International Research Journal of Mathematics, Engineering and IT
Vol. 3, Issue 7, July 2016 IF- 3.563 ISSN: (2349-0322)
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Website: www.aarf.asia Email : editor@aarf.asia , editoraarf@gmail.com

HAZARD FUNCTION OF FSH AND LH RESPONSES TO GNRH BY OVARIES STEROIDS IN THE LUTEAL PHASE OF THE CYCLE OF THE WOMEN

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ABSTRACT

Aim of this paper is to find a mathematical model to determine the role of ovarian steroids in the control of GnRH- induced gonadotrophin secretion in the luteal phase of the cycle of eighteen women subjects, by using probability density function and hazard function of Birnbaum- Saunders distribution. In reliability and survival analysis , it is often interest to determine the point at which the hazard function reaches its maximum and is given by mathematical curves.

Keywords: Birnbaum –Saunders distribution, hazard function, Follicile stimulating hormone , luteinizing hormone , Estradiol and Progesterone.

1. Mathematical Model

1.1.Introduction

The two-parameter Birnbaum-Saunders (BS) distribution was originally proposed by Birnbaum and Saunders[3] as a failure time distribution for fatigue failure caused under cyclic loading. The cumulative distribution function (CDF) of a two-parameter BS random variable T is of the form

$$F(t;\alpha,\beta) = \Phi\left[\frac{1}{\alpha}\left\{\left(\frac{t}{\beta}\right)^{\frac{1}{2}} - \left(\frac{\beta}{t}\right)^{\frac{1}{2}}\right\}\right],\ 0< t <\infty,\ \alpha, \beta> 0, \qquad (1)$$

Where Φ(.) is the standard normal CDF. The parameters α and β in (1) are the shape and scale parameters, respectively. Although the BS distribution was originally proposed as a failure time distribution for fatigue failure under the assumption that the failure is due to development and growth of a dominant crack, a more general derivation was provided by Desmond [4] based on a biological model. Desmond also strengthened the physical justification for the use of this distribution by relaxing the assumptions made originally by Birnbaum and Saunders. Some recent work on the BS distribution can be found in Balakrishnan et al. [2], andNg et al. [13]

It is known from Johnson et al. [6] that the density function of the BS distribution is unimodal. Though several articles have been published in the last three decades regarding different inferential methods for the parameters of the BS distribution and their properties, yet the shape of the hazard function has not been examined possibly due to its complex form. Mann et al. [10] mentioned that the hazard function of the BS distribution is not an increasing function of t, although they did not provide a formal proof for it. In this paper, we first formally prove that the hazard function of the BS distribution is indeed an upside down function of t>0 for all values of the shape α and scale parameter β which is used for our application part.

It is not uncommon to model survival and failure time data by distributions which have monotone hazard function. But in many practical situations, the hazard function is not monotone and in fact it increases up to a point and then decreases. For example, in the study of recovery from breast cancer, it has been observed by Langland's et al. [8] that the maximum mortality occurs after about three years and then it decreases slowly over a fixedperiod of time. In this case, a quantity of natural interest is the point at which the hazard function is maximum; see Gupta et al. [5]. Finally, here we have analysed a real data set and illustrate all the methods discussed.

1.2.Birnbaum-Saunders Distribution

The probability density function (PDF) of a two-parameter BS random variable T corresponding to the CDF in (1) is given by

$$f(t;\ \alpha,\beta) = \frac{1}{2\sqrt{2\pi}\alpha\beta}\left[\left(\frac{\beta}{t}\right)^{\frac{1}{2}} + \left(\frac{\beta}{t}\right)^{\frac{3}{2}}\right] exp\left[-\frac{1}{2\alpha^2}\left(\frac{t}{\beta} + \frac{\beta}{t} - 2\right)\right],\ 0< t <\infty,\ \alpha, \beta> 0, \qquad (2)$$

Consider now the monotone transformation

$$X = \frac{1}{2}\left[\left(\frac{T}{\beta}\right)^{\frac{1}{2}} - \left(\frac{T}{\beta}\right)^{-\frac{1}{2}}\right] \quad (3)$$

$$T=\beta\{1+2X^2+2X(1+X^2)^{1/2}\}; \quad (4)$$

Then from (1), it readily follows that X is distributed as normal with mean zero and variance ($\alpha^2/4$). The transformation in (4) is a very useful transformation as it enables the determination of the moments of T through known results on expectations of functions of X.

