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A Trivariate Weibull Model For Oestradiol Plus Progestrone Treatment During The Preovulatory Period In Normal Premenopasual Women

S. Lakshmi * and K. Sheeja**
**Principal(Rtd.), Kunthavai Naacchiyaar Govt. Arts College for Women,(Autonomous),Thanjavur-613007*
lakshmi291082@yahoo.co.in
***Assistant Professor of Mathematics,SIES (Nerul) College of Arts Science and Commerce, Nerul, Navi Mumbai-410210, Maharastra.*
sheejak@sies.edu.in

ABSTRACT: *In the previous studies a hypothesis was developed from the results that the increase in leptin concentrations during the second half of the menstrual cycle may be related to changes in the steroidal milieu during the preovulatory period and the luteal phase. The present study was undertaken to test this hypothesis further by examining the effect of treatment with oestradiol and progesterone on leptine concentrations in normal pre menopausal women. The trivariate Weibull model is used for finding survival functions and probability density functions for corresponding values of oestradiol, LH and FSH for both untreated and treated with oestradiol and oestradiol plus progesterone respectively.*

Keyword*: Trivariate Weibull, LH, FSH, oestradiol and progesterone*
2010 AMS Classifications: *62HXX, 60EXX*

I. INTRODUCTION

Normal women have significantly higher serum leptin concentrations than normal men [12]. Also in the luteal phase of the normal menstrual cycle, serum leptin concentration are significantly higher than in the follicular phase [7,9], while significant positive correlations have been found between leptin and oestrodiol or progesterone concentrations[10]. Although these studies suggest that ovarian steroids may play a role in leptin secretion in humans no direct evidence has been provided as yet. A significant decrease in serum leptin concentration was found following bilateral ovariectomy in normal women [10], and although treatment with oestradiol was without any effect, the addition of progesterone prevented this decrease, suggesting that progesterone plays an important role in the control of leptin secretion [11]. A hypothesis was developed from these results that the increase in leptin concentration during the second half of the menstrual cycle may be related to changes in the steroidal milieu during the periovulatory period and the luteal phase. The present study was undertaken to test this hypothesis further by examining the effect of treatment with oestrodiol and progesterone on leptin concentration in normal premenopausal women.

II. MATHEMATICAL MODEL

Trivariate Weibull Distribution:

Lu and Bhattacharya [5] developed a joint survival function by letting $h_1(x)$ and $h_2(y)$ be two arbitrary failure rate functions on $[0,\infty)$, and $H_1(x)$ and $H_2(y)$ be their corresponding cumulative failure rate. Given the stress S=s $>$ 0, the joint survival function conditioned on s, as they defined is,

$\bar{F}(x,y/s)=\exp\{-[H_1(x)+H_2(y)]^{\gamma}s\}$, where γ measures the conditional association of X and Y. Further, based on the joint survival function, they proved a theorem that a bivariate survival function $\bar{F}(x,y/s)$ can be derived with the marginals $\bar{F}_x$ and $\bar{F}_y$ given the assumption that the Laplace transform of the stress S exists on $[0,\infty)$ and is strictly decreasing.

From the theorem, they derived a bivariate Weibull Distribution

$$\bar{F}\ (x,y) = exp\left\{-\left[\left(\frac{x}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{y}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}}\right]\right\} \text{ where } 0< \alpha \le 1, 0 < \lambda_1, \lambda_2 \le \infty, 0 < \gamma_1, \gamma_2 < \infty$$

This bivariate Weibull Distribution is exactly the same as developed by Hougaard [8].

