Impact of Severity of Illness on the Function of the Hypothalamo-pituitary-gonadal Axis in Postmenopausal Women with Acute Severe Illness: Implications for Predicting Disease Outcome

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Abstract

Background: While elevated levels of estradiol were predictive of mortality in critically ill surgical and trauma patients, their ability to predict outcome in nonsurgical patients has not been studied. We aimed to study the determinants of gonadotropin levels in acutely ill postmenopausal women with nonsurgical disease and the impact of changes in the gonadal axis on the outcome of these patients.

Methods: Thirty-five postmenopausal women admitted to medical intensive care with acute severe illness and having a Simplified Acute Physiology Score (SAPS II score) ≥30 (in-hospital mortality rate ≥ 10%) were recruited. On the 5th day of hospitalization, fasting samples were collected at 8.00 am and tested for luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, free triiodothyronine, free thyroxine, thyrotropin, prolactin, dehydroepiandrosterone, androstenedione, and sex hormone-binding globulin. Multiple linear regression analysis was performed to identify independent determinants if any of LH and FSH. Receiver operating characteristic (ROC) curves were drawn for different cutoffs of LH, FSH, and estradiol to diagnose mortality and prolonged hospitalization.

Results: There was an independent negative association between the FSH and the SAPS II score (beta = −0.435; P = 0.014), but not with any of the other tested parameters (estradiol, prolactin, or cortisol). Among components of the SAPS II score, the total leukocyte count (TLC) was negatively associated with serum FSH (beta coefficient = −0.635, P = 0.013). None of these parameters were determinants of LH. On ROC analysis, neither estradiol nor gonadotropins were diagnostic for in-hospital mortality. However, among survivors, low estradiol was diagnostic for prolonged hospital stay (area under the curve = 0.785; P = 0.015). Conclusion: FSH, but not LH, is negatively associated with the severity of illness, particularly to its inflammatory component (TLC). Low estradiol in survivors was a predictor of prolonged hospital stay.

Keywords: Critical illness, estradiol, follicle-stimulating hormone, luteinizing hormone, postmenopause, prolactin, receiver operating characteristic curve

INTRODUCTION

It is well known that the hypothalamo-pituitary-gonadal (HPG) axis responds to stress both in men and women by getting suppressed.[1-2] The degree of suppression of follicle-stimulating hormone (FSH) (but not the luteinizing hormone [LH]) in particular has been linked to the severity of the underlying illness.[3] Despite a suppression of the axis (i.e., reduction in the gonadotropins) during acute illness, an increased level of the female sex hormone, estradiol (E2), has also been reported.[4]

Increased adrenal androgen production[4] and increased activity of adipose tissue aromatase have both been documented to occur during stress and may be responsible for the observed

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elevation of estradiol levels. Thus, this occurs possibly through enhanced peripheral (extragonadal) aromatization of adrenal androgens.

Elevated levels of estradiol have been predictive of mortality in several series of critically ill surgical and trauma patients. However, the ability of estradiol levels to predict outcome in acute critically ill nonsurgical (i.e., medical) patients has not been studied.

Further, the previous studies were in mixed populations of adult men and women of various ages. In premenopausal women as well as in men, HPG axis suppression during acute severe illness would be expected to decrease the gonadotropin-mediated estrogen production rates from the gonads. This would in effect dilute the extent of estradiol rise from the stress-induced increased peripheral aromatization of adrenal androgens.

To overcome this problem, we decided to study the estradiol levels in critically ill postmenopausal women admitted to intensive care with a variety of acute severe nonsurgical diseases. In postmenopausal women, the ovary having exhausted all its follicles has no significant direct contribution to the circulating estradiol pool and almost all the circulating estradiol would be derived from the peripheral aromatization of androgens.

Methods
Details of the study population and methodology have been reported elsewhere. Briefly, 35 postmenopausal women (>60 years of age) admitted to the intensive care units (of Departments of Medicine and Neurology) with a variety of acute severe medical illnesses and having a Simplified Acute Physiology Score II (SAPS II) >30 (consistent with an in-hospital mortality rate ≥10%) were recruited for the study. Predicted death rates for in-hospital mortality were calculated from the SAPS II based on the published formula. Patients taking glucocorticoids, estrogen, selective estrogen receptor modulators, thyroxine, dopamine, or any other medication known to affect any of the hormones being measured either during the current admission (before sample collection) or in the recent past were excluded. Patients with known hypothyroidism or hypothyroidism or prior known pituitary disease were also excluded from the study. Thirty-five healthy ambulatory postmenopausal women aged more than 60 years served as controls. However, data from these healthy controls are not being used in this study report.

