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THE CLINICAL AND ENDOCRINOLOGICAL EFFECT OF OESTRADIOL IMPLANTS AT THE TIME OF HYSTERECTOMY AND BILATERAL SALPINGO-OOPHORECTOMY

BY

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Summary

The plasma oestrogen level was maintained within the premenopausal physiological range for 16 months following the insertion of an implant of 100 mg. of oestradiol B.P.C. during the operation of hysterectomy and bilateral salpingo-oophorectomy. The karyopyknotic index (KI) was elevated for the same duration and levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were depressed. None of the 42 patients who had an oestrogen implant developed hot flushes whereas 11 out of 14 without an implant did so and were severely distressed thereby.

s been reported that 85 per cent of women undergo hysterectomy and bilateral ngo-oophorectomy before the menopause op severe hot flushes (Soule, 1951). The ment of this symptom with an oestrogen nt was first described by Bishop (1938), has since been widely practised (Brown 1951; Delaplaine *et al.*, 1952; Kupperman 1951). One of us (J.S.) has used it since but evidence as to the duration of its effect not precise and depended on subjective ment by the patient and, occasionally, the s of vaginal cytology.

The availability of hormone assays has now made it possible to study these patients more scientifically using plasma levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and oestrogen. We have also used the karyopyknotic index (KI) of a vaginal smear.

PATIENTS AND METHODS

Patients

Fifty-six women between the ages of 35 and 52 years at the time of hysterectomy and bilateral salpingo-oophorectomy were interviewed and blood samples were taken on one occasion at times varying from 6 weeks to 34 months after surgery. In 42 of these patients an implant of 100 mg. of oestradiol-17β B.P.C. (Organon Laboratories) had been placed under the rectus sheath then the abdomen was closed. The remaining 14 patients were operated upon by

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surgeons who did not use implants; these patients served as controls.

Hormone assays

Blood samples were placed in lithium-heparin tubes and the separated plasma stored at −23°C. until assayed. Luteinizing hormone (LH) was estimated by radioimmunoassay using a double antibody technique (Midgeley, 1966). The antiserum used showed no cross-reaction with pure FSH or with thyroid stimulating hormone. ^{131}I (Radiochemical Centre, Amersham) was used for iodination (Greenwood *et al.*, 1963). The second international reference preparation of human menopausal gonadotrophin (2nd IRP-HMG) was used as standard.

A double antibody radioimmunoassay was also employed for the assay of FSH. Cross-reaction of the antiserum with LH was eliminated by absorption of the antibody with pure human chorionic gonadotrophin (5 IU of HCG per ml. of antiserum). The 2nd IRP-HMG was used as standard.

Total plasma oestrogen was estimated by radioimmunoassay (Hotchkiss *et al.*, 1971) without chromatographic separation of the oestrogens. This method is specific for endogenous oestrogens, there being no cross-reaction with synthetic steroids (Kharma *et al.*, 1972). The intra-assay coefficient of variation for the three hormones was 10 per cent and the rec of oestrogen throughout the assay was bet 70 and 90 per cent.

Karyopyknotic index (KI)

Vaginal wall smears were stained by Papanicolaou (1954) technique and the KI assessed on a count of 200 cells.

Hot flushes

Hot flushes were graded as severe if occurred more than three times per moderate if they occurred under three times day but above three times per week, and mi they occurred under three times per week.

Results

The mean age of the control patients 46·4 years (S.D. = 4·3) and that of pati receiving an implant was 47·6 years (S.D. 4·1). There is no significant difference betw the age of the two groups.

