Study of endogenous hormones in endometrial cancer patients of premenopausal women

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Abstract

Introduction: Several studies were conducted worldwide to estimate various endogenous hormone levels in endometrial cancer patients of post-menopausal women and very few studies were done in premenopausal women. In India, our study is the first study conducted to estimate the endogenous hormones in endometrial cancer patients of premenopausal age group.

Materials and Methods: 25 number of endometrial cancer patients were taken as cases and 50 number of age matched healthy subjects were selected as controls for this study. Total testosterone, follicular estrogen, mid luteal estrogen, luteal estrogen, and follicular progesterone, mid luteal progesterone, luteal progesterone and fasting insulin were estimated for all the subjects.

Results: Statistical significant increase were observed in the levels of testosterone, follicular progesterone, mid luteal progesterone and luteal progesterone in cases when compared to controls. No statistical significant difference were observed in follicular estrogen, mid luteal estrogen, luteal estrogen and fasting insulin levels between cases and controls.

Conclusion: From our study we conclude that endogenous hormones play a major role in the development of endometrial cancer in pre menopausal women as Testosterone is increased and progesterone is decreased in cases when compared to controls. Extensive studies are required to diagnose endometrial cancer in early stages for better prognosis.

Keywords: Estrogen, Progesterone, Testosterone.

Introduction

Endometrial cancers are the most common gynecologic cancers in developed countries with over 150,000 women diagnosed each year making the fifth most common cancer in women.1 The prevalence of this cancer is also increasing in developing countries like India. Obesity is an important risk factor for this disease in both pre and postmenopausal women, accounting for 40% of the incidence.2 Various measures of fat distribution, such as WHR, have been reported to be associated with increased risk of endometrial cancer, although less consistently than BMI.3,4 The other risk factors for endometrial cancer include diabetes, hypertension, PCOD, nulliparity, infertility, endometrial polyps and estrogen replacement therapy etc.1

Epidemiological studies indicate that estrogens, both endogenous and exogenous, have a major role in endometrial carcinogenesis.5,6 Few studies have investigated a possible differential effect of BMI on endometrial cancer risk before and after menopause7,8 and a possible threshold effect in premenopausal women, whereas in older women there appears to be a linear increase with BMI. Chronic hyperinsulinemia is clearly another important risk factor for endometrial cancer among both pre and postmenopausal women.9 Many epidemiological studies have shown an increased risk of endometrial cancer in both pre and postmenopausal women, with non-insulin dependent diabetes.10,11 Endometrial cancer risk to be associated with serum levels of C-peptide, a marker of pancreatic insulin secretion,13 and higher fasting plasma glucose and insulin levels14 showing an increased risk with hyperinsulinemia even in non diabetic women. Increased endometrial cancer risk has been associated with early menarche and late menopause, suggesting a relationship of risk with greater life time exposure to estrogens at premenopausal levels.5

Epidemiologic studies have produced results which were not only unclear but also very inconsistent among endometrial cancer risk and premenopausal plasma levels of sex steroid hormones and no study is done in Indian population which has estimated the levels of endogenous hormones in endometrial cancer patients. This study is the first of its kind in Indian population as far as our knowledge is concerned. The aim of the present study is to estimate the levels of endogenous hormones like serum testosterone, estrogen and progesterone in their follicular, mid luteal and luteal phases in endometrial cancer cases.

Materials and Methods

The present study was conducted in the Department of Biochemistry of Saveetha Medical College. 25 diagnosed cases of endometrial cancer after careful examination of FNAC report and histopathological examination belonging to premenopausal age group < 45 years (premenopausal women are taken by the fact that they have continuous
9 menstrual cycles over previous 12 months before the sample collection\(^5\)) were included in this study. 50 age matched women who have no history of endometrial diseases were taken as controls. Exclusion criteria included patients on hormonal replacement therapy, oral contraceptive usage, individuals suffering with benign disorders like fibroadenoma, lactating mothers, hypertension, chronic illness, autoimmune diseases, renal disorders and liver disorders. The following information was obtained from both the cases and controls like parity, menopausal status, hereditary information, life style factors including, tobacco usage, alcohol consumption, dietary habits, obesity, and hormonal replacement therapy. Informed consent was obtained from all the cases and controls. Due permission was obtained from Ethical Clearance Committee for this study. 10ml of fasting blood samples were collected by venipuncture from all cases and controls during follicular phase (15 to -2 days), mid cycle phase (-1 to +1 days) and luteal phase (+2 to +15 days), by day in cycle relative to LH peak. Estradiol and Testosterone were estimated by CMIA (Chemi Luminescent Microparticle Immuno Assay) and Total Progesterone by CLIA (Chemi Luminescent Immuno Assay). Serum fasting insulin was estimated by using enzymatic method by automated analyzer. The data were analysed by using paired t test, independent sample test and Mann-Whitney test using SPSS version 23.