1.3.Shape of the Hazard

To examine the shape of the hazard function, let us assume that the scale parameter $\beta=1$, without loss of generality. Let us consider the function

$$\in(t) = t^{\frac{1}{2}} - t^{-\frac{1}{2}}$$

For which $\in'(t) = \frac{d}{dt} \in (t) = \frac{1}{2}\left(t^{-\frac{1}{2}} + t^{-\frac{3}{2}}\right) = \frac{1}{2t}\left(t^{\frac{1}{2}} + t^{-\frac{1}{2}}\right)$

$$\in''(t) = \frac{d}{dt} \in'(t) = -\frac{1}{4t^2}\left(t^{\frac{1}{2}} + 3t^{-\frac{1}{2}}\right)$$

And also $\in^2(t) = t + \frac{1}{t} - 2$

The density function of the BS distribution in (2) (for $\beta=1$) is then

$$f(t; \alpha) = \frac{1}{\sqrt{2\pi}\alpha} \in'(t) e^{-\frac{1}{2\alpha^2}\in^2(t)} \quad (5)$$

Which, in conjunction with the expression of the distribution function in (1), gives the hazard function as

$$h(t; \alpha) = \frac{f(t;\alpha)}{1 - F(t;\alpha,1)} = \frac{\frac{1}{\sqrt{2\pi}\alpha}\in'(t)e^{-\frac{1}{2\alpha^2}\in^2(t)}}{\Phi\left(-\frac{\in(t)}{\alpha}\right)} \quad (6)$$

From (6), the shape of $h(t;\alpha)$ is not at all clear. We need the following lemmas for establishing our main result regarding the shape of the hazard function $h(t;\alpha)$ in (6).

Lemma 1: Suppose f(t), for t>0, is the density function of a positive real-valued continuous random variable, $f'(t)$ is the derivative of f(t), and $\eta(t) = f'(t)\backslash f(t)$. Then, if there exists a t_0 such

that $\eta'(t)>0\ \forall t\epsilon\ (t_0,\infty)$, the hazard function corresponding to f(t) is either an upside down of a decreasing function of t.

Lemma 2: The hazard function of Birnbaum-Saunders distribution is either an upside down or a decreasing function of t>0, for all values of the shape parameter α.

Lemma 3: For α>0, the hazard function of the BS distribution is indeed an upside down function.

Proof: Note that it is enough to prove that$\lim_{t\to 0} h(t,\alpha) = 0$. From (6), we have

$$h(t,\alpha) = \frac{\frac{\epsilon'(t)}{\alpha}\phi\left(\frac{\epsilon(t)}{\alpha}\right)}{\Phi\left(-\frac{\epsilon(t)}{\alpha}\right)} \qquad (7)$$

Since $\lim_{t\to 0} \Phi\left(-\frac{\epsilon(t)}{\alpha}\right) = 1$, we consider only the numerator of h(t , α). Note that

$$\frac{1}{\alpha}\epsilon'(t)\phi\left(\frac{\epsilon(t)}{\alpha}\right) = ke^{-\frac{(\epsilon(t))^2}{2\alpha^2}}\left(t^{-\frac{1}{2}} + t^{-\frac{3}{2}}\right) \qquad (8)$$

Where k is a positive constant. Now consider

$$\lim_{t\to 0}\left[ln\left(e^{-\frac{(\epsilon(t))^2}{2\alpha^2}}t^{-\frac{1}{2}}\right)\right] = \lim_{t\to 0}\left[-\frac{(\epsilon(t))^2}{2\alpha^2} - \frac{1}{2}lnt\right]$$

$$= \lim_{t\to 0}\frac{1}{2\alpha^2}[-t - t^{-1} + 2 - \alpha^2 lnt] = -\infty$$

Therefore,$\lim_{t\to 0}\left[\left(e^{-\frac{(\epsilon(t))^2}{2\alpha^2}}t^{-\frac{1}{2}}\right)\right] = 0$

Similarly, it can be shown that$\lim_{t\to 0}\left[\left(e^{-\frac{(\epsilon(t))^2}{2\alpha^2}}t^{-\frac{3}{2}}\right)\right] = 0$

Which completes the proof of the lemma.

By combining all these results, we can now state the following result.

Theorem1: The hazard function of the BS distribution is an upside down function for all values of the shape parameter α.