Plasma oestrogen levels after surgery shown in Figure 1. The mean value of the control patients was 5·6 ng./100 ml. (S.D. 2·8). Thirty-four of the 42 patients with implant had a significantly raised plas oestrogen level (more than two standard de tions above the mean of the control value) can be seen that all 23 patients studied during first 15 months, and 11 out of 15 patients stud

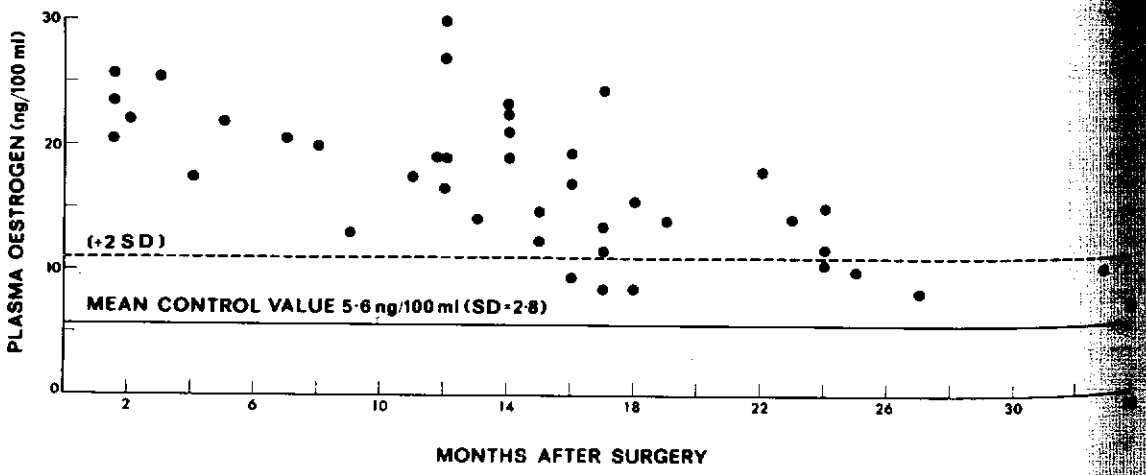
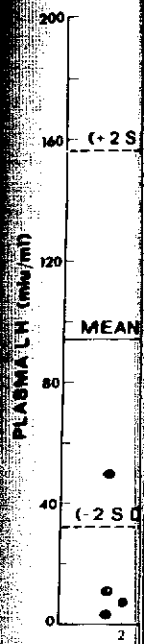


FIG. 1

Plasma oestrogen values after hysterectomy and removal of ovaries with oestradiol implant (●) compared to the mean control value of those without implant.



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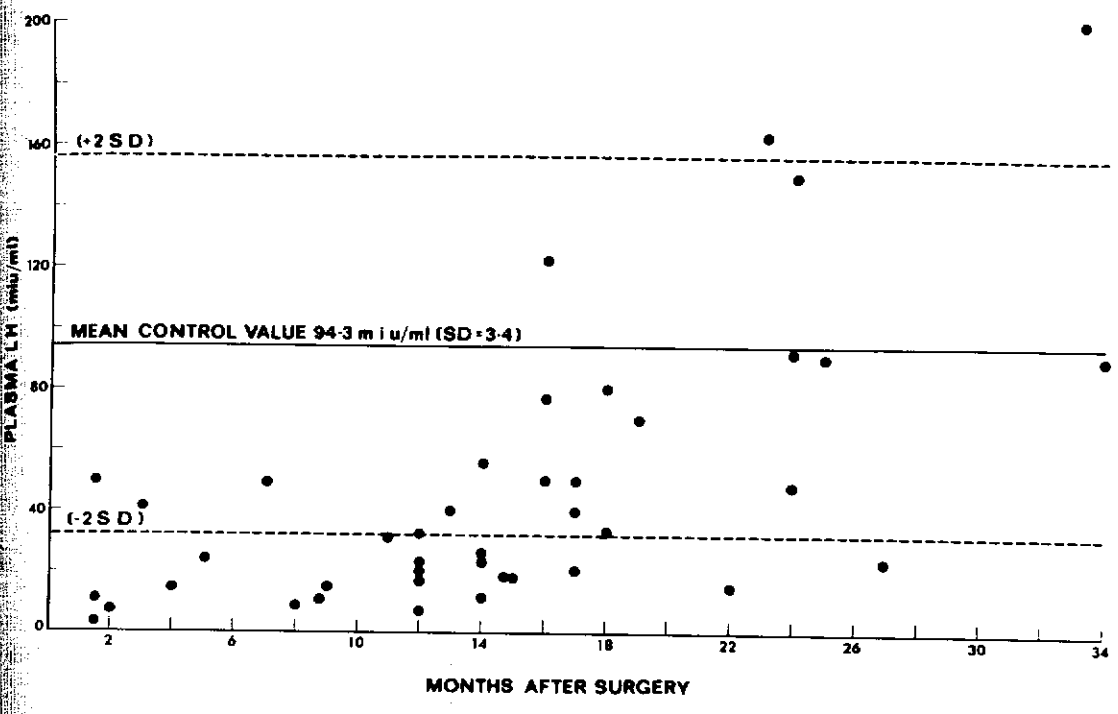

