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Mathematical Model for the Effect of Ghrelinon basal,GNRH Induced FSH and LH Secretion in Normal Women by using four Variate Weibull Distribution

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ABSTRACT: *In this paper, we introduce probability density function of four variate Weibull distributions. A multivariate survival function of Weibull Distribution is used for four variables. From the survival function, the probability density function and cumulative probability function are derived. Ghrelin may affect reproductive function in animals and humans.In the application part the experimental conditions of an acute injection of ghrelin (1μg/kg) to normal women, basal and GnRH-induced LH and FSH secretion were not affected and suggested that ghrelin does not play a major physiological role in gonadotrophin secretion in women.In the mathematical part, we have found that the Survival function of the curveis suddenly decreased in Mid-luteal phase compare with other phases. Pdf of the curve is suppressed in late follicular phase and it will be increased at the time of7min.Pdf for early follicular phase of control cycleis increased from 4 min .Also Pdf curve for early follicular phase with ghrelin administration and mid-luteal phase with ghrelin and GnRH are also increased at the time of 5 and 3 minutes respectively.*

Keywords: *Ghrelin, FSH, LH, GnRH, Estradiol, Progesterone, four variate Weibull Distribution, Survival function, PDF.*

I. MATHEMATICAL MODEL

1.1. Introduction

Lu and Bhattacharyya (1990, [10]) 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 $H_2(y)$ 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 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 Marginal $\bar{F}_x$ and $\bar{F}_y$ given the assumption that the Laplace transform of the stress S exist on $[0,\infty)$ and is strictly decreasing. From the theorem, they derived a bivariate Weibull Distribution

$$\bar{F}(x, y) = exp\left\{-\left[\left(\frac{x}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{y}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}}\right]^{\alpha}\right\},$$

Where $0<\alpha\leq 1$, $0<\lambda_1, \lambda_2<\infty$, and $0<\gamma_1, \gamma_2<\infty$. This bivariate Weibull Distribution is exactly the same as developed by Hougaard(1986, [3]).

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

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

Where α measures the association among the variables, $0<\alpha\leq 1$, $0<\lambda_1, \lambda_2, \ldots\ldots \lambda_n<\infty$, and $0<\gamma_1, \gamma_2 \ldots\ldots\ldots \gamma_n<\infty$.

1.2 Probability density function of the Multivariate Weibull Distribution

The multivariate probability density function $f(x_1, x_2, \ldots\ldots, x_n)$ of a multivariate distribution function can be obtained by differentiating the multivariate survival function with respect to each variable. Li (1997, [9]) has shown that

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

Using Li's derivation and one of the special cases of the multivariate Faa di Bruno formula by Constantine and Savits (1996[2]), the probability density function is

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

$$\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}-1}\left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}-1}\ldots.\left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}-1}\right].\sum_{i=1}^{p(n)}\left\{(-1)^{k_i}P_s(n,i)\left(\prod_{j=1}^{k_i}\alpha^{\overrightarrow{n_j}}\right)\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \cdots + \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}}\right]^{k_i\alpha-n}\right\} \quad (2)$$

Where $k_i$is the number of summands of the i^{th} partition of n such that $n_1 + n_2 + \ldots. + n_{ki} = n$,

$n_1 \geq n_2 \geq \ldots. \geq n_{ki} > 0$, $1 \leq k_i \leq n$; $\alpha^{\overrightarrow{n_j}}$ is equal to $\alpha(\alpha-1)\ldots..(\alpha - n_j + 1)$, the falling factorial of α(Kunth, 1992, [7]); P(n) is the total number of partitions of n ; $P_s(n, i)$ is the total number of set partitions of the set $S_n = \{1, \ldots., n\}$ corresponding to the i^{th} partition of n. The specific way of partitioning n and S_n is given by Mccullagh and Wilks (1988,[12]).