The study was approved by the Institutional Ethics Committee. Informed consent was obtained from the patient/participant herself if she had the mental capacity. Otherwise consent was taken from the next responsible caregiver.

On the 5th day of hospitalization, fasting venous blood samples were collected at 8.00 am. Following tests were performed on the collected samples: LH, FSH, estradiol (E2), free triiodothyronine, free thyroxine, thyrotropin, cortisol, prolactin, dehydroepiandrosterone, androstenedione, and sex hormone-binding globulin. Details of the assays used are available elsewhere.

Patients were then followed up until the time of their discharge or death in-hospital. Among survivors, the total duration of hospitalization in days was recorded.

Statistical analysis
Sample size for the original study was calculated for an expected 25% or greater reduction in mean gonadotropin levels in sick postmenopausal women when compared to healthy postmenopausal controls for a power of ≥80% and a significance level ($P < 0.05$). The obtained minimum sample size was 27 for detecting change in LH and 29 for change in FSH. However, 35 patients were included as mentioned earlier.

Estradiol and gonadotropin levels in the sick postmenopausal women were expressed as median (interquartile range). The percentages of those who died in the hospital were compared between tertiles of LH, FSH, and estradiol separately by the Chi-square test. Comparison of patient data between those who survived and those who died during hospital stay was performed by the nonparametric Mann–Whitney U-test. Ability to predict mortality or prolonged hospital stay for each of the above hormones was assessed by drawing receiver operating characteristic (ROC curves) and determining the area under the curve (AUC). A two-tailed $P < 0.05$ was taken as statistically significant. Statistical analysis was carried out using SPSS for Windows, version 13, (SPSS Inc., Chicago, IL, USA) statistical software.

Results
Comparison of gonadotropins and estradiol levels between sick patients and healthy controls recruited into this study has been reported earlier. Briefly, gonadotropin (both LH and FSH) levels were lower in patients than in controls. Paradoxically, estradiol levels were significantly elevated in the sick postmenopausal women than in the controls.

The diagnoses of the patients, their SAPS II, predicted in-hospital mortality rates as % derived from SAPS II, and the final mortality outcome (survived or expired) are summarized in Table 1.

Patients who died were older than those who survived. There was no difference in the SAPS II among the critically ill postmenopausal women who died as compared to those who survived. Among the critically ill patients, there was no difference in any hormone between the patients who died and those who survived (Table 2).

Determinant of gonadotropins in acutely sick postmenopausal women
Multiple linear regression analysis was done to assess any independent association of the gonadotropins (LH and FSH separately) with the severity of the disease (as represented by the SAPS II) and with various hormones that are known...


