CHAPTER 2
CIRCULATING LEVELS OF STEROID HORMONES IN EPITHELIAL OVARIAN CANCER.

In Chapter I, we have described the importance of steroid-and epidermal growth factor-receptors in epithelial ovarian carcinoma patients. Owing to the importance of receptor determinations for the management of epithelial ovarian cancer patients, a detailed knowledge is needed concerning the factors which affect receptor levels. Epidemiologic, experimental and clinical observations have implicated hormones in the pathogenesis and growth regulation of epithelial ovarian carcinomas (Nash et al., 1989).

It is well known that epithelial ovarian neoplasms are usually not regarded as functional tumors, since the epithelial cells themselves only rarely show hormone production.

Only a few reports of circulating hormone concentrations in epithelial ovarian cancer have been reported (Jakobovits, 1963; Edwards et al., 1971 and Heinonen et al., 1982). This resultant hormonal imbalance may precede and presumably favour the onset of epithelial ovarian cancer or they may be related with the evolution of the disease. Keeping these
facts in mind, in the present study, we have estimated the circulating levels of estradiol, progesterone, testosterone and its immediate major precursor androstenedione and have correlated it with clinically important prognosticators (i.e. disease stage, histologic type and grade, and disease outcome). We also have studied: (1) the effect of chemotherapy on these hormones and (2) correlation of circulating estradiol and progesterone with estrogen - and progesterone - receptors.

STUDY DESIGN:

A total of 72 patients with histologically confirmed epithelial ovarian cancer and 15 controls (frank menopausal) enrolled from June 1984 to June 1989 were selected for the study. The details of age, FIGO (International Federation of Gynaecology and Obstetrics) stage, residual disease and disease status were noted from disease charts maintained at The Gujarat Cancer and Research Institute, Ahmedabad, India. Histological typing was done according to World Health Organization (WHO) criteria (Serov et al, 1973) and histologic grading described by Day et al. (1975) was followed. The clinical data and treatment schedule were described in the previous
Chapter. Surgery was followed by chemotherapy and the preoperative level of these hormones was compared to those during chemotherapy (i.e. after 2 cycles of chemotherapy) and after completion of chemotherapy.

PATIENT SAMPLING:

In a serial follow-up programme conducted at the Endocrinology Division, venous blood samples were collected strictly between 9.0 to 12.0 A.M., preoperatively to obtain baseline level of the individual patients and monthly/bimonthly on each occasion.

Serum was separated within two hours, aliquoted and preserved at -70°C till analysis. Studies were performed retrospectively using frozen samples.

STEROID HORMONE ASSAYS:

Serum estradiol (E$_2$), progesterone (Pg), testosterone (T) and androstenedione (Andro) were estimated by RIA (Radioimmunoassay) kits procured from Diagnostic Products Corporation, Los Angeles, USA, according to the manufacturer's instructions. All the estimations were performed in duplicate with an intraassay and an interassay coefficient of variation (CV) of 3% to 5% and 5% to 8%
respectively along with internal quality controls. The sensitivity of the assays were:

(1) 8.0 pg/ml for E
(2) 0.05 ng/ml for Pg
(3) 0.11 ng/ml for T and
(4) 0.02 ng/ml for Andro.

The normal range for postmenopausal controls was:

(1) Undetectable to 14.0 pg/ml for E
(2) Undetectable to 0.5 ng/ml for Pg
(3) Undetectable to 0.3 ng/ml for T and
(4) 0.5 to 1.5 ng/ml for Andro.

Depending on disease progression or regression, the patients were grouped into two:

(I) Patients with progressive disease and
(II) Patients who responded to treatment at the end of 18 months.

(I) Patients with progressive disease (N=12):

Amongst the patients with progressive disease, (i) the preoperative level of steroid hormones was compared to (ii) the level preceding progression and (iii) the level at progression.
(II) Patients who responded to treatment modalities (N=11):

Amongst responders, the preoperative level of steroid hormones was compared to the level at last follow-up (i.e. at the end of 18 months) when the patient responded to surgery followed by chemotherapy.

CORRELATION OF E AND Pg WITH STEROID RECEPTORS:

Using cut off values of 14.0 pg/ml for E and 0.5 ng/ml for Pg, the preoperative levels were divided into two groups i.e.

(i) Patients with <14.0 pg/ml of E and
(ii) Patients with >14.0 pg/ml of E and
(i) Patients with <0.5 ng/ml of Pg and
(ii) Patients with >0.5 ng/ml of Pg and compared with ER and PR status. They were correlated with the stage of the disease.