FIG. 2

Plasma LH values after hysterectomy and removal of ovaries with oestradiol implant (●) compared to the mean control value of those without implant.

between 16 and 24 months after operation had significantly raised levels. After 24 months there was no difference between the two groups.

Plasma LH levels are shown in Figure 2. The mean value in the 14 control patients was 94·3 miu/ml. (S.D. = 31·4). Twenty of the 42 patients with implants had a significantly depressed plasma LH level (more than two standard deviations below the mean control value). It can be seen that only 17 of the 23 patients studied during the first 15 months and 2 out of 15 patients studied between 16 and 24 months after operation, had significantly depressed LH levels. After 24 months one out of four patients still had a significantly depressed LH level.

Plasma FSH levels are shown in Figure 3. The mean value of the 14 control patients was 108·3 miu/ml. (S.D. = 27·6). Thirty-three of the 42 patients with an implant had a significantly depressed FSH level (more than two standard deviations below the mean of the control value). Twenty-two out of 23 patients studied in the first 15 months, and 9 out of the 15 patients studied between 16 and 24 months after operation had significantly depressed FSH levels. Two of the 4 patients seen after 24 months still had significantly depressed FSH levels.

KI values after surgery are shown in Figure 4. The mean value of the 14 control patients was 3·1 per cent (S.D. = 3·8). Only 35 of the 42 patients with an implant had the KI estimated and in 23 of these it was significantly elevated (more than two standard deviations above the mean of the control value). Sixteen out of 18 patients studied in the first 15 months, and 6 out of 15 patients studied between 16 and 24 months after operation had significantly raised KI values. One of two patients seen after 24 months still had a significantly raised KI value.

None of the 56 women had hot flushes before surgery. However 11 of the 14 patients with no implant developed severe flushes postoperatively and five patients required oestrogen therapy. None of the 23 patients with an implant seen in