**Results**

**Table 1: Baseline characteristics of endometrial cancer cases and controls**

| Parameter                     | Cases (n=25) | Controls (n=50) |
|-------------------------------|--------------|-----------------|
| Mean age at menarche          | 13.6         | 13.5            |
| Mean length of menstrual cycle| 30.1         | 29.2            |
| Mean height (cms)             | 151          | 149             |
| Mean weight                   | 67           | 59              |
| Mean BMI                      | 27.3         | 24.5            |
| Percentage parous             | 77.1         | 91.6            |
| Percentage reporting first degree family history | 19.6     | 4.0             |
| Percentage reporting past use of oral contraceptives | 65.7     | 19.7            |

**Table 2: Comparison of Biochemical parameters between cases and controls**

| Parameters                      | Mean±SD Cases (n=25) | Mean±SD Controls (n=50) | Standard Error Mean |
|---------------------------------|----------------------|-------------------------|---------------------|
| Testosterone(ng/mL)             | 2.5204±0.96513       | 0.3792±0.25127          | 0.03554             |
| Follicular estrogen(pg/mL)      | 136.04±52.325        | 130.28±56.310           | 7.962               |
| Mid luteal estrogen(pg/mL)      | 247.20±97.559        | 232.96±106.774          | 15.100              |
| Luteal estrogen(pg/mL)          | 129.24±65.553        | 133.04±69.665           | 9.852               |
| Follicular progesterone(ng/mL)  | .0824±.03919         | .6858±.41157            | .05821              |
| Mid luteal progesterone(ng/mL)  | 3.4260±1.57397       | 17.4940±5.99879         | .84836              |
| Luteal progesterone(ng/mL)      | 3.1348±1.45586       | 18.4942±5.61731         | .79441              |
| Insulin(mIU/L)                  | 13.548±5.9189       | 14.172±6.5235           | .9226               |

**Table 3: Independent Samples Test for cases and controls**

| Parameter       | Levene’s test for Equality of Variances | t- test for Equality of Means | 95% confidence interval of the difference |
|-----------------|----------------------------------------|------------------------------|-----------------------------------------|
| Testosterone    | Equal                                  | 51.567°F                      | .000                                     | 14.805 73 .000 2.14120 .14463 1.85296 2.42944 |
### Study of endogenous hormones in endometrial cancer patients of premenopausal women

**G. S. R. Kedari et al.**

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| (ng/mL)                  | Equal variances assumed | Equal variances not assumed |  |  |  |  |
|-------------------------|------------------------|-----------------------------|---|---|---|---|
| Follicular Estrogen (pg/mL) | 10.910 25.640 .000 2.14120 .19627 1.73749 2.54491 | | | | | |
| Mid luteal Estrogen (pg/mL) | 25.640 .670 5.760 13.478 -21.103 32.623 | | | | | |
| Luteal estrogen (pg/mL) | 5.760 13.150 -20.634 32.154 | | | | | |
| Follicular progesterone (ng/mL) | 36.953 .000 -11.494 73 .000 -14.06800 1.22399 -16.50740 -11.62860 | | | | | |
| Mid luteal progesterone (ng/mL) | -15.547 61.059 .000 -14.06800 .90488 -15.87738 -12.25862 | | | | | |
| Luteal progesterone (ng/mL) | 24.456 .000 -13.406 73 .000 -15.35940 1.14570 -17.64277 -13.07603 | | | | | |
| Insulin (mIU/L) | .785 .378 -.402 73 .689 -.6240 1.5008 -3.7147 2.4667 | | | | | |

In all cases, variances are assumed or not assumed as indicated.
Table 4: Mann-Whitney test

| Parameters                      | Mean rank | Sum of ranks |
|--------------------------------|-----------|--------------|
|                                | Cases(n=25) | Controls(n=25) | Cases(n=25) | Controls(n=50) |
| Testosterone(ng/mL)            | 62.74     | 25.63        | 1568.50     | 1281.50        |
| Follicular estrogen(pg/mL)     | 40.10     | 36.95        | 1002.50     | 1847.50        |
| Mid Luteal Estrogen(pg/mL)     | 40.40     | 36.80        | 1010.00     | 1840.00        |
| Luteal estrogen(pg/mL)         | 37.40     | 38.30        | 935.00      | 1915.00        |
| Follicular progesterone(ng/mL) | 13.00     | 50.50        | 325.00      | 2525.00        |
| Mid luteal progesterone(ng/mL) | 13.24     | 50.38        | 331.00      | 2519.00        |
| Luteal progesterone(ng/mL)     | 13.16     | 50.42        | 329.00      | 2521.00        |
| Insulin(mIU/L)                 | 36.64     | 38.68        | 916.00      | 1934.00        |