STATISTICAL ANALYSIS:

Significance was calculated using an exact contingency table test for order data and Fisher's two sided exact test (Mehta and Patel, 1983). P values less than 0.05 were considered statistically significant.
RESULTS:

PART A:
INCIDENCE OF STEROID HORMONES:

Circulating preoperative steroid hormone levels in patients with epithelial ovarian cancer were compared with controls. E, Pg and T were significantly elevated in patients when compared to controls (E and Pg: $P < 0.001$; T: $P < 0.0001$; Table 1). However, high levels of E, Pg and T were observed in 27/72 (38%), 28/70 (40%) and 32/71 (45%) patients respectively. Abnormal levels of Andro were present in 29/49 (59%) patients and the difference was statistically nonsignificant when compared with controls. 21/49 (43%) patients had Andro above upper normal limit (i.e. > 1.5 ng/ml), while 8/49 (16%) had subnormal levels (i.e. < 0.5 ng/ml). In this study, 2 patients had very high levels of Pg (i.e. > 900 ng/ml) and 1 patient had high level of T (13.2 ng/ml).

RELATION OF STEROID HORMONES TO DISEASE STAGE:

Significant correlation was not observed between the preoperative steroid hormone levels and stage of the disease. However, Pg showed a decreased trend as stage advanced (Table 2a). It was observed that 17/22 (77.2%)
stage IV patients had undetectable level of E (Fig. 1). When patients with serous tumors were grouped according to stage of the disease, no correlation was found between preoperative steroid hormone levels and disease stage (Table 2b).

STEROID HORMONES VERSUS HISTOLOGIC TYPES:

E and T were high, while Pg was low in patients with serous and endometrioid tumors compared to those with mucinous tumors and the differences were statistically nonsignificant. Pg was significantly low in endometrioid tumors compared to serous tumors (P < 0.02; Table 3), while no such correlation was seen in Andro levels.

STEROID HORMONES IN RELATION TO HISTOLOGIC GRADE:

The mean value of E and Andro were similar in patients with grade I, II and III tumors. Pg showed a decreasing trend from grade I to III tumors. T was significantly elevated in grade II+III tumors than grade I tumors (P < 0.02; Table 4a). The patients with serous tumors were further subgrouped according to their tumor differentiation and no significant correlation was observed between grade II and III tumors (Table 4b).
STEROID HORMONES IN RELATION TO DISEASE OUTCOME:

(I) Patients with progressive disease:

In patients with progressive disease, all four hormones were elevated at progression in comparison to the levels preceding progression and the differences were statistically nonsignificant. When the circulating levels of E, Pg, T and Andro at progression were compared to the preoperative levels, no significant differences were noticed (Table 5).

(II) In responders:

In responders, the preoperative values and the levels at last follow-up were correlated. All the hormones except \( \text{E}_2 \) showed decreased levels at last follow-up (Andro: \( P < 0.02 \); Table 5). Moreover, the preoperative levels of Pg and T were high in responders compared to patients with progressive disease and the differences were statistically nonsignificant.

EFFECT OF CHEMOTHERAPY ON STEROID HORMONES:

(i) In patients with progressive disease:

In patients with progressive disease, completion of
chemotherapy resulted in a nonsignificant decline of circulating E and Pg, while no significant difference was observed in T and Andro when compared to the preoperative values. When the levels during chemotherapy (i.e. after 2 cycles of chemotherapy) were correlated with those after completion of chemotherapy, it was observed that circulating levels of E decreased, while the levels of Pg, T and Andro were same (Table 6; Figs. 2 - 4).

(ii) In responders:

In responders, completion of chemotherapy resulted in a nonsignificant decline of Pg, T and Andro, while no such correlation was observed in E when compared with the preoperative values. These hormones were also compared to those during chemotherapy. It was noted that completion of chemotherapy resulted in a nonsignificant decrease of E and Pg. Two cycles of chemotherapy showed a decrease in the preoperative level of Pg, T and Andro, while preoperative level of E was elevated and the differences were however, statistically nonsignificant (Table 6; Figs. 5 and 6).

RELATIONSHIP BETWEEN E AND Pg TO ER AND PR:

Significant differences in E were not seen in ER / PR and ER / PR patients. However, Pg was significantly low in ER patients than ER patients (P < 0.05 ; Table 7).
CORRELATION OF E AND Pg WITH RECEPTOR STATUS ACCORDING TO DISEASE STAGE:

Using a cut off value of 14.0 pg/ml for E, the epithelial ovarian cancer patients were divided into two groups: (i) \( E < 14.0 \text{ pg/ml} \) and (ii) \( E > 14.0 \text{ pg/ml} \). These patients were further subgrouped according to disease stage and steroid receptor positivity or negativity.

(i) \( E < 14.0 \text{ pg/ml} \):

In this group, patients with stage III or IV disease had higher content of PR than ER which was statistically significant only in stage III patients \( (P < 0.02; \text{ Table 8a}) \). Moreover, the ER/PR concentrations were low in stage III patients compared to stage IV patients. The difference was statistically significant only in ER patients \( (P < 0.05) \).

(ii) \( E > 14.0 \text{ pg/ml} \):

Significant correlation between ER and PR patients was not seen in all stages. However, stage III ER patients had significantly more ER than stage III ER patients with \( E < 14.0 \text{ pg/ml} \) \( (P < 0.05; \text{ Table 8a}) \).