2.Application

2.1.Introduction

It has been established that ovarian steroids play an important role in the control of gonadotrophin secretion from the pititary. Clinical experiments have shown that exogenous estrogen is able to suppress basal levels of LH and FSH during the follicular phase of the cycle . On the other hand, changes in the production of endogenous estrogen, such as after ovarian stimulation with FSH of after bilateral ovariectomy, result repectively in a decrease or increase of endogenous gonadotrophin values (Kamel et al., 1991[7]; Alexandris et al., 1997[1]). In the case of ovariectomy, the pattern of LH increase following the operation is similar to that of FSH, but the values for both gonadotrophins are peristently lower in women oophorectomized in the luteal rather than the follicular phase of the cycle [1]. Although the difference in gondotrophin values between the two phases of the cycle can be attributed to the increased concentrations of progesterone during the luteal phase, information regarding the contribution of this steroid to the negative feedback mechanism at that stage is limited .

In-vivo experiments have shown marked changes in the reponsiveness of the pituitary to GnRH during the normal menstrual cycle, with a significant increase from the early follicular phase to mid cycle and a progressive decline there after . Although estradiol is the primary factor that sensitizes the pituitary to GnRH during the follicular phase (Lasley et al., 1975, [9]), the role of ovarian steroids in the control of pituitary sensitivity to GnRH during the luetal phase has not been investigated. In a recent study in women, we have demonstrated that following ovariectomy in the luetal phase of the cycle, the response of FSH ato GnRH increased progressively, while that of LH declined markedly. This indicates a differential control of FSH and LH by the ovaries [1], but the mechanism is not clear.

The present study was undertaken to investigate the mechanism through which the ovaries control GnRH induced LH and FSH secretion during the luteal phase of the menstrual cycle by treating normal premenopausal women with estradiol and progesterone in order to prevent the ovariectomy-induced decline in the concentrations of these two steroids.

Materials and Methods

Patients

The study included 18 normally cycling women aged 42-46 years, with normal FSH values in the early follicular phase (<10IU/I) and ovulatory progesterone levels on cycle day 21 (>20 n mol/l). Approval for the study was obtained from the loval ethics committee and

the women gave written informed consent. All women were studied during the week following bilateral ovariectomy plus total hysterectomy performed by laparotomy under general anaesthesia (09:00 h). The ovaries were normal and the indications for the operation were benign uterine lesions, such as fibroids and menorrhagia. The women were dided space into space three groups based on whether they were treated or not with ovary and steroids. In group 1 (n=6) no hormonal treatment was given to the women post-operatively. In group 2 (n=6) the women receive estradiol through skin patches (estradern) TTS; Novartis, athens, greece). The first patch was applied on the day of ovariectomy immediately after the operation at the dose of hundred new gene/24 h. Further patches were applied on post operative days three and six. In group 3 (n=6) the women received estradiol, as in group 2, + progesterone (utrogestan capsules 100 mg/capsule;faran, athens, greece) intravaginally at the dose of 300 mg/day (100mg every 8 hour). The first dose of progesterone was applied after the end of the operation and the last dose on the post operative day 6. In women receiving hormonal treatment, contraindication for the administration of the steroids were identified. The operation was performed in the early to mid luteal phase of the cyle, i.e. five days after the endogenous LH peak detected by LH measurement in daily bed samples taken from the time the follici size was 16 mm in diameter as assesed by ultrasound. In all women the pituitary response to GnRH (**10 U** g.i.v.) was investigated on a daily basis, starting in the morning before the operation until post operative day7, i.e. the day of discharge. Bllod samples in realtion to each GnRH injection (time zero) were obtained at -15,0 and 30 minutes. The 30 minute point was chosen because at that time a maximal response to GnRH has been reported and this represents pituitary sensitivity to GnRH . FSH and LH were measured in all blood samples, while basal values of estradiol and progesterone were measured in the samples taken at -15 and 0 minute. During the operation, the presence of a corpusluteum was confirmed. Before the operation, all women have normal haemoglobin levels (>12g/dl) and the operations were performed without any complications. The blood loss was < 300 ml in all patients and the post operative period was unevenful.