1.3. PDF of Fourvariate Weibull Distribution

The Probability density function is$f(x_1,x_2,x_3,x_4)$ =

$$\left(\frac{-1}{\alpha}\right)^4 exp\left\{-\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} + \left(\frac{x_4}{\lambda_4}\right)^{\frac{\gamma_4}{\alpha}}\right]^{\alpha}\right\}\left[\left(\frac{\gamma_1}{\lambda_1}\right)\left(\frac{\gamma_2}{\lambda_2}\right)\left(\frac{\gamma_3}{\lambda_3}\right)\left(\frac{\gamma_4}{\lambda_4}\right)\right]\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}-1}\left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}-1}\left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}-1}\left(\frac{x_4}{\lambda_4}\right)^{\frac{\gamma_4}{\alpha}-1}\right]$$

$$\left\{-\alpha(\alpha-1)(\alpha-2)(\alpha-3)\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} + \left(\frac{x_4}{\lambda_4}\right)^{\frac{\gamma_4}{\alpha}}\right]^{\alpha-4} + (\alpha^4(\alpha-1)(\alpha-2) + \alpha^2(2\alpha-3)(2\alpha-1))\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} + \left(\frac{x_4}{\lambda_4}\right)^{\frac{\gamma_4}{\alpha}}\right]^{2\alpha-4} + (-6\alpha^3(\alpha-1))\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} + \left(\frac{x_4}{\lambda_4}\right)^{\frac{\gamma_4}{\alpha}}\right]^{3\alpha-4} + \left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} + \left(\frac{x_4}{\lambda_4}\right)^{\frac{\gamma_4}{\alpha}}\right]^{4\alpha-4}\right\} \quad (3)$$

II. APPLICATION

2.1. Introduction

Ghrelin, a 28-amino acid peptide, was discovered a few years ago as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) (Kojima et al., 1999,[4]). It is produced primarily in the mucosa of the stomach, although it is also expressed in a variety of other tissues. Ghrelin circulates in the blood and stimulates the secretion of GH, prolactin and adrenocorticotrophic hormone from the pituitary (Takaya et al., 2000,[14]). The role of ghrelin in the secretion of gonadotrophin in humans, data are scanty and only available in men. In the first published study [14] different dosages of ghrelin increased GH but did not affect LH values in normal males. There are only another two studies in men, one showing a delay and a suppression of the amplitude of LH pulses following the i.v. administration of four consecutive ghrelin boluses (Kluge et al., 2007,[6]) and the other showing an inhibitory effect of ghrelin infusion on LH pulsatility and on LH response to naloxone without affecting the response of LH to GnRH (Lanfranco et al., 2008,[8]). No studies as yet have investigated whether ghrelin can affect the secretion of LH in women.The present study was undertaken to investigate the effect of ghrelin on basal and GnRH-induced LH secretion in normal women during the normal menstrual cycle.

The study included 10 volunteer women with normal menstrual cycles who gave written informed consent. All women were healthy and never used any type of hormonal contraception or any other medical treatments for at least the last 6 months before entering the study. All women were studied during the early follicular phase (Day 3 of the cycle) of three consecutive spontaneous cycles. In the first cycle (cycle 1), a single

dose (1 mg/kg) of ghrelin was administered i.v. In the second cycle (cycle 2), a single dose (100 mg) of GnRH was also administered i.v, while in the third cycle (cycle 3) the same bolus of ghrelin as in cycle 1, followed immediately by the same bolus of GnRH, as in cycle 2, were administered i.v. Furthermore, in cycle 1 all women were also given a single dose (1 mg/kg) of ghrelin i.v. in the late follicular phase, when the leading follicle was 16 – 17 mm on ultrasound examination, and in the mid-luteal phase, i.e. 7 days after ovulation which was confirmed with serial ultrasound examinations. In all women, blood samples were taken immediately before the ghrelin, GnRH or ghrelin and GnRH injections (time 0) as well as at -15, 15, 30, 45, 60, 75, 90 and 120 min. All experiments were performed, after overnight fasting, in the morning (1000 – 1200 h). In a spontaneous cycle, preceding cycle 1 (control cycle), a single dose of normal saline (2 ml) was administered in the early and late follicular and in the mid-luteal phase and blood samples were taken as described above. Total plasma ghrelin and serum FSH, LH, Estradiol (E2) and progesterone were measured in all blood samples. Also, GH was measured in the blood samples taken in the early follicular phase of the control cycle and of cycles 1, 2 and 3.