Similarly using cut off 0.5 ng/ml for Pg, the patients were divided into two groups: (i) \( Pg < 0.5 \text{ ng/ml} \) and (ii) \( Pg > 0.5 \).
ng/ml. They were further subgrouped according to the disease stage and steroid receptor status.

(i) $\text{Pg} < 0.5$ ng/ml :

Significant correlation between ER and PR patients was not seen in all stages of disease.

(ii) $\text{Pg} > 0.5$ ng/ml :

Patients with stage III and IV disease had higher concentrations of PR than ER. The difference was statistically significant only in stage III patients ($P < 0.001$; Table 8b). Moreover, stage III patients had low content of ER and PR when compared to stage IV patients. The difference was statistically significant only in ER$^+$ patients ($P < 0.05$). Stage III ER$^+$ patients had low levels of ER when compared to stage III ER$^+$ patients with $\text{Pg} < 0.5$ ng/ml ($P < 0.05$; Table 8b).

**DISCUSSION :**

The results presented here show that circulating $E_2$, $\text{Pg}$ and $T$ were significantly high in epithelial ovarian cancer patients when compared with postmenopausal controls. This was in accordance with the results of Backstrom et al. (1983), Heinonen et al. (1986), Mahlck
et al. (1986) and Mahlck et al. (1988). Heinonen et al. (1986) have reported elevated plasma \( E_2 \) concentrations in women with epithelial ovarian cancer compared to postmenopausal controls. Furthermore, it has been suggested that in postmenopausal women, \( P_g \) is exclusively of adrenal origin (Vermeulen, 1976). The lower peripheral serum concentrations of \( P_g \) after bilateral oophorectomy confirm the view that postmenopausal women with epithelial ovarian tumors secrete \( P_g \) (Heinonen et al., 1985). Thus, a contribution from ovarian tumor to elevated levels of steroid hormones seems evident, though the underlying mechanism is obscure. Woodruff et al. (1963) described cells in the peripheral parts of the tumor belonging to intact ovary and resembling theca cells of the developing follicle responsible for steroid production. Tuimala et al. (1983) suggested conversion of adrenal precursors by the tumor tissue as an alternative explanation for elevated \( E_2 \) in epithelial ovarian cancer patients. The elevated \( E_2 \) levels in turn promoted SHBG production and high SHBG may be responsible for elevated circulating \( T \) levels because of greater binding (Mahlck et al., 1986).

The present findings showed that stage had no influence on the steroid hormone concentrations. The volume of the tumor
seemed to be more significant for Pg secretion than for malignancy or stage of the disease (Backstrom et al, 1983). Our finding of low progesterone in advanced stages is at variance with the results of Backstrom et al. (1983) who have reported elevated progesterone with increasing stage of the tumor. In 17/22 (77.2%) stage IV patients, we observed undetectable levels of E₂ (Fig. 1). One of the reason for this, as pointed out by Jeppson et al. (1982) could be that if the excessive amounts emanate (directly or indirectly) from the persisting ovarian cells, probably stimulated by an increasing blood supply, then this increase would appear at an early stage and while the tumor is still small.

Histologic and histochemical studies have shown that the excessive steroid activity has its origin in the hyperplastic ovarian stroma associated with these tumors (Jakobovits, 1963; Woodruff et al, 1963; Plotz et al, 1966 and Fathalla et al, 1968). The mechanism of action leading to hormonal activity in tumors with functioning stroma is still unknown. It has been proposed that tumor cells in the ovarian stroma induce transformation of the quiescent cells into actively secreting cells (Scott et al, 1987). It is not yet known which cell type is the source of steroid hormone production. We observed elevated levels of Pg in
mucinous tumors compared to serous and endometrioid tumors. This is in accordance with the results of Heinonen et al. (1985). Moreover, $E_2$ and $T$ were high when compared to controls. These findings support the view that mucinous tumors have hormonal activity (MacDonald et al., 1976; Cotton et al., 1981 and Rome et al., 1981). This might have resulted from either increased androgen production and extraglandular conversion to estrone resulting in a massive increase in endogenous estrogen formation (MacDonald et al., 1976). We also observed that histologic grade II + III tumors had significantly high levels of $T$.

Significant correlations of steroid hormones with disease outcome or chemotherapy were not seen. Amongst the nonresponders, 5/12 patients had undetectable preoperative levels of $E_2$ and $Pg$. In the responder group, 4/11 patients had undetectable preoperative levels of $E_2$ and $Pg$. A possible explanation for this could be that low initial estradiol at an advanced stage might have disturbed the estradiol prognosis pattern. Mahlick et al. (1988) on the other hand reported reduction of $E_2$ during the course of chemotherapy.