| Patient | Diagnosis                                                                 | SAPS II | Survived/expired | PDR (%) |
|---------|---------------------------------------------------------------------------|---------|------------------|---------|
| 1       | Urinary tract infection, pyelonephritis, sepsis with renal failure, multiple organ dysfunction syndrome, left ventricular dysfunction, Type 2 diabetes mellitus | 53      | Survived         | 53      |
| 2       | Left upper zone pneumonia with pericardial effusion, chronic kidney disease on hemodialysis | 47      | Survived         | 39.2    |
| 3       | Pneumonia with left lower zone consolidation, right pleural effusion with Type 2 respiratory failure, old pulmonary tuberculosis, Type 2 diabetes mellitus, hypertension | 38      | Expired          | 21.3    |
| 4       | Acute gastroenteritis with acute renal failure with shock and metabolic encephalopathy | 49      | Survived         | 43.8    |
| 5       | Type 2 diabetes mellitus with hyperglycemic hyperosmolar syndrome with acute kidney injury and urinary tract infection | 48      | Survived         | 41.5    |
| 6       | Type 2 diabetes mellitus, hypertension, acute exacerbation of bronchial asthma with cor pulmonale | 40      | Expired          | 24.7    |
| 7       | Leptospirosis, anemia with acute kidney injury, hepatic dysfunction, cholelithiasis | 46      | Survived         | 37      |
| 8       | Type 2 diabetes mellitus, hypertension, chronic kidney disease, left pyelonephritis | 66      | Survived         | 78.5    |
| 9       | Type 2 diabetes mellitus, hypertension, pneumonia with septicemia with shock | 48      | Survived         | 41.5    |
| 10      | Leptospirosis, thrombocytopenia, Type 2 diabetes mellitus with ketosis, cerebral sinus thrombosis, survived a cardiorespiratory arrest | 32      | Survived         | 12.8    |
| 11      | Aspiration pneumonia with urinary tract infection | 45      | Expired          | 34.8    |
| 12      | Cerebrovascular accident - right-middle cerebral artery infarct with history of snake bite Possibly Viperidae | 44      | Survived         | 32.6    |
| 13      | Acute posterior circulatory stroke, Type 2 diabetes mellitus, hypertension | 32      | Survived         | 12.8    |
| 14      | Cerebrovascular accident - right-middle cerebral artery infarct with Type 2 diabetes mellitus | 38      | Survived         | 21.3    |
| 15      | Carcinoma cervix, cerebrovascular accident - left-middle cerebral artery infarct-right hemiplegia, sinus bradycardia, coronary artery disease, hypertension, Type 2 diabetes mellitus | 38      | Survived         | 21.3    |
| 16      | Cerebrovascular accident, right capsulogangliconic infarct, and left parieto-occipital hemorrhage with intraventricular extension, mass effect and midline shift | 43      | Survived         | 30.6    |
| 17      | Type 2 diabetes mellitus, acute on chronic kidney disease, epilepsy partialis continua, sepsis with multiple organ dysfunction syndrome and shock | 56      | Expired          | 59.8    |
| 18      | Cerebrovascular accident - right-hemiplegia, hypertension | 43      | Expired          | 30.6    |
| 19      | Acute meningoencephalitis, hypertension, status epilepticus | 41      | Survived         | 26.6    |
| 20      | Type 2 diabetes mellitus with hyperglycemic hyperosmolar syndrome, acute gastroenteritis, hypertension, cerebrovascular accident - right posterior circulatory stroke | 49      | Expired          | 43.8    |
| 21      | Hypertension, cerebrovascular accident - left-hemiplegia-recurrent stroke | 34      | Survived         | 15.3    |
| 22      | Type 2 diabetes mellitus, hypertension, left complex partial seizures with heimiplegia due to right frontoparietal acute subdural hematoma | 32      | Survived         | 12.8    |
| 23      | Coronary artery disease, Inferior wall acute myocardial infarction, left ventricular dysfunction, chronic obstructive pulmonary disease, acute decompensated heart failure | 37      | Survived         | 19.6    |
| 24      | Left frontoparietal subdural hemorrhage with mass effect, chronic rheumatic heart disease with mitral valve replacement | 36      | Expired          | 18.1    |
| 25      | Cerebrovascular accident - right-hemiplegia due to left-thalamic bleed | 39      | Survived         | 23      |
| 26      | Hypertension, old cerebrovascular accident-left hemiparesis, metabolic encephalopathy, hyponatremia | 46      | Survived         | 37      |
| 27      | Type 2 diabetes mellitus, hyperglycemic hyperosmolar state, hypertension, left hemiplegia - multi-infarct state, metabolic/ischemic seizures, aspiration pneumonia, hypophysathamia | 53      | Survived         | 53      |
| 28      | Hypertension, cerebrovascular accident-right hemiplegia with global aphasia, hypermnatriemia and anemia | 30      | Expired          | 10.6    |
| 29      | Left lentiform bleed, Binswanger’s disease, Fahr disease, hypertension, diabetes mellitus (de novo detected), global aphasia, hyponatraemia, thrombocytopenia | 32      | Survived         | 12.8    |
| 30      | Cerebrovascular accident-right hemiplegia, aphasia, hypertension, poststroke seizures, chronic kidney disease, acute diarrheal disease, bed sore, hyperuricemia, old pulmonary tuberculosis, status postleft pneumonectomy, right UMN facial nerve palsy | 40      | Survived         | 24.7    |
| 31      | Cerebrovascular accident-left hemiplegia, hypertension, Type 2 diabetes mellitus, atrial fibrillation with controlled ventricular rate, hypokalemia | 50      | Expired          | 46.1    |
| 32      | Septic shock with multi organ failure, encephalopathy, microcystic hypochromic anemia | 65      | Expired          | 76.9    |
| 33      | Cerebrovascular accident with right capsuloganglionic bleed with intraventricular extension, septicemia, Type 2 diabetes mellitus, hypermnatriemia, enemia, thrombocytopenia, grade1 diastolic dysfunction | 55      | Survived         | 57.5    |