Following the same steps the theorem can be expanded to more than random variables and , therefore, a multivariate survival function of Weibull Distribution is constructed as

$$S(x_1,x_2,\ldots x_n)=exp\left\{-\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \cdots \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}}\right]^{\alpha}\right\}$$

Where α *measures the association among the variables,* $0 \le \alpha < 1, and\ 0 < \lambda_1, \lambda_{2,} \ldots. \lambda_n < \infty\ and\ 0 < \gamma_1, \gamma_2, \ldots.. \gamma_n < \infty$ *[2,3]*

Probability Density Function of the Multivariate Weibull Distribution:

The multivariate probability density function $f(x_1,x_2,\ldots x_n)$ *of a multivariate distribution can be obtained by differentiating the multivariate survival function with respect to each variable. Li [4], and Yi and Weng [13] had shown that*

$$f(x_1,x_2,\ldots x_n)= (-1)^n \frac{\partial^n S(x_1,x_2\ldots.x_n)}{\partial x_1 \partial x_2 \ldots\ldots \partial x_n}$$

using Li's derivation and one of the special cases of the multivariate Faa di druno formula by Constantine and Savits [2], the probability density function is

$$f(x_1,x_2,\ldots x_n) = \left(\frac{-1}{\alpha}\right)^n exp\left\{-\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \cdots \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}}\right]\right\}$$

$$. \left[\left(\frac{\gamma_1}{\lambda_1}\right)\left(\frac{\gamma_2}{\lambda_2}\right)\ldots\left(\frac{\gamma_n}{\lambda_n}\right)\right]\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}-1} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}-1} + \cdots \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}-1}\right]$$

$$\sum_{i=1}^{p(n)}\left\{(-1)^{k_i} P_s(n,i)\left(\prod_{i=1}^{n} \alpha^{n_j} - \left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}-1} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}-1} + \cdots \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}-1}\right]^{k_i\alpha-n}\right)\right\}$$

where k_i *is the number of summands of the* i^{th} *partition of n such that* $n_1+n_2+\ldots.n_{k_i} = n$ *,* $n_1 \ge n_2 \ge \cdots n_{k_i} > 0$*,* $1\le k_i \le n$*;* α^{n_j} *is equal to* $(\alpha - 1)\ldots.. (\alpha - n_j - 1)$*, the falling of* α *; p(n) is the total number of set partitions of the set* $S_n = \{1,\ldots,n\}$ *corresponding to the* i^{th} *partition of n.*

The PDF of trivariate Weibull is

$$f(x_1,x_2,\ldots x_n)= (-1)^3 \frac{\partial^3 S(x_1,x_2,x_3)}{\partial x_1\, \partial x_2\, \partial x_3}$$

$$= \frac{\gamma_1\gamma_1\gamma_1}{\alpha^2 x_1 x_2 x_3}\quad exp\left\{-\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right]^{\alpha}\right\}$$

$$. \left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}}\left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}}\left(\frac{x_1}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} .\left(\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{-3+\alpha}$$

$$.\left(2 + 3\alpha\left(-1 + \left(\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)\right)^{\alpha} + \alpha^2\left(1 - 3\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right]^{\alpha} + \right.\right.$$

x1λ1γ1α+x2λ2γ2α+x3λ3γ3α2α

III. RESULTS AND DISCUSSION

Serum concentrations of oestradiol, progesterone LH and FSH during the administration of oestradiol (oestradiol cycles)and the control cycles in the 10 women are shown in Figure [1 to 3]. Concentrations of these hormones on cycle day 2 were similar between the oestradiol and the control cycles. A marked increase in oestradiol concentrations was seen in all women from the onset of treatment on cycle day 2 to day 5. Subsequently, oestradiol concentrations declined rapidly and returned to pretreatment level on cycle day 7, and showed no significant changes thereafter. In the control cycle, serum oestradiol concentrations increased slightly from days 2 to 7 and progressively from days 7 to 10. From days 3 to 6 oestradiol concentrations was slightly higher, and on days 9 and

10 were slightly lower, in the oestradiol cycle than in control cycle. Serum progesterone concentrations were low throughout the experimental period in both the oestradiol and control cycle.