In 4/23 patients, $Pg$ levels were undetectable throughout the course of disease (Figs. 6-9). Furthermore, in two
stage III patients with serous cystadenocarcinoma, the initial serum levels of Pg were remarkably high ( \( > 900 \) ng/ml). In one patient there was a gradual decrease of Pg level after surgery followed by chemotherapy, while in the other patient there was a steep fall after surgery. Also one stage IV patient with serous cystadenocarcinoma had very high level of testosterone. The divergence of endocrine manifestations in such tumors is of considerable interest. These divergent endocrine manifestations have led to suggest that stromal hyperplasia could be responsible for such high levels. It has been suggested that growth promoting mitogenic factors produced by the tumor cells induce stromal hyperplasia thereby making it more sensitive to LH stimulation (MacDonald et al, 1976). The elevated LH levels (80% of our patients had elevated LH) in turn stimulated steroidogenesis. Thus seemingly, any ovarian tumor may be associated with extensive ovarian androgen and / or estrogen secretion. The cells of a functional tumor likely secrete the steroids whereas a tumor not ordinarily associated with such sex - steroid secretion appears to stimulate hyperplasia and luteinization of surrounding ovarian stroma.

In order to obtain more information about the endocrine characteristics of the tumor, ER and PR were correlated with
E and Pg according to disease stage. In the present study, circulating \( E < 14.0 \text{ pg/ml} \) and \( Pg > 0.5 \text{ ng/ml} \) were associated with high concentrations of PR than ER in advanced stages. Moreover, stage III ER patients with \( E < 14.0 \text{ pg/ml} \) and \( Pg > 0.5 \text{ ng/ml} \) had low content of ER in comparison to stage IV ER patients. On the contrary, Hahnel et al. (1982) were unable to observe any correlation of ER and PR, with \( E \) and \( Pg \) in ovarian tumors. Their study group consisted of 28 pre- and post-menopausal patients with malignant and benign ovarian tumors. In breast cancer, Vihko et al. (1980) found a positive correlation of ER and PR with \( E \). From our results, we conclude that circulating levels of \( E \) and \( Pg \) influence the concentrations of ER and PR.

**ABSTRACT:**

Part A of this chapter describes the significance of circulating steroid hormones i.e. \( E, Pg, T \) and its immediate precursor androstenedione in 72 epithelial ovarian cancer patients. These hormones were grouped according to the stage, histologic type and grade of the tumor. Progesterone level showed a decreased trend as stage advanced. Moreover, its level was significantly low in endometrioid tumors as compared to serous tumors. Grade II
and III tumors had elevated testosterone levels than grade I tumors. The distribution of E and androstenedione was more or less similar in all stages and histologic grade of the tumor.

In part B, these steroid hormones are correlated with disease outcome (progression/remission). Circulating levels of these hormones at diagnosis were compared with those preceding clinical progression and at the time of clinical recurrence. All four hormones were elevated at recurrence when compared to preceding levels. Amongst responders, the values at diagnosis and at last follow-up (at the end of 18 months) were correlated. All the hormones except E showed decreased levels at last follow-up.

This section also describes the effect of chemotherapy on these hormones amongst patients who developed recurrence and in responders. Steroid hormones were correlated with the ER and PR status. It was observed that serum progesterone was significantly low in ER tumors than ER tumors.
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TABLES
Table 1: Steroid hormones in epithelial ovarian cancer patients (M ± SE)

<table>
<thead>
<tr>
<th></th>
<th>E 2</th>
<th>Pg</th>
<th>T</th>
<th>Andro</th>
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</thead>
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<tr>
<td>Controls</td>
<td>15</td>
<td>0.546 ± 1.49</td>
<td>0.16 ± 0.04</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>Patients</td>
<td>72</td>
<td>19.77 ± 3.76</td>
<td>0.01 ± 0.15</td>
<td>0.42 ± 0.06</td>
</tr>
<tr>
<td>% abnormal</td>
<td>38</td>
<td>40</td>
<td>45</td>
<td>59</td>
</tr>
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* P < 0.001
+ P < 0.01
$ P < 0.0001$
Table 2a: Relation of steroid hormones to disease stage (Mean + SE)

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>E2</th>
<th>Pg</th>
<th>T</th>
<th>Andro</th>
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<tr>
<td></td>
<td></td>
<td>pg/ml</td>
<td>ng/ml</td>
<td>ng/ml</td>
<td>ng/ml(N)</td>
</tr>
<tr>
<td>II</td>
<td>03</td>
<td>19.61 ± 0.83</td>
<td>1.93 ± 0.75</td>
<td>0.24 ± 0.07</td>
<td>1.15 ± 0.74 (02)</td>
</tr>
<tr>
<td>III</td>
<td>35</td>
<td>19.87 ± 0.89</td>
<td>0.90 ± 0.28</td>
<td>0.40 ± 0.07</td>
<td>1.03 ± 0.29 (27)</td>
</tr>
<tr>
<td>IV</td>
<td>22</td>
<td>17.56 ± 0.96</td>
<td>0.39 ± 0.15</td>
<td>0.35 ± 0.08</td>
<td>1.20 ± 0.27 (15)</td>
</tr>
<tr>
<td>Rec.</td>
<td>12</td>
<td>23.55 ± 12.76</td>
<td>0.68 ± 0.29</td>
<td>0.66 ± 0.28</td>
<td>1.05 ± 0.31 (87)</td>
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<tr>
<td>III + IV</td>
<td>57</td>
<td>18.98 ± 0.89</td>
<td>0.78 ± 0.10</td>
<td>0.38 ± 0.05</td>
<td>1.62 ± 0.22 (40)</td>
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Table 2b: Relation of steroid hormones to disease stage in patients with serous tumors (N ± SE)