Contd...
to suppress gonadotropins (namely, estradiol, cortisol, and prolactin). No independent association was observed between LH and any of the above four parameters [Table 3]. However, there was a significant independent negative association between the FSH and the SAPS II (beta = −0.435; \( P = 0.014 \)), but not with any of the other parameters [Table 4].

Again, an attempt was made to tease out what component of the SAPS II (i.e., age, Glasgow Coma Scale, systolic blood pressure, heart rate, temperature, urine output in 24 h, blood urea, total leukocyte count (TLC), serum potassium, sodium, bicarbonate, and bilirubin) has an independent association with LH and FSH separately. On a multiple linear regression model involving the above parameters as independent variables, the LH showed no independent association with any of these [Table 5]. As compared to this, the FSH showed a very definite independent negative association with the TLC (beta coefficient = −0.635, \( P = 0.013 \)) but not with any of the other parameters [Table 6].

### Table 1: Comparison of Simplified Acute Physiology Scores II, age and hormones between critically ill patients who died and those who survived the hospital stay

| Parameter (units)          | Patients who survived (n=25) | Patients who died (n=10) | \( P \) |
|----------------------------|-----------------------------|--------------------------|--------|
| SAPS II                    | 43 (37.0-48.0)              | 47 (37.5-56.0)           | 0.323  |
| Age (years)                | 62 (60-70)                  | 71 (64.2-75)             | 0.04   |
| LH (IU/L)                  | 10.5 (2.1-32.2)             | 14.5 (1.6-26.9)          | 0.855  |
| FSH (IU/L)                 | 25 (16.0-45.5)              | 21.7 (2.4-31.4)          | 0.273  |
| Estradiol (pg/mL)          | 66 (24.0-112.5)             | 49.5 (29.7-72.2)         | 0.422  |
| Sex hormone-binding globulin (mmol/L) | 54 (36.5-73.0)              | 32 (17.2-60.0)           | 0.073  |
| Free triiodothyronine (pmol/L) | 3.0 (2.6-3.4)               | 2.8 (2.6-3.5)            | 0.942  |
| Free thyroxine (ng/mL)     | 1.1 (0.8-1.6)               | 1.1 (1.0-1.9)            | 0.621  |
| Thrytropin (µIU/mL)        | 1.3 (0.8-3.6)               | 1.2 (0.6-4.4)            | 0.927  |
| Cortisol (µg/dL)           | 31 (23.5-50.0)              | 38 (23.7-55.0)           | 0.510  |
| Androstenedione (ng/mL)    | 1.0 (0.6-2.5)               | 2.1 (0.6-5.5)            | 0.324  |
| Dehydroepiandrosterone (ng/mL) | 6.8 (2.0-12.0)             | 6.3 (2.5-12.5)           | 0.942  |
| Prolactin (ng/mL)          | 16.3 (7.8-32.2)             | 22.9 (9.2-35.7)          | 0.596  |

Expected values in normal postmenopausal women - LH: 16-66 IU/L, FSH: 32-103 IU/L, estradiol: <40 pg/mL, free thyroxine: 0.95-2.23 ng/dL, free triiodothyronine: 3.8-6.0 pmol/L, thyrotrphin: 0.5-5.0 µIU/mL, cortisol (8.00 am): 7-25 µg/dL, androstenedione: 10-29.9 ng/mL, sex hormone-binding globulin: 30-100 nmol/L, prolactin: 2.74-19.64 ng/mL, dehydroepiandrosterone 1-12 ng/mL. SAPS II: Simplified Acute Physiology Score II, LH: Luteinizing hormone, IQR: Interquartile range, FSH: Follicle-stimulating hormone

Likewise, ROC curves were drawn up for the diagnosis of mortality using different cutoff thresholds of LH, FSH, and estradiol. However, the AUC for each of these three curves was low (0.588 for estradiol, 0.620 for FSH, and 0.520 for LH) which was not significantly different \( (P > 0.05) \) from that associated with the null hypothesis being true (i.e., AUC = 0.5). Thus, none of the above hormones served as a useful test to predict in-hospital mortality.