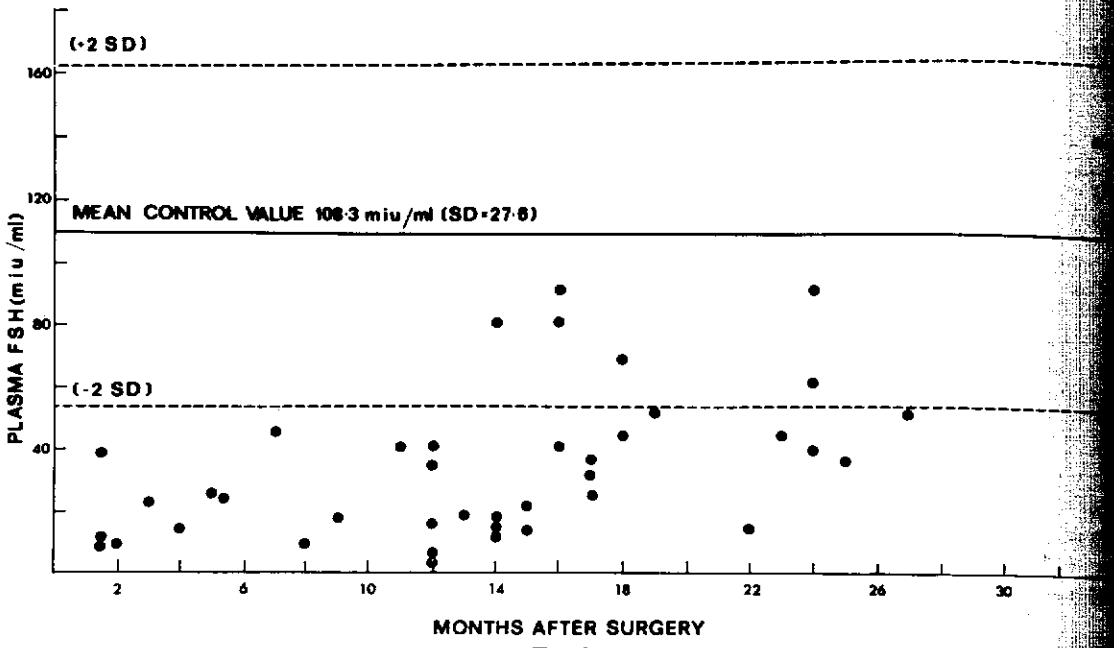

FIG. 3

Plasma FSH values after hysterectomy and removal of ovaries with oestradiol implant (●) compared to the m control value of those without implant.

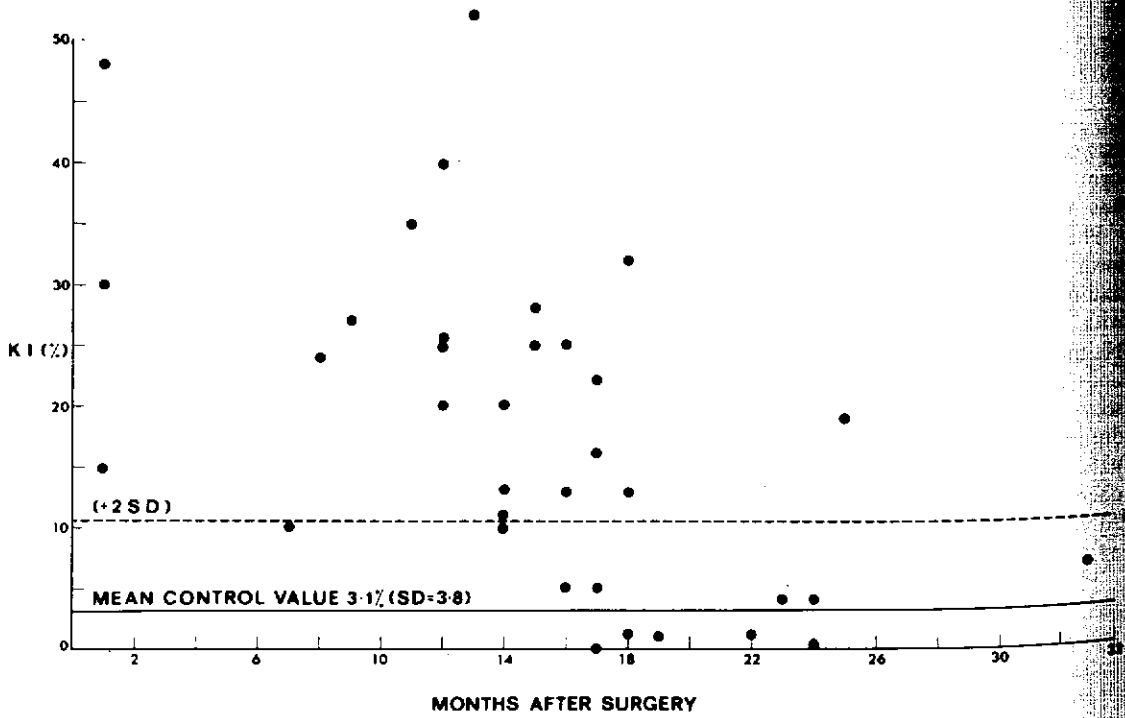

FIG. 4

Karyopyknotic indices (KI) after hysterectomy and removal of ovaries with oestradiol implant (●) compared to the control value of those without implant.