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>E₂ (pg/ml)</th>
<th>Fq (ng/ml)</th>
<th>T (ng/ml)</th>
<th>Andro (ng/ml(N))</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>02</td>
<td>29.42 ± 05.60</td>
<td>1.35 ± 0.88</td>
<td>0.27 ± 0.10</td>
<td>0.10 ± 0.10</td>
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<tr>
<td>III</td>
<td>28</td>
<td>19.99 ± 04.46</td>
<td>1.00 ± 0.35</td>
<td>0.39 ± 0.08</td>
<td>1.75 ± 0.28</td>
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<tr>
<td>IV</td>
<td>16</td>
<td>16.53 ± 09.85</td>
<td>0.71 ± 0.19</td>
<td>0.34 ± 0.11</td>
<td>1.15 ± 0.26</td>
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<td>Rec.</td>
<td>09</td>
<td>26.07 ± 16.34</td>
<td>0.74 ± 0.39</td>
<td>0.80 ± 0.37</td>
<td>1.72 ± 0.40</td>
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<tr>
<td>III + IV</td>
<td>44</td>
<td>18.73 ± 04.57</td>
<td>0.89 ± 0.23</td>
<td>0.38 ± 0.07</td>
<td>1.58 ± 0.22</td>
</tr>
<tr>
<td>Histologic type</td>
<td>N</td>
<td>E (pg/ml)</td>
<td>Pg (ng/ml)</td>
<td>T (ng/ml)</td>
<td>Andro (ng/ml)</td>
</tr>
<tr>
<td>-----------------</td>
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<td>-----------</td>
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<td>---------------</td>
</tr>
<tr>
<td>Serous</td>
<td>55</td>
<td>26.32 ± 04.56</td>
<td>0.88 ± 0.19</td>
<td>0.44 ± 0.08</td>
<td>1.56 ± 0.19 (35)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>05</td>
<td>12.40 ± 11.09</td>
<td>1.01 ± 0.48</td>
<td>0.26 ± 0.08</td>
<td>1.11 ± 0.32 (04)</td>
</tr>
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<td>Endometrioid</td>
<td>04</td>
<td>17.19 ± 09.50</td>
<td>0.29 ± 0.15</td>
<td>0.31 ± 0.06</td>
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<td>Undiff. Ca.</td>
<td>02</td>
<td>88.84 ± 06.25</td>
<td>0.57 ± 0.25</td>
<td>0.48 ± 0.34</td>
<td>5.10 (01)</td>
</tr>
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<td>Mixed</td>
<td>02</td>
<td>21.55 ± 13.69</td>
<td>0.59 ± 0.24</td>
<td>0.20 ± 0.01</td>
<td>0.38 (01)</td>
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<tr>
<td>Mucin-secreting</td>
<td>04</td>
<td>26.47 ± 16.58</td>
<td>0.38 ± 0.12</td>
<td>0.52 ± 0.13</td>
<td>2.21 ± 0.96 (04)</td>
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♯ P < 0.05
△ P < 0.02
★ P < 0.01
Table 4a: Steroid hormones in relation to histologic grade (N ± SE)

<table>
<thead>
<tr>
<th>Histologic grade</th>
<th>N</th>
<th>E₂ (pg/ml)</th>
<th>Pg (ng/ml)</th>
<th>T (ng/ml)</th>
<th>Andro (ng/ml(N))</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>06</td>
<td>17.15 ± 10.21</td>
<td>1.03 ± 0.38</td>
<td>0.19 ± 0.06</td>
<td>1.14 ± 0.43 (85)</td>
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<tr>
<td>II</td>
<td>34</td>
<td>22.64 ± 68.77</td>
<td>0.74 ± 0.18</td>
<td>0.34 ± 0.07</td>
<td>1.66 ± 0.21 (25)</td>
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<tr>
<td>III</td>
<td>24</td>
<td>21.98 ± 64.06</td>
<td>0.10 ± 0.37</td>
<td>0.43 ± 0.08</td>
<td>1.94 ± 1.35 (17)</td>
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<td>II + III</td>
<td>38</td>
<td>22.37 ± 64.45</td>
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<td>0.38 ± 0.05</td>
<td>1.77 ± 0.21 (42)</td>
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<td>08</td>
<td>02.87 ± 02.68</td>
<td>0.39 ± 0.08</td>
<td>0.94 ± 0.41</td>
<td>0.59 ± 0.14 (04)</td>
</tr>
</tbody>
</table>

