent girls with and without a family history of breast cancer

Phase of cycle	Control	Any family history	Mothers only
Progesterone (ng/ml)			
Follicular			
Geometric mean	2.3	2.8	2.5
	3.2; 1.7*	4.4; 1.8	3.0; 2.0
n	26	16	10
Luteal			
Geometric mean	8.7	6.2	6.5
	20.0; 3.8	15.9; 2.4	17.4; 2.4
n	29	13	8
Unknown			
Geometric mean	2.5	2.3	2.1
	4.0; 1.5	3.2; 1.6	3.0; 1.5
n	24	13	8
Oestradiol (pg/ml)			
Follicular			
Geometric mean	47	49	42
	79; 28	87; 28	78; 22
n	26	16	10
Luteal			
Geometric mean	68	60	65
	151; 30	105; 35	110; 38
n	28	13	8
Unknown			
Geometric mean	74	58	59
	141; 39	107; 31	112; 31
n	23	12	8

*These figures refer to the geometric mean + 1 S.D. and the geometric mean − 1 S.D. respectively.

present study are comparable with those found in adults bled at the same time of day [20].

Scatter diagrams showing the relationship between serum prolactin and oestradiol levels for the two groups of girls are shown in Fig. 1(a and b). There is no obvious difference between the prolactin/oestradiol ratios in girls with or without a family history during either the follicular or the luteal phase of the menstrual cycle.

DISCUSSION

We can find no differences between the serum levels of prolactin, oestradiol, progesterone, androstenedione and dehydroepiandrosterone sulphate in adolescent girls with or without a family history of breast cancer.

One of the greatest problems encountered in this study was in the menstrual cycle irregularities, which are common in adolescent girls [21, 22]. There were great difficulties in classifying volunteers as being in the follicular or luteal phase of the cycle and, certainly, we would have no confidence in using terms such as "day 6" or "day 22" as having any physiological meaning. Indeed, even knowing the date of the subsequent menstrual period and a determination of progesterone, the menstrual cycles of one quarter of the volunteers could not be classified.

Other indices of ovulation, such as basal body temperature, vaginal cytology and endometrial biopsy, although informative, do not necessarily provide satisfactory guidance for the quantitative assessment of the luteal phase [23]. Ideally, serial blood samples would be required to determine menstrual status but this was impossible in this study. This apparently seems to have been the case in the studies of Henderson, Pike *et al.* [2, 3]. Indeed, it may be asked whether any truly "normal" volunteer would provide such a large number of blood specimens and whether those who did would be a remarkably biased sample of the population. Assays of steroid hormones in saliva afford an attractive alternative, although it is unlikely that protein hormones could be measured.

Not only is there considerable variation in cycle length, but there is also the problem of a high proportion of sporadic anovulatory cycles in adolescent girls. The rough estimate of about 20% of anovulatory cycles (Table 1) is in agreement with results from other studies [24, 25] and it is quite apparent that a considerable number of low progesterone values

Table 3. Serum androstenedione and dehydroepiandrosterone sulphate in adolescent girls with and without a family history of breast cancer

Phase of cycle	Control	Any family history	Mothers only
Androstenedione (pg/ml)			
Follicular			
Geometric mean	2089	1778	1738
	3311; 1318*	2399; 1318	2455; 1230
n	26	17	11
Luteal			
Geometric mean	1862	2239	2344
	3548; 977	3467; 1445	3890; 1412
n	29	13	8
Unknown			
Geometric mean	2138	2042	1905
	3162; 1445	2884; 1445	2754; 1318
n	24	13	8
Dehydroepiandrosterone sulphate (μg/100 ml)			
Follicular			
Geometric mean	132	85	98
	219; 79	200; 36	148; 65
n	24	13	8
Luteal			
Geometric mean	118	155	135
	204; 68	209; 115	174; 105
n	28	11	7
Unknown			
Geometric mean	115	105	105
	200; 66	158; 69	158; 69
n	19	10	7

*This figure refers to the geometric mean + 1 S.D. and the geometric mean − 1 S.D. respectively.

Table 4. Serum prolactin in adolescent girls with and without a family history of breast cancer

Phase of cycle	Control	Any family history	Mothers only
Follicular			
Geometric mean	11.5	10.2	10.7
	20.0; 6.6*	18.2; 5.8	20.4; 5.6
n	26	17	11
Luteal			
Geometric mean	12.3	13.5	13.5
	23.4; 6.5	26.9; 6.8	25.7; 7.1
n	28	13	8
Unknown			
Geometric mean	10.2	12.0	12.0
	14.5; 7.2	19.5; 7.4	20.4; 7.1
n	24	13	8

*These figures refer to the geometric mean + 1 S.D. and the geometric mean − 1 S.D. respectively.

All results are expressed as ng/ml.