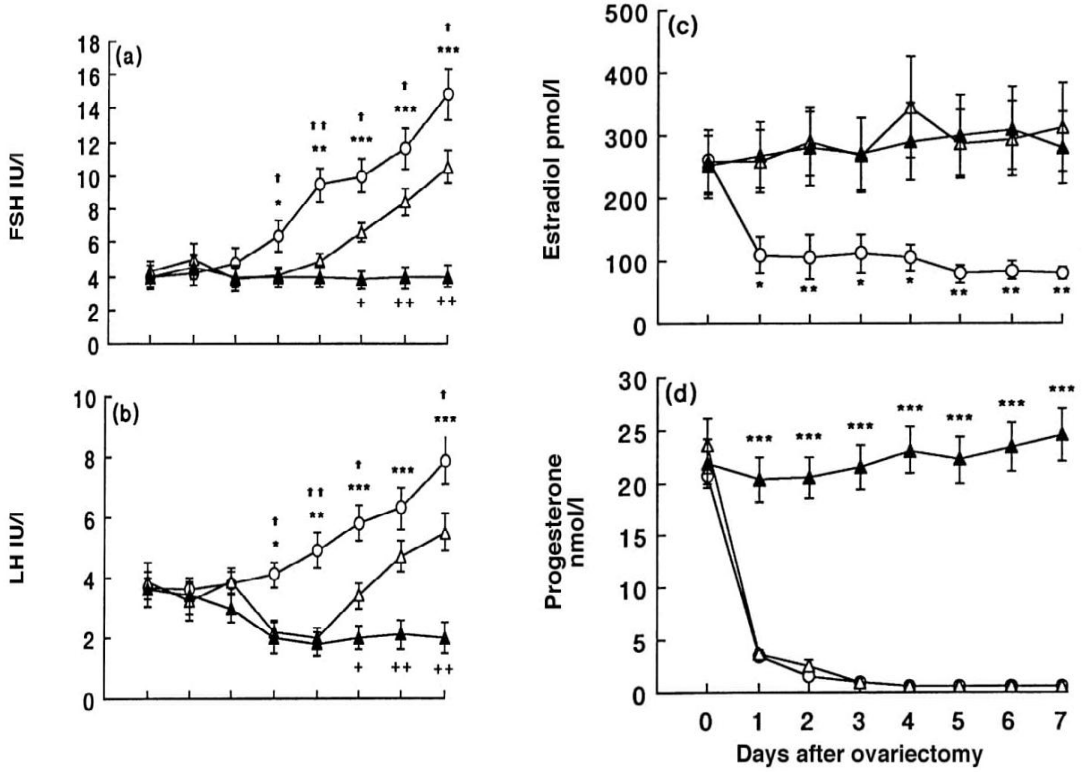


Figure1. Serum FSH , LH, estradiol and progesterone values before and after bilateral ovariectomy plus hysterectomy performed in early to mid-luteal phase(day0)in 18 normally ovulating women. six of the women(o)received no hormonal treatment post operatively(group 1), six (Δ) received estradiol through skin patches on days 0, 3 and 6 (group 2) and the remaining six (m) received estradiol, as in group 2, plus progesterone intravaginally from days 0-6 (group 3).**(a)** and **(b)***P<0.05 ; **P<0.01;***P<0.001 (difference from group 3).†P<0.05; ††P<0.01(difference from group 2).+P<0.05; ++P<0.01(difference from group 2).**(c)** *P<0.05; **P<0.01(difference from group2,and3) **(d)** ***P< 0.001 (difference from group 1 and 2).

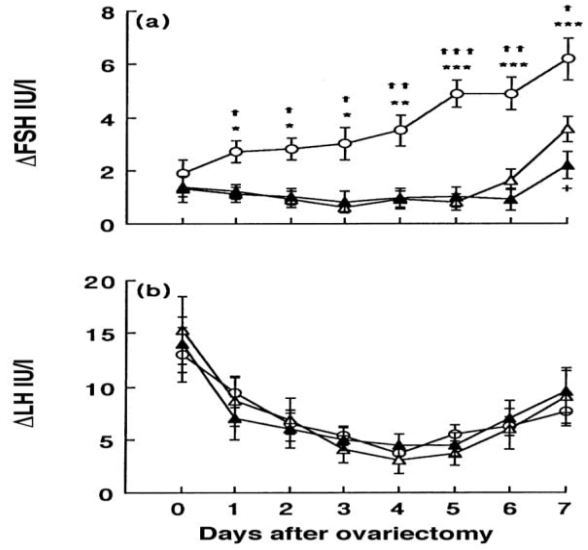


Figure2.Responses of FSH(ΔFSH) and LH (ΔLH)at 30 min to GnRH(10μg i.v) before and after bilateral ovariectomy plus hysterectomy performed in early to mid-luteal phase (day0)in 18 normally ovulating women. six of the women(o)received no hormonal treatment post operatively (group 1), six (Δ) received estradiol through skin patches on days 0, 3 and 6 (group 2) and the remaining six (m) received estradiol, as in group 2, plus progesterone intravaginally from days 0-6 (group 3). (a) and (b) *P<0.05 ; **P<0.01 ;***P<0.001 (difference from group 3). †P< 0.05; ††P<0.01(difference from group 1).+P<0.05; (difference from group 2).