The changes in serum oestradiol, progesterone ,LH and FSH concentrations in the six cycles treated with oestradiol plus progesterone and in the corresponding control cycles are shown in Figure [4 to6]. Pretreatment concentrations of these hormones on cycle day 2 did not differ significantly between the two groups of cycle. During treatment with oestradiol and progesterone serum oestradiol concentration showed a pattern of increase similar to that in oestradiol cycle, with no significant difference at the corresponding points. Oestradiol concentrations were significantly higher on days 3, 4, and 5 and significantly lower on days 9 and 10 in the oestradiol plus progesterone cycles than in the control cycles. Serum progesterone concentrations in the oestradiol + progesterone cycles showed an abrupt increase from days 3 to 4, remaining high on days 5 and 6 and decreasing thereafter.

This study is first to show an increase in preovulatory concentration in normal women during treatment with exogenous oestradiol and progesterone. It is of interest that when oestradiol alone was given to the women there was no change in preovulatory concentration, but the increase was observed when progesterone was added to the oestradiol regimen. This suggests that in the presence of progesterone and normal oestradiol the preovulatory concentration increases, but however whether the progesterone has the same effect in the presence of low oestradiol needs to be investigated. The aim of this study was to examine whether a sequence of events in terms of changes in oestradiol and progesterone concentrations resembling those in the normal menstrual cycle, can affect preovulatory concentration. During treatment with oestradiol and progesterone , serum concentration of oestradiol showed a pattern of increase similar to that seen during the preovulatory period of the normal menstrual cycle, and although progesterone concentration showed an abrupt increase, the concentration was similar to those seen in luteal phase of the cycle.

IV. CONCLUSION

The medical conclusion shows that the preovulatory concentrations of oestradiol induced in the early follicular phase of the cycle by the administration of oestradiol. However induction of luteal phase concentrations of progesterone , in addition to the increased concentration of oestradiol can stimulate ovulatory concentration. Mathematical Figure 7 and 8 shows the survival function of combined effect of LH, FSH and Oestradiol with administration of oestradiol and oestrodiol plus progesterone for the untreated and treated cases. Figure 9 and 10 show that the probability density function of combined effect of LH, FSH and Oestradiol with administration of oestradiol and oestrodiol plus progesterone for the untreated and treated cases.