### Gonadotropin or estradiol levels in sick postmenopausal women in relation to mortality

The percentages of those who died in the hospital were compared between tertiles of LH, FSH, and estradiol separately by the Chi-square test. There were no significant differences observed \( (P > 0.05) \).
then the sensitivity for diagnosing prolonged hospital stay was 83.3% with a specificity of 77% [Figure 1], this cutoff being the one associated with the highest sensitivity available at a reasonable specificity. One hundred percent sensitivity was achieved at an estradiol level ≤192.5 pg/mL, but at this level, the specificity was only 24.1%. For a specificity >80%

**Table 3: Multiple linear regression model with luteinizing hormone as dependent variable and Simplified Acute Physiology Score II, prolactin, cortisol, and estradiol as independent variables**

| Independent variable | Unstandardized coefficients | Standardized coefficients | P  |
|----------------------|-----------------------------|---------------------------|----|
| Estradiol            | −0.018                      | −0.064                    | 0.718 |
| Cortisol             | −0.276                      | −0.314                    | 0.065 |
| Prolactin            | −0.090                      | −0.093                    | 0.589 |
| SAPS II              | −0.670                      | −0.293                    | 0.096 |

SAPS II: Simplified Acute Physiology Score II, SE: Standard error

**Table 4: Multiple linear regression model with follicle-stimulating hormone as dependent variable and Simplified Acute Physiology Score II, prolactin, cortisol, and estradiol as independent variables**

| Independent variable | Unstandardized coefficients | Standardized coefficients | P  |
|----------------------|-----------------------------|---------------------------|----|
| Estradiol            | 0.054                       | 0.200                     | 0.256 |
| Cortisol             | −0.221                      | −0.261                    | 0.113 |
| Prolactin            | −0.023                      | −0.025                    | 0.883 |
| SAPS II              | −0.962                      | −0.435                    | 0.014 |

SAPS II: Simplified Acute Physiology Score II, SE: Standard error

**Table 5: Multiple linear regression model studying the association between luteinizing hormone as the dependent factor and various components of the Simplified Acute Physiology Score II as independent factors**

| Components of SAPS II | Unstandardized coefficients | Standardized coefficients | P  |
|-----------------------|-----------------------------|---------------------------|----|
| Age                   | −0.914                      | −0.285                    | 0.135 |
| Glasgow Coma Scale    | 0.349                       | 0.058                     | 0.774 |
| Systolic blood pressure| 0.121                      | 0.225                     | 0.279 |
| Heart rate            | −0.142                      | −0.135                    | 0.473 |
| Temperature           | 0.924                       | 0.084                     | 0.644 |
| Urine output          | 0.007                       | 0.287                     | 0.137 |
| Urea                  | 0.039                       | 0.110                     | 0.657 |
| TLC                   | −0.001                      | −0.329                    | 0.169 |
| Serum potassium       | 1.536                       | 0.070                     | 0.746 |
| Serum sodium          | −0.220                      | −0.088                    | 0.670 |
| Serum bicarbonate     | 0.192                       | 0.073                     | 0.716 |
| Serum bilirubin       | 0.411                       | 0.046                     | 0.835 |

SAPS II: Simplified Acute Physiology Score II, SE: Standard error, TLC: Total leukocyte count

**Figure 1:** Receiver operating characteristic curve for diagnosis of prolonged hospital stay (≥11 days) at or below (≤) different cutoffs of estradiol (in pg/mL). Area under curve = 0.785 (P = 0.015)

**Discussion**

Acute illness or stress is associated with a transient functional hypogonadotropic hypogonadism. The postmenopausal state is an ideal state to study the extent of gonadotropin suppression, as in this state, the gonadotropins are normally elevated and do not show the cyclical variation that is typically observed in premenopausal women. Only a few studies regarding gonadotropins in critical illness have been previously performed in this population and all have uniformly demonstrated the suppression of these trophic hormones during critical illness. In our previous report as well, both LH and FSH were significantly lower (P ≤ 0.001) in our critically ill postmenopausal women as compared to healthy controls.