Discussion

In the present study, the increasing basal values of FSH and LH following ovariectomy in the women who did not receive hormonal treatment are in agreement with our previous data [1]. The greater increase in serum FSH values compared with LH is probably related to the lower metabolic clearance rate and higher production rate of FSH .In the women who were treated with estradiol, this increase was only postponed for a few days, thus indicating that estradiol alone contributes to, but is not sufficient to maintain, the ovarian suppressing effect on gonadotrophin secretion towards the mid-luteal phase of the cycle. There is only one study in the literature in which women were treated immediately after ovariectomy with estradiol that, similarly to the present study, prevented the increase in FSH and LH levels, but serial blood samples were taken only for the first four post-operative days [7]. Low plasma FSH and LH concentrations were also maintained in women undergoing abdominal surgery, in whom, however, estradiol levels remained high post-operatively, not with exo-genousestrogen, but with the conservation of the ovaries. When in the present study estradiol was combined with progesterone, there was no increase in FSH and LH levels for at least a week after ovariectomy. Since with these treatments the high luteal concentrations of estradiol and progesterone were maintained following ovariectomy, it is evident that both steroids are required to keep low secretion of gonadotrophins in the early to mid-luteal phase of the cycle. The present study is the first to investigate the effect of estradiol and progesterone on pituitary sensitivity to GnRH in premenopausal women following bilateral ovariectomy. In terms of changes in GnRH-induced FSH secretion in the untreated (control) group of women, the pattern was similar to that previously reported, i.e. a continuous rise following ovariectomy[1], thus illustrating a suppressing effect of the ovaries on the pituitary at that stage of the cycle. We infer that estradiol contributes to, but is not solely responsible for, this suppressing effect, since in the women who were treated with estradiol alone the increase in ΔFSH values was delayed but not abolished. Although with the addition of

progesterone the period of the estradiol-induced suppression was extended, the rise in ΔFSH eventually occurred, suggesting that the two steroids together are not sufficient to mediate completely the ovarian suppressing effect on FSH and that other ovarian factors also play a role.

The decreasing values of ΔLH in the women who did not receive hormonal treatment could be interpreted as indicating that the ovaries exerted a sensitizing effect on LH secretion before the operation. However, the fact that the pattern of changes in ΔLH values was unaffected by treatment with the steroids suggests that estradiol and progesterone are not mediators of such an ovarian effect on LH response to GnRH in the mid-luteal phase. It is possible, therefore, that either a sensitizing effect of the ovaries on the pituitary is exerted through unspecified substances, or that the decrease in ΔLH values following ovariectomy is controlled by extra-ovarian mechanisms. Such mechanisms could be related to depleted stores of pituitary gonadotrophins as a result of the preceding mid-cycle LH surge that affected LH reserves more than those of FSH. The latter possibility is more likely based on previous data that a declining pattern of LH response to GnRH during the luteal phase of the cycle has been also reported in women with intact ovaries (Messinis et al., 1993, [11]). The fact, however, that following ovariectomy the decline in ΔLH was interrupted shortly after the operation, i.e. —4 days from the mid-luteal stage (Figure 2), while in women with intact ovaries the decline continues until the end of the luteal phase [11], indicates an earlier recovery of the pituitary in the ovariectomized than in the non-ovariectomized women. This suggests that GnRH-induced LH secretion in the luteal phase is not entirely unaffected by the ovaries. It is possible that a factor, different from estradiol and progesterone, maintains a low responsiveness of LH to GnRH towards the end of the cycle. Such a factor that specifically reduces LH response to GnRH is gonadotrophin surge attenuating factor (GnSAF) (Messinis and Templeton, 1989 [12]), but its role at that stage of the cycle needs to be further investigated.

3. Mathematical Result

- Pdf of FSH , LH , Estradiol and Progesterone are given in the figures1(a) , 1(b), 1(c) , 1(d), 2(a) and 2(b) respectively by using the equation (2) are given in the following figures 3(a) ,3(b) , 3(c), 3(d), 4(a) and 4(b)

respectively.All the curves are monotonically decreasing towards time axis in days.

- Hazard rate of FSH , LH, Estradiol and Progesterone of the corresponding medical figures 1(a) , 1(b), 1(c) 1(d), 2(a) and 2(b) respectively by using the equation (7) are given in the following figures 5(a) ,5(b) , 5(c), 5(d), 6(a) and 6(b) respectively. All the curves of Hazard function are upside down function for all values of α.