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Figure:1

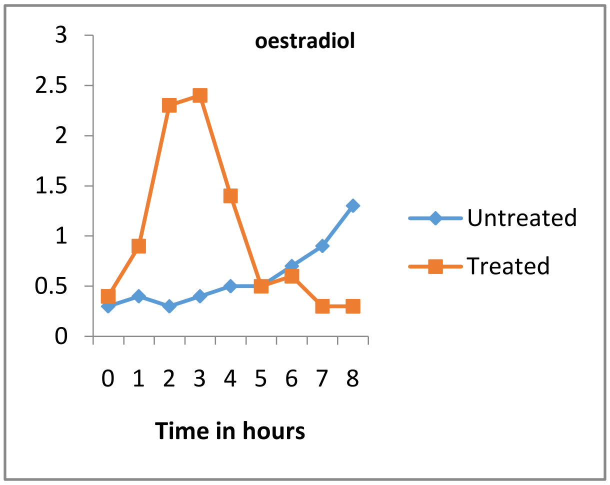


Figure:4

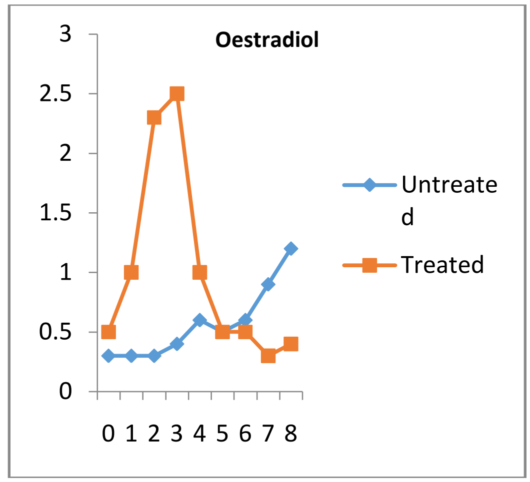
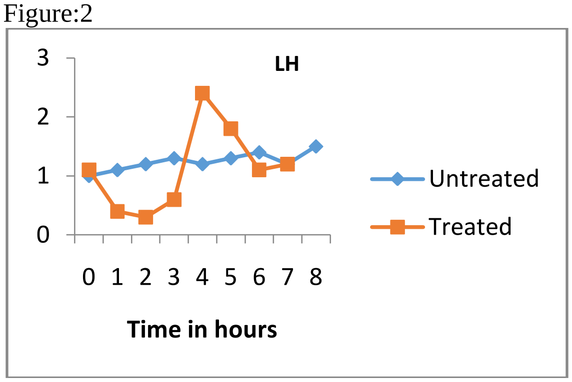


Figure:2



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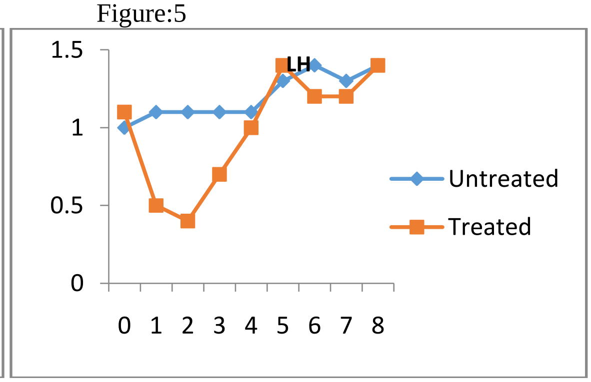

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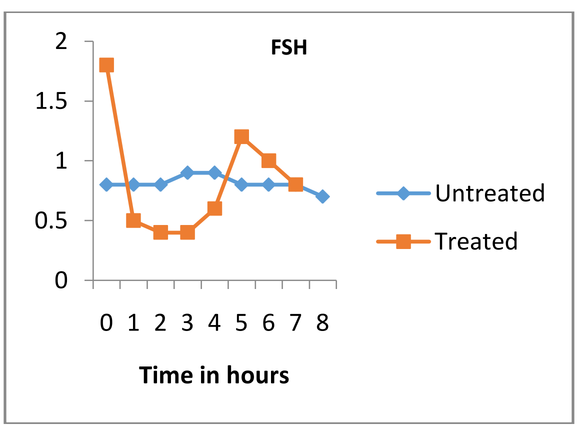

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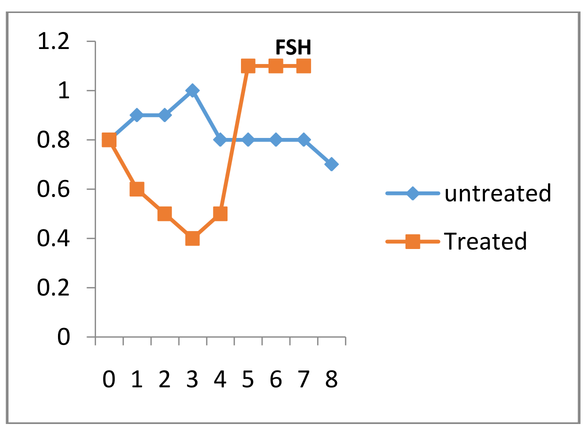

Figure[1,2,3]: Serum oestradiol, progesterone,LH and FSH concentration during the follicular phase untreated spontaneous cycles and cycles treated with oestradiol through skin patches in normally cycling women.

Figure[4,5,6]: Serum oestradiol, progesterone,LH and FSH concentration during the follicular phase untreated spontaneous cycles and cycles treated with oestradiol through skin patches plus progesterone intravaginally in normally ovulating women.