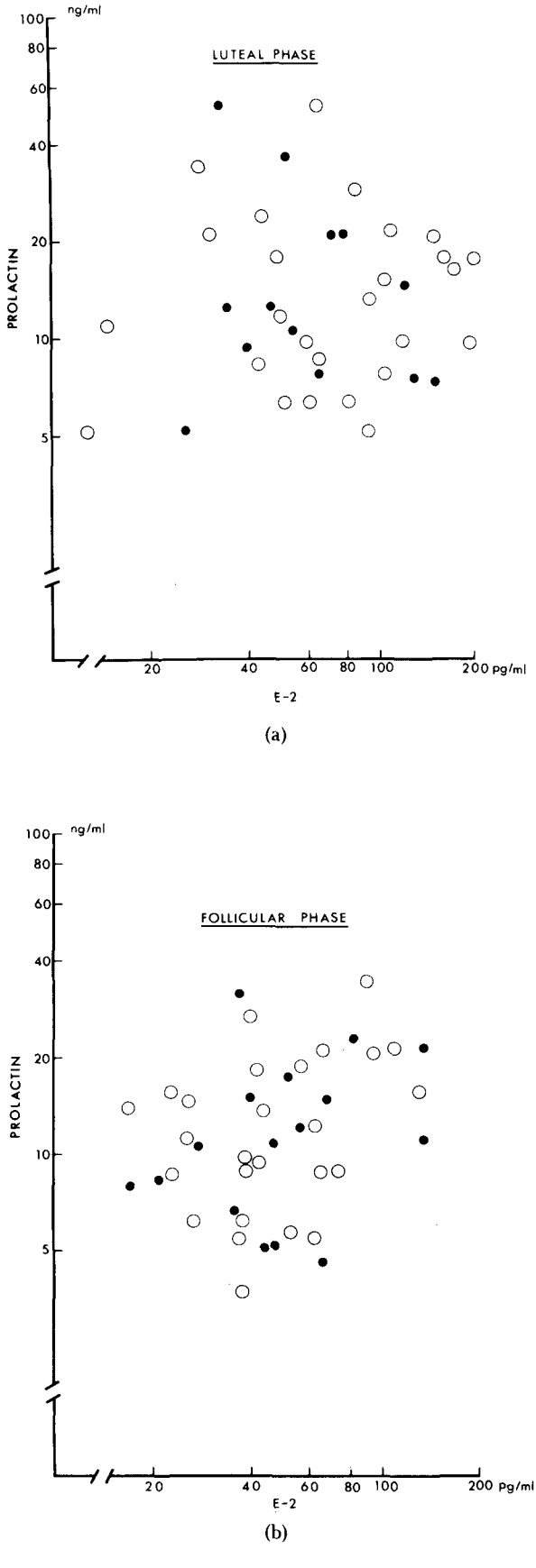

Fig. 1. Serum prolactin and oestradiol levels in adolescent girls with and without familial history of breast cancer.
Serum levels of prolactin and oestradiol during the luteal (a) and follicular (b) phases of the menstrual cycle are shown for girls with a family history (●) and without a family history (○).

were found in the "luteal" phase of the cycle in the populations studied by Henderson and his coleagues [2, 3].

The similarity in serum prolactin levels in young girls with or without family history of breast cancer is in contrast with an earlier report that adult women with a family history have elevated evening levels of prolactin [5, 10]. This discrepancy could be due to the wide disparity in the age between the subjects in the present study (14–20 years) and that in the volunteers investigated by Kwa *et al.* (age 35 or over) [5]. If this is the correct explanation, it indicates that the abnormality in blood prolactin levels is a late rather than an early event.

Our findings do not necessarily mean that there are no endocrine abnormalities in teenaged girls with a family history of breast cancer. They simply indicate that there are no gross differences. The small-scale studies so far carried out are inadequate for the detection of subtle abnormalities which might still be of physiological importance. Furthermore, the interrelationships between the various hormones in the two groups of girls has still to be properly examined. An explanation for the discrepancy between the present results and those of Pike *et al.* [3] might be that there are slight endocrine differences within sub-sets of an American population which may not be detectable in British populations living in a different environment and, in addition, the volunteers in the present study were bled in the evening.

There is some preliminary evidence [6] that one determinant of risk in adult pre-menopausal women is a deficiency in progesterone production by the corpus luteum (see also [26]). Since women with breast cancer achieve almost the same parity as those without the disease, it can be inferred that the progesterone deficiency is intermittent. If the frequency of anovulatory cycles were also a determinant of risk in adolescent girls, such an abnormality would be undetectable in any of the studies so far carried out. It is difficult to decide whether a menstrual cycle is really anovulatory when progesterone levels are monitored only once during the cycle, even when the dates of the last period and subsequent period are known. In view of the menstrual cycle chaos that exists in pubertal girls [21, 22, 24, 25] and the wide range of luteal phase progesterone levels, a very large population indeed would be required to determine whether such an abnormality is an important aetiological factor.

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