**Gonadotropins and the severity of illness**

Our study uses the SAPS II scoring system to quantify the severity of the underlying illness and to predict the likelihood of mortality. We chose to include only those patients who had predicted in-hospital mortality ≥10% to ensure that only genuinely critically ill patients were included as cases in our study. A significant negative correlation has been observed between the severity of illness as quantified by the SAPS II and the serum FSH but not with LH. Further, on studying the association of various hormones (estradiol, prolactin, and cortisol) known to be capable of suppressing the gonadotropins...
Elevation of estrogens and androstenedione in critically ill postmenopausal women has been noted by Spratt et al.\textsuperscript{[4]} In another report, Spratt et al.\textsuperscript{[5]} showed that increased peripheral aromatization of androgens to estrogens is responsible for the rise in serum estrogen levels during sickness. Thus, not only the increased supply of androstenedione\textsuperscript{[4]} as a precursor but also increased aromatization may result in elevated estrogens during acute illness.

**Estrogens and mortality**

The clinical significance of this estrogen elevation is not clear. In our previous report, there was no significant correlation between the SAPS II and the levels of estrogen.\textsuperscript{[10]} Neither were the estrogen levels different between survivors and nonsurvivors [Table 2]. There were no differences between mortality rates between tertiles of estrogen or for that matter between tertiles of gonadotropins. Further ROC curves drawn for mortality showed no diagnostic value of LH, FSH, or estradiol for mortality. However, other workers have shown that estrogen levels could be a predictor of mortality in critically ill and injured patients in both sexes as the level of estrogen elevation correlated with the severity of illness.\textsuperscript{[6-8]} Estradiol levels were higher in nonsurvivors than survivors.\textsuperscript{[6-8]} However, their studies were in mixed populations of men and women, while our study was confined to postmenopausal women only. Moreover, all the three previous studies\textsuperscript{[6-8]} were in surgical/injured patients while all our patients were suffering from medical disorders and admitted to medical intensive care. There may be differences in estrogen response to critical illness and its predictiveness of mortality in different populations. It is also highly likely that our study may not have been sufficiently powered to analyze the relationship between estrogen and mortality. Further research is required to determine whether estrogen is merely a marker of severity of illness and consequently mortality of whether it contributes in any way to the death of the patient.

**Estrogen and duration of hospital stay**

However, among postmenopausal survivors of acute severe illness (n = 25), lower estrogen levels were diagnostic for prolonged hospital stay (>11 days, 11 days being the median duration of stay) with variable sensitivity and specificity depending on the cutoff chosen. If the estradiol was equal to or below a cutoff of 69 pg/mL, then the sensitivity for diagnosing prolonged hospital stay was 83.3% with a specificity of 77%. Conversely, it may be argued that higher estrogen is predictive of lack of prolonged hospital stay (i.e., short hospital stay) and is therefore protective.

### Table 6: Multiple linear regression model studying the association between follicle-stimulating hormone as the dependent factor and various components of the Simplified Acute Physiology Score II as independent factors

| Components of SAPS II | Unstandardized coefficients | Standardized coefficients | P |
|-----------------------|-----------------------------|---------------------------|---|
|                       | B                           | SE                        | β  |
| Age                   | −0.253                      | 0.575                     | −0.082 | 0.665 |
| Glasgow Coma Scale    | −0.113                      | 1.174                     | −0.020 | 0.924 |
| Systolic blood pressure | 0.096                      | 0.106                     | 0.187 | 0.373 |
| Heart rate            | −0.099                      | 0.191                     | −0.097 | 0.608 |
| Temperature           | 0.858                      | 1.928                     | 0.081 | 0.661 |
| Urine output          | 0.002                      | 0.004                     | 0.078 | 0.685 |
| Urea                  | −0.020                      | 0.084                     | −0.058 | 0.815 |
| TLC                   | −0.002                      | 0.001                     | −0.635 | 0.013 |
| Serum potassium       | −2.563                      | 4.571                     | −0.122 | 0.581 |
| Serum sodium          | −0.354                      | 0.499                     | −0.146 | 0.486 |
| Serum bicarbonate     | −0.333                      | 0.508                     | −0.131 | 0.519 |
| Serum bilirubin       | 1.233                      | 1.907                     | 0.144 | 0.525 |