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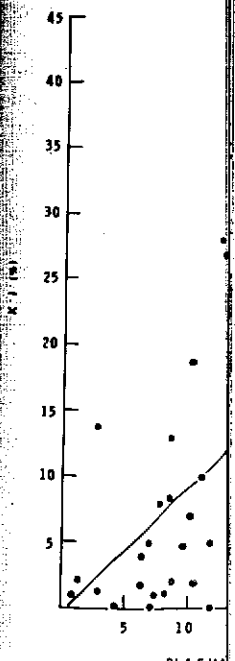

Correlation between

the first 15 months after surgery had hot flushes. One of the 15 patients seen between 16 and 24 months after surgery had developed mild flushes as had 2 out of the 4 patients examined after 24 months. All three dated the onset of flushes to approximately 18 months after operation.

The relationship between plasma oestrogen level and KI value is shown in Figure 5 ($r = +0{\cdot}58$). The relationship between plasma oestrogen and LH level is shown in Figure 6 ($r = -0{\cdot}53$) and the relationship between plasma oestrogen and FSH is shown in Figure 7 ($r = -0{\cdot}71$). All of these correlations are highly significant ($p<0{\cdot}001$).

Discussion

The plasma oestrogen level assayed by this method in healthy ovulating women ranges from 1 to 8 ng./100 ml. in the follicular phase to 24 to 45 ng./100 ml. at the time of the ovulatory peak. It would appear, therefore, that the plasma oestrogen level is maintained within the normal premenopausal physiological range for at least 15 months after an implant of 100 mg. of oestradiol-17β B.P.C.

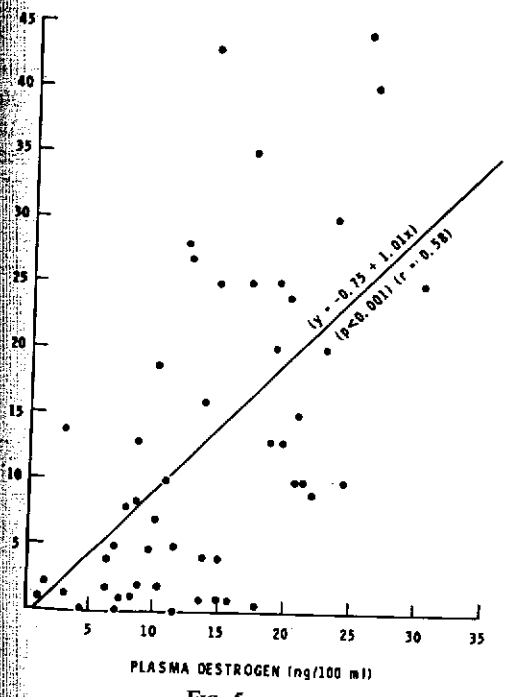

FIG. 5
Correlation between plasma oestrogen and KI.

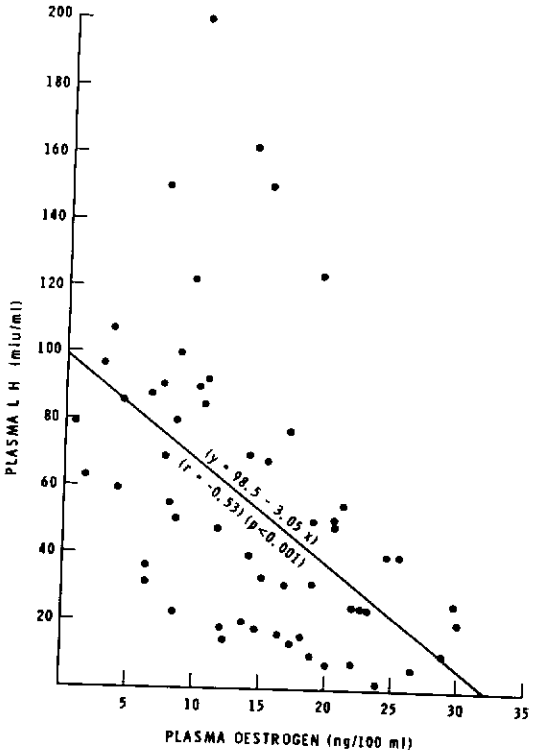

FIG. 6
Correlation between plasma oestrogen and plasma LH levels.

Although there appears to be a steady downward trend in plasma oestrogen levels, they were raised significantly for 15 months after surgery in all patients studied and were still significantly raised in most patients studied between 16 and 24 months after operation. Only four patients with an oestradiol implant were seen more than two years after operation, but the plasma oestrogen value in all four was still above the mean value of the control patients.