The clinical and hormonal characteristics of the women during the three phases of cycle 1. Hormone values in the early follicular phase of cycles 2 and 3 were similar to those in cycle 1 (data not presented). The duration of cycles 1, 2 and 3 ranged between 27 and 30 days and all women ovulated in the three cycles. In cycle 1, serum E2 and progesterone levels showed the expected variations of a normal menstrual cycle, with higher E2 levels in the late follicular as compared with the early follicular phase ($P < 0.05$), and higher progesterone levels in the mid-luteal as compared with the early and late follicular phase ($P < 0.001$) .

Injection of normal saline had no effect on serum FSH, LH, E2 and progesterone levels in the three phases of the control cycle. Nevertheless, to reduce complexity only results of the early follicular phase are shown in Fig.2.1. 1. In cycle 1, in which ghrelin was administered in the three phases, serum FSH, LH, E2 and progesterone levels showed no significant changes and remained stable throughout the whole experiment (Fig 2.1.1). As expected, serum FSH levels were significantly lower in the mid-luteal phase as compared with the early and late follicular phases ($P < 0.05$) and LH values were significantly higher in the late follicular phase as compared with the early and mid-luteal phases ($P < 0.05$), at all-time points (Fig.2.1. 1). Similarly, significant differences were also found in E2 values between the three phases of the cycle ($P < 0.05$). In particular, E2 values were significantly higher in the late follicular as compared with the early follicular phases at all-time points ($P < 0.05$), and in the late follicular as compared with all other phases at the time points of 15, 45, 60 and 90 min ($P < 0.05$). Progesterone values were significantly higher in the mid-luteal as compared with the follicular phases ($P < 0.001$, Fig.2.1. 1).

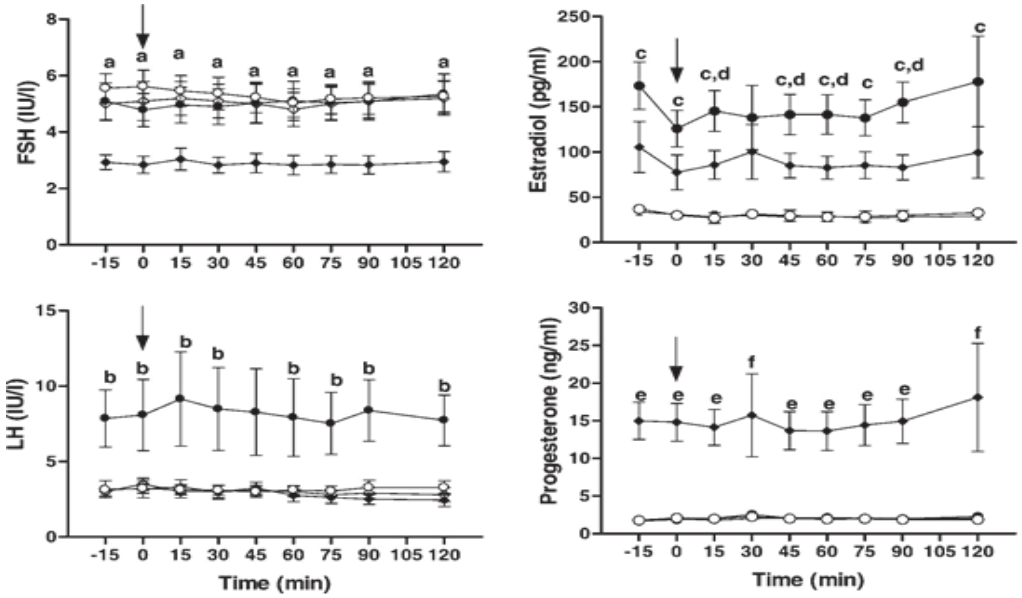


Figure.2.1.1 Serum FSH, LH, E and progesterone concentrations before and after a single i.v injection (arrow) of normal saline (2ml) to normal women (n = 10) during the (◊) early follicular phase of the control cycle, and after a single i.v injection (arrow) of ghrelin (1µg/ kg) to the same women during the (o) early follicular, (•) late follicular and (♦) mid luteal phase of a subsequent cycle (cycle1).