Table 5: Test Statistics

| Parameters                        | Mann-Whitney U test | Wilcoxon W | Z     | Asymp. Sig (2-tailed) |
|-----------------------------------|---------------------|------------|-------|----------------------|
| Testosterone(ng/mL)               | 6.500               | 1281.50    | -6.954| .000*                |
| Follicular estrogen(pg/mL)        | 572.500             | 1847.50    | -.590 | .555                 |
| Mid luteal estrogen(pg/mL)        | 565.000             | 1840.00    | -.674 | .500                 |
| Luteal estrogen(pg/mL)            | 610.000             | 935.00     | -.169 | .866                 |
| Follicular progesterone(ng/mL)    | .000                | 325.00     | -7.026| .000*                |
| Mid luteal progesterone(ng/mL)    | 6.000               | 331.00     | -6.958| .000*                |
| Luteal progesterone(ng/mL)        | 4.000               | 329.00     | -6.981| .000*                |
| Insulin(mIU/L)                    | 591.000             | 916.00     | -382  | .702                 |

Discussion

From our study it was found that there was statistical significant increase in the levels of testosterone in cases when compared to controls. There were also statistical significant decrease in the levels of follicular progesterone, mid luteal and luteal progesterone in cases when compared with controls. No statistical differences were observed in the levels of follicular, mid luteal and luteal estrogen and fasting insulin levels between cases and controls.

Our study shows that premenopausal women who have increased levels of serum testosterone are more prone for endometrial cancer. Few prospective studies have shown no statistical association between the levels of testosterone and endometrial cancer in premenopausal women\(^9\) whereas positive association between testosterone levels and endometrial cancer risk was observed in post menopausal women in many studies.\(^6,16,17\) Many case control studies have shown that endometrial cancer risk is also increased in both pre and postmenopausal women with elevated plasma levels of androstenedione\(^18,19\) and testosterone\(^20\) and few did not show the association.\(^21,22\) Androgens do not appear to have any direct stimulatory effect on endometrial cell proliferation and the results from in vitro studies suggest a reduction in proliferation rates.\(^23,24\) The association of plasma androgen levels with endometrial cancer risk is thus more likely to be explained by an increase in estrogens, unopposed by progesterone and in premenopausal women, intraovarian androgen excess contributes to follicular atresia, and can lead to chronic anovulation and reduced levels of progesterone.\(^9\)

In our study, statistically significant difference was observed in the levels of follicular, mid luteal and luteal levels of progesterone in cases when compared to controls. In premenopausal women developing endometrial cancer, low progesterone levels rather than increased estrogen may be a more important determinant of risk.\(^25\) Few epidemiological studies showed higher endometrial cancer risk among women with polycystic ovarian syndrome, a condition
characterized by obesity, ovarian hyperandrogenism, anovulation, and progesterone deficiency. The importance of low progesterone is also supported by observations that obesity, a major risk factor for endometrial cancer in both pre and postmenopausal women, does not increase total or bioavailable estrogens in premenopausal women, but in some women can cause chronic anovulation and strongly reduce progesterone synthesis. No statistical significance were observed in the levels of follicular, mid luteal and luteal estrogen levels between cases and controls in our study. In premenopausal women, developing endometrial cancer, circulating estradiol levels generally are above a threshold of 50pg/mL and endometrial cancer risk is not related to between subject differences in circulating estradiol levels, but that low progesterone levels may be a more important determinant of risk. Our results are consistent with few studies which showed decreased total and bioavailable estradiol in endometrial cancer patients and they also had lower levels of estrone in premenopausal women developing endometrial cancer.

No statistical significance was observed in the levels of fasting insulin levels between cases and controls in our study. In postmenopausal women, insulin provides a key stimulus to ovarian and adrenal androgen synthesis in Polycystic ovarian syndrome (PCOS) and leads to estrogen excess and progesterone deficiency. The limitation of our study include less sample size, nonestimation of FSH, LH and their association with estrogen, progesterone and testosterone levels. Women with menstrual cycles who will vary largely both intra and inter individually may also influence the levels of endogenous hormones.

**Conclusion**

From our study we conclude that endogenous hormones play a major role in the development of endometrial cancer in premenopausal women as testosterone is increased and progesterone is decreased in cases when compared to controls. We conclude that in future more studies are required to diagnose the risk of endometrial cancer in very early stages to reduce the mortality and morbidity in endometrial cancer patients.

**Conflict of interest:** Nil

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