* P < 0.05

** P < 0.02
Table 4b: Steroid hormones according to histologic grade in patients with serous tumors ( mean ± SE )

<table>
<thead>
<tr>
<th>Histologic grade</th>
<th>N</th>
<th>E&lt;sub&gt;2&lt;/sub&gt; pg/ml</th>
<th>Pg ng/ml</th>
<th>T ng/ml</th>
<th>Andro ng/ml(N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>01</td>
<td>0.0</td>
<td>0.38</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>31</td>
<td>23.76 ± 07.34</td>
<td>0.79 ± 0.20</td>
<td>0.32 ± 0.07</td>
<td>1.46 ± 0.24 (22)</td>
</tr>
<tr>
<td>III</td>
<td>16</td>
<td>22.37 ± 05.48</td>
<td>1.30 ± 0.55</td>
<td>0.46 ± 0.10</td>
<td>2.12 ± 0.34 (10)</td>
</tr>
<tr>
<td>Unknown</td>
<td>01</td>
<td>3.28 ± 03.04</td>
<td>0.42 ± 0.08</td>
<td>1.00 ± 0.47</td>
<td>0.44 ± 0.08 (03)</td>
</tr>
</tbody>
</table>
Table 5: Steroid hormones in relation to disease outcome (M ± SE)

<table>
<thead>
<tr>
<th></th>
<th>E (pg/ml)</th>
<th>Pg (ng/ml)</th>
<th>T (ng/ml)</th>
<th>Andro (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>progressive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>21.50 ± 0.56</td>
<td>0.35 ± 0.12</td>
<td>0.21 ± 0.04</td>
<td>1.76 ± 0.38</td>
</tr>
<tr>
<td>Before progression</td>
<td>10.29 ± 0.16</td>
<td>0.16 ± 0.09</td>
<td>0.26 ± 0.07</td>
<td>0.96 ± 0.15</td>
</tr>
<tr>
<td>At progression</td>
<td>24.71 ± 14.59</td>
<td>0.38 ± 0.10</td>
<td>0.32 ± 0.07</td>
<td>1.68 ± 0.42</td>
</tr>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>18.50 ± 0.46</td>
<td>0.61 ± 0.38</td>
<td>0.45 ± 0.11</td>
<td>1.89 ± 0.38</td>
</tr>
<tr>
<td>At last follow-up</td>
<td>25.27 ± 0.75</td>
<td>0.87 ± 0.04</td>
<td>0.35 ± 0.10</td>
<td>0.80 ± 0.14</td>
</tr>
</tbody>
</table>

* P < 0.02
Table 6: Effect of chemotherapy on steroid hormones in patients with progressive disease and in responders (M ± SE)

<table>
<thead>
<tr>
<th></th>
<th>E 2 (pg/ml)</th>
<th>Pg (ng/ml)</th>
<th>T (ng/ml)</th>
<th>Andro (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with progressive disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>17.97 ± 68.75</td>
<td>0.38 ± 0.10</td>
<td>0.21 ± 0.05</td>
<td>1.52 ± 0.45</td>
</tr>
<tr>
<td>During chemotherapy</td>
<td>21.17 ± 84.53</td>
<td>0.10 ± 0.04</td>
<td>0.20 ± 0.05</td>
<td>1.09 ± 0.24</td>
</tr>
<tr>
<td>After chemotherapy</td>
<td>9.63 ± 82.74</td>
<td>0.14 ± 0.09</td>
<td>0.26 ± 0.08</td>
<td>1.34 ± 0.17</td>
</tr>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>24.01 ± 87.09</td>
<td>0.75 ± 0.46</td>
<td>0.52 ± 0.14</td>
<td>1.30 ± 0.29</td>
</tr>
<tr>
<td>During chemotherapy</td>
<td>37.08 ± 10.63</td>
<td>0.14 ± 0.06</td>
<td>0.27 ± 0.09</td>
<td>0.67 ± 0.15</td>
</tr>
<tr>
<td>After chemotherapy</td>
<td>25.72 ± 88.83</td>
<td>0.03 ± 0.03</td>
<td>0.29 ± 0.11</td>
<td>0.79 ± 0.16</td>
</tr>
</tbody>
</table>
Table 7: Relationship between estradiol and progesterone to ER and PR (M ± SE)

| Receptor | E₂ status | E₂ pg/ml | N | Pg ng/ml | N | *
|----------|-----------|----------|---|----------|---|---
| ER       | +         | 20.05 ± 04.31 | 33 | 0.47 ± 0.13 | 32 | *
| ER       | -         | 30.18 ± 09.46 | 22 | 1.41 ± 0.40 | 22 | *
| PR       | +         | 22.84 ± 04.05 | 37 | 0.93 ± 0.27 | 36 | *
| PR       | -         | 26.85 ± 11.41 | 18 | 0.72 ± 0.22 | 18 | *

* P < 0.05
Table 8a: Correlation of estradiol with ER and PR (fso/μg protein) according to disease stage (N ± SE)