Figure.3(a) **Figure.3(b)**

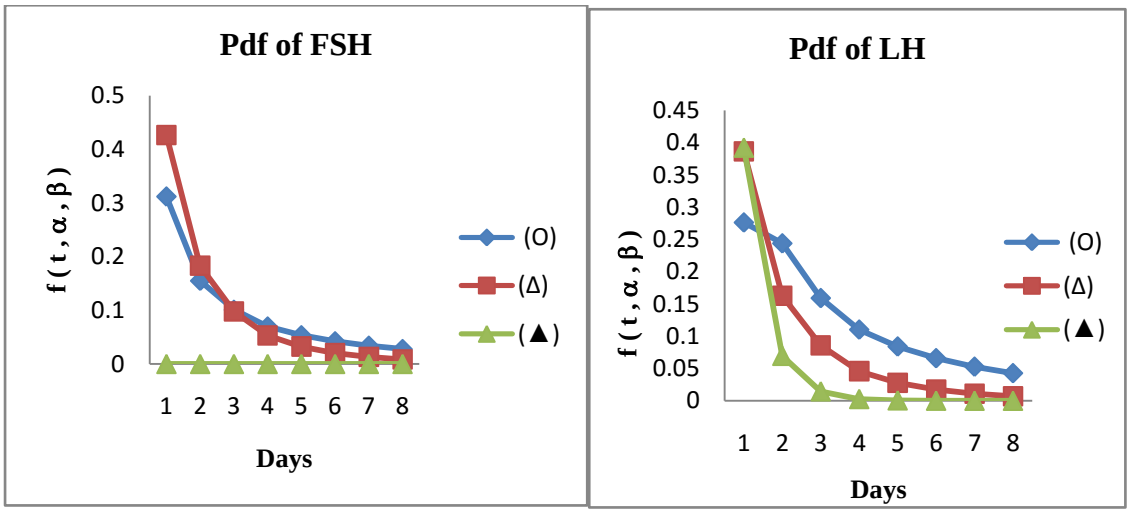


Figure 3(c) **Figure 3(d)**

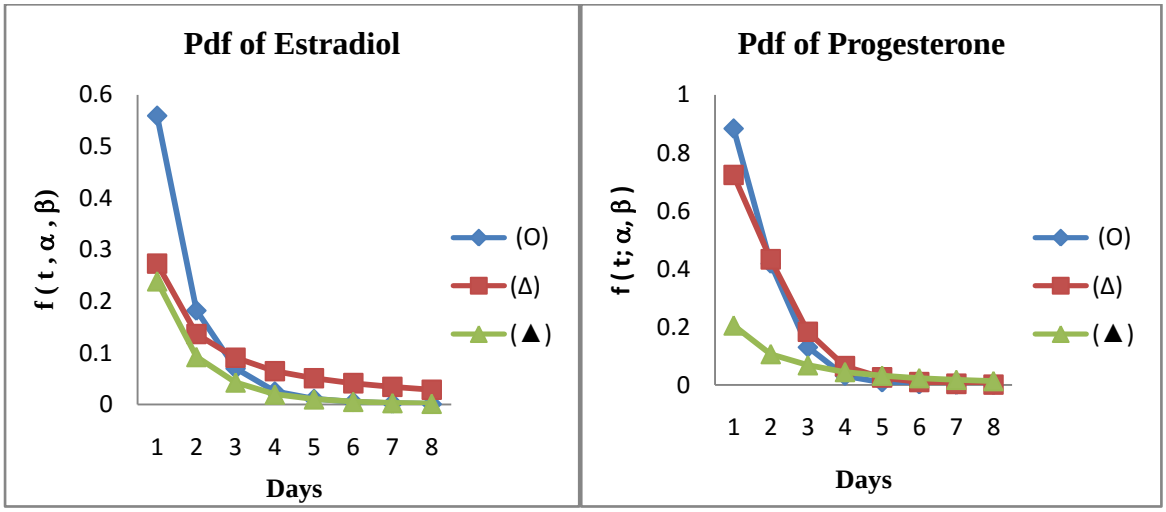


Figure 4(a)