MATHEMATICAL FIGURES

Survival functions

Figure:7

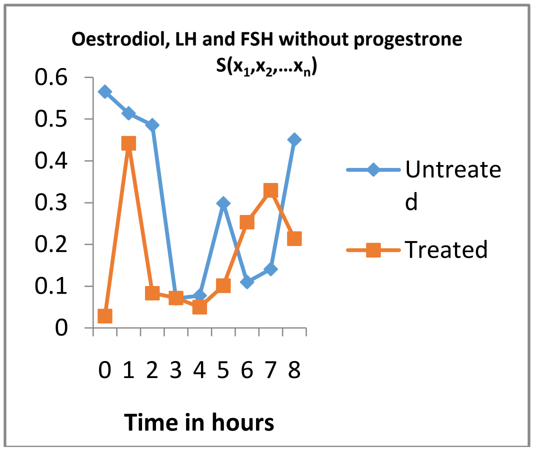

Figure: 8

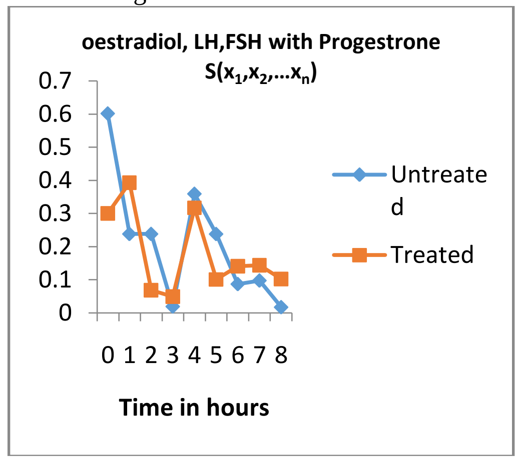

Figure:7 : Denotes Survival functions of oestrodiol, LH and FSH when treated with only oestrodiol

Figure:8 : Denotes Survival functions of oestrodiol, LH and FSH when treated with oestrodiol plus progesterone.

Pdf Figures:

Figure 9

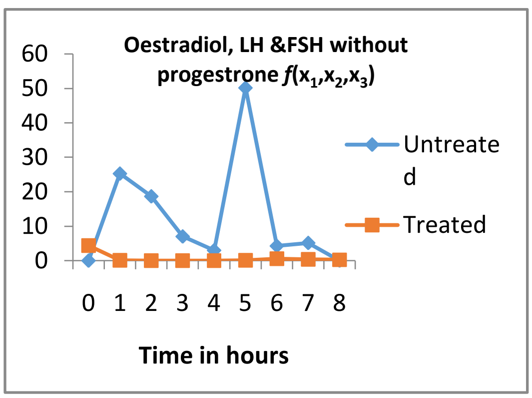

Figure: 9: Denotes trivariate Probability density function of oestrodiol, LH & FSH when treated with only oestrodiol

Figure:10

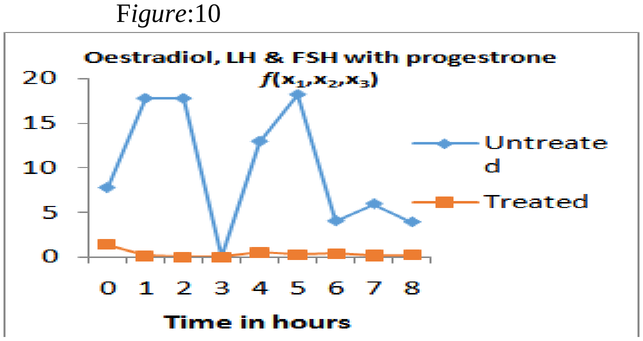

Figure: 10 : Denotes trivariate Probability density function of oestrodiol, LH and FSH when treated with oestrodiol plus progesterone