### E < 14.0 pg/ml

<table>
<thead>
<tr>
<th>Stage</th>
<th>ER</th>
<th>ER</th>
<th>PR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>(N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| II    | 74.0 |    | 13.0 |    |
|       | (01) |    | (01) |    |

| III   | 018.7 ± 01.52 | 08 | 30.75 ± 03.72 | 03 |
|       | (08) |    | (13) |    |

| IV    | 039.63 ± 07.65 | 01 | 06.33 ± 07.17 | 04 |
|       | (08) |    | (03) |    |

| Rec.  | 100.66 ± 04.48 | 03 | 19.0 | 05 |
|       | (03) |    | (01) |    |

| III + IV | 028.46 ± 05.39 | 09 | 41.86 ± 09.90 | 07 |
|          | (14) |    | (16) |    |

### E > 14.0 pg/ml

<table>
<thead>
<tr>
<th>Stage</th>
<th>ER</th>
<th>ER</th>
<th>PR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>(N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| II    |    | 02 | 28.0 | 01 |
|       |    | (01) |    |    |

| III   | 40.44 ± 04.06 | 05 | 43.65 ± 05.53 | 02 |
|       | (09) |    | (12) |    |

| IV    | 26.00 ± 01.82 | 02 | 44.00 ± 10.16 | 02 |
|       | (04) |    | (04) |    |

| Rec.  | 58.00 ± 24.74 | 01 | 68.00 ± 18.60 | 01 |
|       | (02) |    | (02) |    |

| III + IV | 36.00 ± 06.63 | 07 | 43.73 ± 04.86 | 04 |
|          | (13) |    | (16) |    |

*; *; P < 0.05  &; P < 0.02
Table 8b: Correlation of progesterone with ER and PR (fmol/mg protein)

according to disease stage (N ± SE)

\[Pg < 0.5 \text{ ng/ml}\]

<table>
<thead>
<tr>
<th>Stage</th>
<th>ER + (N)</th>
<th>ER - (N)</th>
<th>PR + (N)</th>
<th>PR - (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>74.0</td>
<td>01</td>
<td>13.0</td>
<td>01</td>
</tr>
<tr>
<td></td>
<td>(01)</td>
<td>(01)</td>
<td>(01)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>36.72 ± 07.78</td>
<td>06</td>
<td>32.92 ± 05.15</td>
<td>04</td>
</tr>
<tr>
<td></td>
<td>(12)</td>
<td>(14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>73.00 ± 02.90</td>
<td>01</td>
<td>35.75 ± 11.74</td>
<td>02</td>
</tr>
<tr>
<td></td>
<td>(05)</td>
<td>(04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rec.</td>
<td>81.25 ± 51.19</td>
<td>01</td>
<td>53.00</td>
<td>04</td>
</tr>
<tr>
<td></td>
<td>(04)</td>
<td>(01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III + IV</td>
<td>32.68 ± 05.61</td>
<td>07</td>
<td>33.58 ± 04.82</td>
<td>06</td>
</tr>
<tr>
<td></td>
<td>(17)</td>
<td>(18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[Pg > 0.5 \text{ ng/ml}\]

<table>
<thead>
<tr>
<th>Stage</th>
<th>ER + (N)</th>
<th>ER - (N)</th>
<th>PR + (N)</th>
<th>PR - (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>74.0</td>
<td>01</td>
<td>13.0</td>
<td>01</td>
</tr>
<tr>
<td></td>
<td>(01)</td>
<td>(01)</td>
<td>(01)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17.00 ± 03.00</td>
<td>07</td>
<td>43.48 ± 04.94</td>
<td>01</td>
</tr>
<tr>
<td></td>
<td>(04)</td>
<td>(10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>44.00 ± 10.39</td>
<td>02</td>
<td>97.33 ± 30.64</td>
<td>04</td>
</tr>
<tr>
<td></td>
<td>(05)</td>
<td>(03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rec.</td>
<td>95.00</td>
<td>03</td>
<td>51.00 ± 22.62</td>
<td>02</td>
</tr>
<tr>
<td></td>
<td>(01)</td>
<td>(02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III + IV</td>
<td>37.44 ± 07.50</td>
<td>09</td>
<td>55.90 ± 10.20</td>
<td>05</td>
</tr>
<tr>
<td></td>
<td>(09)</td>
<td>(13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\# P < 0.05

\& P < 0.001
LEGENDS TO FIGURES:
Fig. 1

Incidence of E and Pg in relation to disease stage.
Stage III, grade III patient with papillary serous cystadenocarcinoma (PSCAC) was treated with surgery followed by chemotherapy (CT). She responded to chemotherapy but 8.5 months after completion of chemotherapy, she developed progressive disease. The preoperative values of $E$ and $T$ were high, while $Pg$ and Andro were within normal limit. Two cycles of chemotherapy resulted into a decrease in $E$, $Pg$, $T$ and Andro with no significant change in Andro. At the time of disease progression, $E$ was undetectable, while $Pg$, $T$ and Andro showed no significant changes.
Stage III Andro PSCAC
* Pg HG III - T Res.dis.>2 cm

Fig-2

Lap. CR

MONTHS

E2 pg/ml
Andro ng/ml

Pg & T ng/ml

1.0
0.5
0.0

1 6 12 18 MONTHS

Fig-2
Stage III, grade III patient with endometrioid tumor was treated with surgery followed by chemotherapy. One year later, she developed lung metastases with pleural effusion. Exploratory laparotomy was done and she had massive generalised carcinomatosis. She died within 15 days after operation.