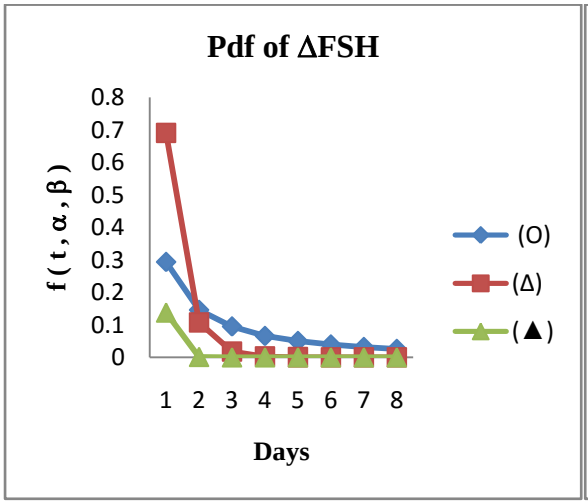


Figure 4(b)

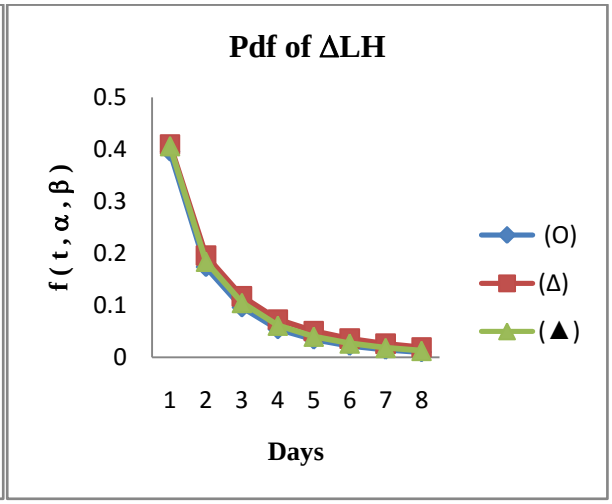


Figure 5(a)

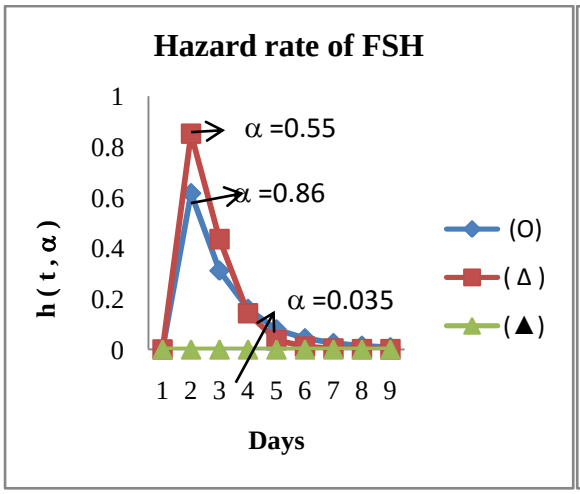


Figure.5(b)

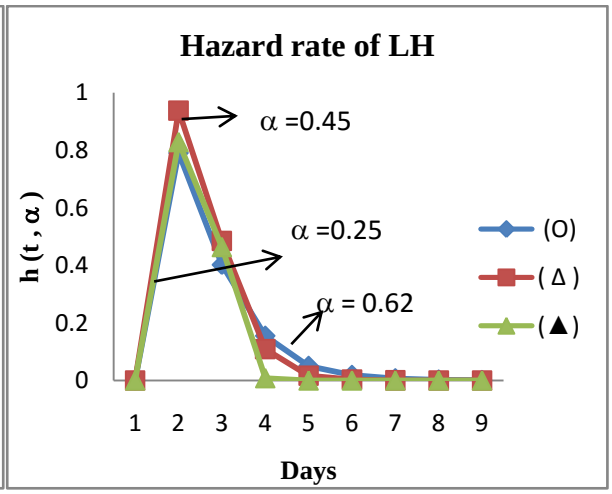


Figure 5(c)

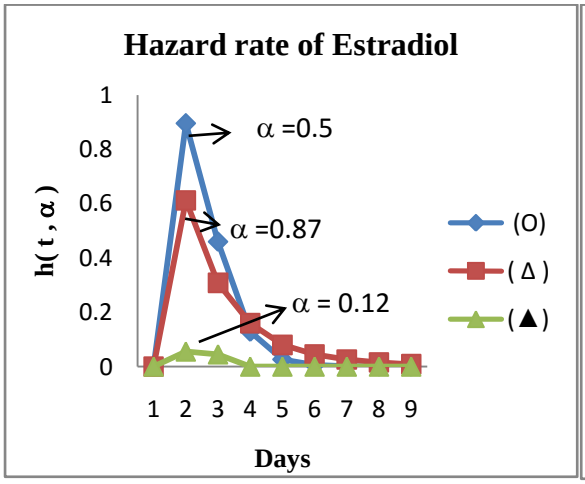


Figure 5(d)