The FSH levels bore a closer correlation to plasma oestrogen levels than did LH levels. During the first 15 months after operation when all patients had a significantly raised plasma oestrogen level more patients had depressed FSH levels than LH levels. Between 16 and 24 months, when the majority of patients still had raised plasma oestrogen levels, the majority still had depressed FSH levels while only a minority had depressed LH levels. These results seem to support the observations of Adamopoulos *et al.*

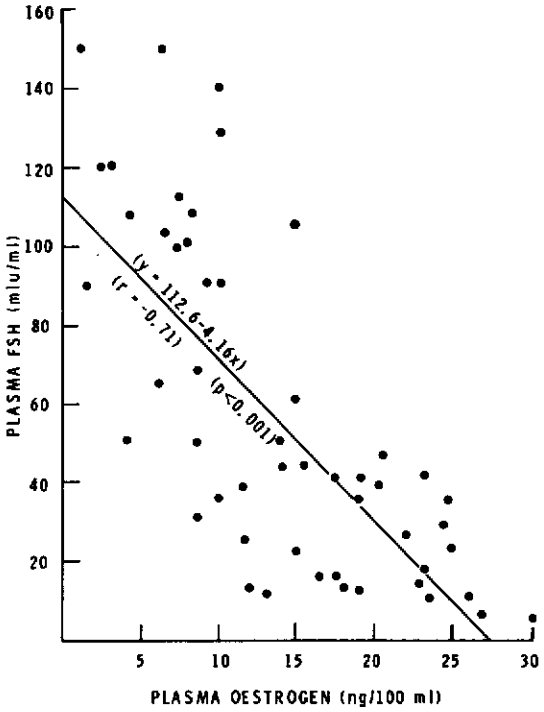

FIG. 7
Correlation between plasma oestrogen and plasma FSH levels.

(1971) that the release of LH (but not of FSH) becomes "insensitive" to oestrogen levels as the menopause approaches.

The KI value has for many years been used as an index of oestrogenic activity. Grönroos (1965) demonstrated a significant correlation ($r = +0{\cdot}52$) between the urinary excretion of oestrogens and KI and this is very near to the correlation reported here ($r = +0{\cdot}58$) between total plasma oestrogen levels and KI. However significant it may be, the correlation is poor and its clinical application is therefore limited. Whereas the majority of patients between 16 and 24 months after surgery had a significantly raised plasma oestrogen level, only the minority showed a raised KI. The smear would have been misleading in the patient seen 22 months after an implant because the plasma oestrogen was 18·5 ng./100 ml. while the KI was only 1 per cent. In the patient seen at 25 months, on the other hand, the KI was 19 per cent while the plasma oestrogen was only 9·8 ng./100 ml. It has recently been reported by Utian (1970) that the superfi count showed a disappointing respo post-menopausal women to oral oes valerate. This is surprising as the respo parenteral oestradiol in this study was with KI values between 20 and 40 per c study of urinary oestrogen levels afte administration of oestrogens might clari discrepancy.

The most striking clinical differences be the two groups was the absence of flush patients with an implant. Their general f of wellbeing contrasted with the severe ma tation of a surgical menopause in 11 out women without an implant. The severity o flushes was unrelated to the plasma leve FSH, LH, or oestrogen. Whether it is the oestrogen or the subsequent rise in FSH o that are important, or whether it is the r change of the level of these hormones that c hot flushes is at present being evaluated.

The evidence submitted justifies the prac implanting a pellet of 100 mg. of oestradio B.P.C. at the time of hysterectomy whe ovaries are removed. We believe that an im is also justified when the ovaries are conserv the patient complains of flushes before hyst tomy.

Contraindications to the use of an oestr implant are the same as those generally acce for the administration of any exogenous oe gen. They are the presence of genital or br carcinoma, hepatic disease or a history o thromboembolic disorder. Investigations determine the effects of the implant on clott factors are in progress but none of the patie reported here had clinical evidence of po operative thrombo-embolic complications.

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