SAPS II: Simplified Acute Physiology Score II, SE: Standard error, TLC: Total leukocyte count.

as well as the SAPS II, only the SAPS II showed an independent negative association, again with FSH [Table 4] but not with the LH [Table 3]. This suggests that some nonhormonal phenomena associated with acute illness which is reflected in the total SAPS II are associated with and possibly responsible for the suppression of FSH. Spratt et al.\textsuperscript{[14]} have likewise used the APACHE II scoring system to divide their patients into mild, moderate, and severe illness. They reported that in 42 postmenopausal women nadir, serum FSH but not LH levels during hospitalization were lower in patients with APACHE II scores >15 than in patients with APACHE scores of <15 (P < 0.05). Thus, while both gonadotropins are suppressed in acute illness, it is the FSH and not the LH whose level of suppression correlates with and is negatively associated with the severity of the illness.

**Gonadotropins and inflammation**

To determine what component of the SAPS II was independently associated with FSH, a multivariate regression analysis was performed with each of the SAPS II components as independent variables and FSH as the dependent variable [Table 6]. We found that the TLC alone showed a significant negative association with the FSH, independent of all other factors in the equation. Previously, Van Steenbergen et al.\textsuperscript{[12]} had also shown that on logistic regression analysis, suppressed gonadotropins are associated with elevated erythrocyte sedimentation rate (ESR) in their study of 126 postmenopausal women (aged 69–90 years) admitted to a geriatric ward. Both the TLC and the ESR reflect inflammation and suggest that the inflammatory component of the acute sickness is responsible for the gonadotropin suppression. Cytokines are the probable mediators of the gonadotropin suppression in the sick patients through their negative impact on GnRH pulses. Injection of interleukin-1α in primates caused suppression of gonadotropin secretion that was reversed by the administration of corticotrophin-releasing hormone (CRH) antagonist, implying the role of CRH in reducing GnRH pulses in cytokine-induced gonadotropin suppression.\textsuperscript{[14]} Systemic inflammation being an evidence of poor health, it makes sense from a teleological perspective, to have evolved a mechanism to shut down the reproductive axis so as to prioritize survival itself over reproduction under such adverse circumstances.
Estrogen has been shown to have many beneficial effects during acute severe illness. Physiologic levels of estrogen, like those seen during the estrus/menstrual cycle, stimulate the immune response, whereas high levels of estrogen such as those found during pregnancy are suggested to downregulate cell-mediated immune responses.[15] Estrogen receptors are found in reproductive tissue, as well as certain immune cells including T-cells, monocytes, dendritic cells, and macrophages, and it modulates the function of these cells.[16-20] Mao et al.[21] showed that estrogen promotes the granulocyte-monocyte colony-stimulating factor mediated differentiation of dendritic cells from murine bone marrow progenitor cells as well as the further development of dendritic cells to epidermal Langerhans cells. Cutolo et al.[22] showed that estrogens have an anti-apoptotic effect on cultured human macrophage cell lines through their modulation of nuclear factor-kappa B complex. Ali et al.[23] showed that estrogen has a protective effect in pneumonia as it enhances the transport of IgA into the respiratory mucosal cells by increasing toll-like receptor 4 expression. It also inhibited the movement of bacteria (Klebsiella pneumonia) across the respiratory epithelium. Estrogens also have prothrombotic effects[24] which may be of help with hemostasis in acute trauma patients.

**Conclusion**

FSH but not the LH levels are negatively associated with the severity of illness in postmenopausal women with acute severe illness. Further, among the various components of a disease score, the negative association was observed only with the TLC, suggesting thereby that it is the systemic inflammatory component that may be responsible for the suppression of FSH. Furthermore, while estradiol had no relationship to mortality, we observed that higher estradiol among survivors was a negative predictor for prolonged hospital stay. There is a need for further larger studies on the role of estradiol to determine whether it is merely a predictor of outcome or whether it actively alters the course of the disease.

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**Conflicts of interest**

There are no conflicts of interest.

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