The preoperative values of E and T were high, while Pg was undetectable and Andro was subnormal. Two cycles of chemotherapy resulted into an increase of all the hormones compared to their preoperative values. Further courses of chemotherapy, resulted into a decline of E and Pg with no significant change in T and Andro. At the time of lung metastases, E and Pg were low, while T was slightly elevated and Andro showed no significant change compared to their preceding levels.
Andro Endometrioid
Pg HG III
— T Res. dis. >2 cm

E2 pg/ml
Andro ng/ml

Lung met. with
Pl. efu.
Expl. Lap.
Exp.

E2 Stage III
Andro Endometrioid
Pg HG III
T Res. dis. >2 cm

Pg & T ng/ml

Fig-3
Stage III, grade III patient was operated and further treated with chemotherapy. After 10 courses of chemotherapy, she complained of abdominal distension and finally died. The preoperative value of $E$ was high, while the preoperative values of $T$ and $\text{Andro}$ were within normal limit. Two cycles of chemotherapy resulted into an increase in $P_g$ with no significant change in $E$, $T$ and $\text{Andro}$ when compared to preoperative levels. Further courses of chemotherapy resulted into a decline of $E$ with elevation of $P_g$ and no significant change in $T$ and $\text{Andro}$. At the time of disease progression, there was slight elevation of $E$ with no significant change in $P_g$, $T$ and $\text{Andro}$ when compared to their preceding levels.
E2 Stage III
Andro PSCAC
Pg HG III
T Res.dis.>2cm

0-5
Pg & T ng/ml
r H
1-0

X----------------------X
¥----------¥
CL
X
UJ
f ^  I  i
E2 pg/ml
Andro ng/ml

G-

11 MONTHS Fig-

--- E2  Stage III
--- Andro  PSCAC
--- Pg  HG III
--- T  Res.dis.>2 cm

--- E2 pg/ml
--- Andro ng/ml

Fig-4

--- Pg & T ng/ml

0 1 2 3 4 5 6 7 8 9 10 11
0 0.5 1.0 1.1

MONTHS
Fig. 5

Stage III, grade III patient was treated with surgery followed by chemotherapy. She responded to chemotherapy and was well at the end of 18 months. The preoperative value of Pg and Andro were high, while E and T were within normal limit. Two cycles of chemotherapy resulted into an elevation of E, while Pg, T and Andro were low when compared to their preoperative levels. At last follow-up, E was high, while Pg, T and Andro were within normal limit.
Stage III
Andro PSCAC
Pg HG III
Res. dis>2cm

Fig-5

E2 pg/ml

Andro ng/ml

MONTHS

18

12

6

0

0

5

10

15

20

25

30
Stage III, grade II patient was treated with surgery followed by chemotherapy. She had < 2cm residual disease. She responded to chemotherapy and was well at the end of 18 months. The preoperative value of $E$ was high, while $P_g$, $T_2$ and Andro were within normal limit. Two cycles of chemotherapy, resulted into a decline of $E_2$ with slight elevation of $T_2$ and no significant change in $P_g$ and Andro when compared to preoperative values. At last follow-up, all the hormones were within normal limit. $P_g$ was undetectable throughout the course of the disease.
Stage III
E2P9/ml - Andro PSCAC
Res. dis. < 2 cm
Pg & T ng/ml
L Pg HG II
T Res. dis. < 2 cm
Andro ng/ml
76.0 ng/ml
18 MONTHS
Fig-6
Stage III, grade II patient was treated with surgery followed by chemotherapy. She responded to chemotherapy but after 7 courses of chemotherapy developed progressive disease. Except for the preoperative value, Pg was undetectable throughout the course of the disease.
Stage III
PSCAC
HG II
Res. dis. >2 cm

E₂ pg/ml
Andro ng/ml

0 1 6 12 18
MONTHS

Fig-7
Stage III, grade II patient was treated with surgery followed by chemotherapy. She was irregular in treatment. After 7 months, she developed ascitis. Finally she developed liver metastasis and died.

Pg was undetectable throughout the course of the disease.
Stage III, grade II patient was treated with surgery followed by radiotherapy (RT) and then chemotherapy. She was irregular in treatment. After 13 months she developed ascitis which was tapped. Chemotherapy was started again and she responded to it. Pg was undetectable throughout the course of the disease.
Stage III
PSCAC
HG II
Res. dis. > 2 cm
Pg & T ng/ml

E2 pg/ml
Andro ng/ml

18 MONTHS

Fig. 9