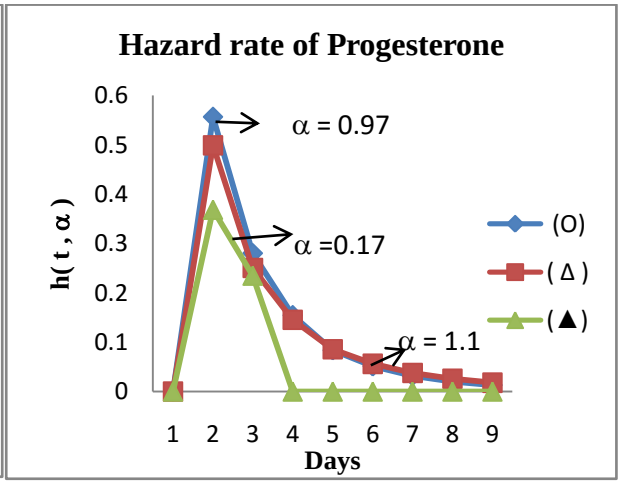
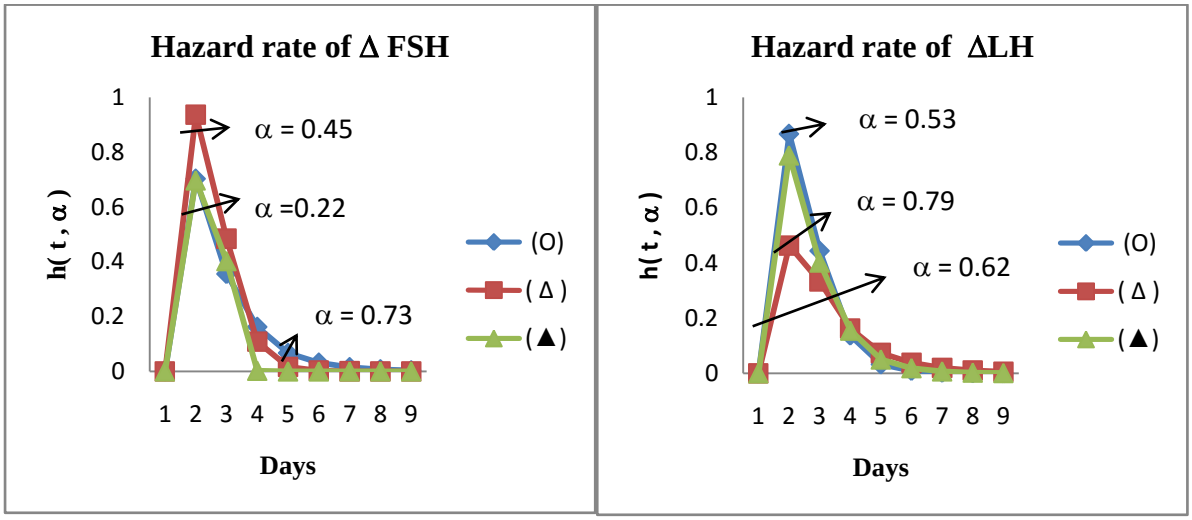


Figure 6(a) **Figure 6(b)**



4.Conclusion

In conclusion, the present study provides evidence that in the early to mid-luteal phase of the cycle, estradiol and progesterone are important components of the suppressing effect of the ovaries on basal FSH and LH secretion. However, in terms of gonadotropin response to GnRH, the study demonstrates for the first time that these two steroids participate in the control of FSH, but not of LH, secretion. It is possible that in the luteal phase the response of LH to GnRH is partly controlled by GnSAF.

Mathematical results : P.d.f of FSH , LH , Estradiol and Progesterone are given in the figures1(a) , 1(b), 1(c) , 1(d), 2(a) and 2(b) respectively by using the equation (2) are given in the figures 3(a), 3(b), 3(c), 3(d), 4(a) and 4(b) respectively. All the curves are monotonically decreasing towards time axis in days. Similarly Hazard rate of FSH , LH, Estradiol and Progesterone of the corresponding medical figures 1(a) , 1(b), 1(c) 1(d), 2(a) and 2(b) respectively have been obtained by using the equation (7) and are given in the figures 5(a) ,5(b) , 5(c), 5(d), 6(a) and 6(b) respectively. All the curves of the Hazard functions are upside down function for all values of α. These results will beuseful for medical professionals for further research.

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