Discussion

This study demonstrates for the first time that serum basal LH and FSH levels were not affected in normal women following an acute injection of ghrelin. The present results could be interpreted as indicating that under the present experimental conditions ghrelin is not involved in the control of gonadotrophin secretion in normal women. Although, the literature lacks similar data in women for comparison, studies in normal men have shown that the same or even higher doses of ghrelin (i.e. 5 – 10 mg/kg) given as a bolus also did not have an effect on LH levels [14],(Nagaya et al., 2001,[13]). In contrast, a decrease in LH was seen in normal males when ghrelin was given either as multiple boluses or infused at a rate of 2 mg/kg/h over a period of 4 hr [6, 8].

The results clearly differentiate the action of ghrelin on the GH and gonadotrophin systems in women. Ghrelin was able to stimulate a marked increase in GH levels at a time when gonadotrophins were not affected. It is likely that the threshold level of ghrelin required for suppressing LH is much higher than that needed to stimulate the release of GH. This differentiation between hormones suggests that, in contrast to GH secretion, ghrelin is not a primary factor playing a role in LH secretion in humans. In terms of FSH, neither in the present study nor in the studies in men was an effect of ghrelin found [6, 8], although in rats chronic administration of ghrelin suppressed FSH levels (Martini et al., 2006,[11]).

In the present study, it is also investigated the effect of ghrelin on the secretion of gonadotropins in response to GnRH. The well-known stimulating effect of GnRH was clearly evident but it was unaffected by the bolus of ghrelin. The LH and FSH response to GnRH has been examined previously in only one study in men and the response was not affected by a 210 min infusion of ghrelin [8]. The present results that ghrelin is not important for the control of GnRH-induced gonadotrophin secretion in humans.Ghrelin given to normal women in this study did not affect serum E2 and progesteroneconcentrations. Whether gonadal hormones affect the action of ghrelin on gonadotrophin secretion has not been investigated. The present experiments were performed during three different stages of the normal menstrual cycle and showed no differences in the gonadotrophin response to ghrelin. Although previous data have shown that exogenous E2 given to post-menopausal women can enhance the stimulating effect of ghrelin on GH secretion (Kok et al., 2008,[5]), it is tempting to speculate from the present findings that endogenous ovarian steroids do not affect the action of ghrelin on gonadotrophin secretion in women.

III. MATHEMATICAL RESULT

- Survival function of four variate Weibull distribution is suddenly decreased in Mid-luteal phase compare with other phases.
- Pdf of four variate Weibull distribution is supressed in late follicular phase and it will be increased at 8min.
- Pdf of four variate Weibull distribution is increased in early follicular phase with control cycle, early follicular phase, mid-luteal phase at the time 4, 5 and 3minutes.

Survival function of four variate Weibull distribution

Figure 3.1(a)

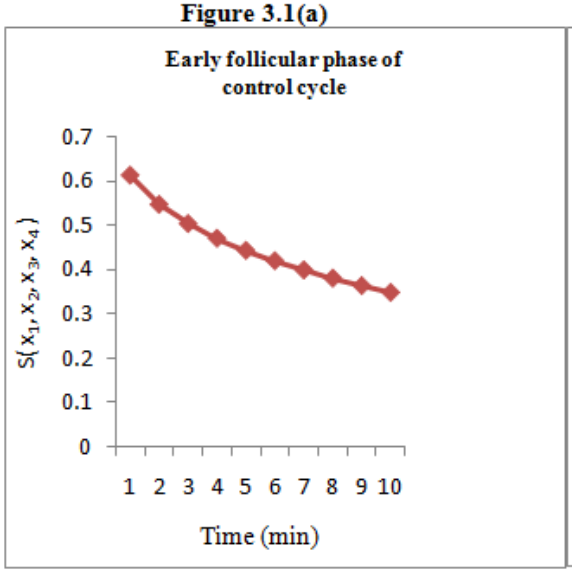


Figure.3.1(c)

Figure.3.1 (b)

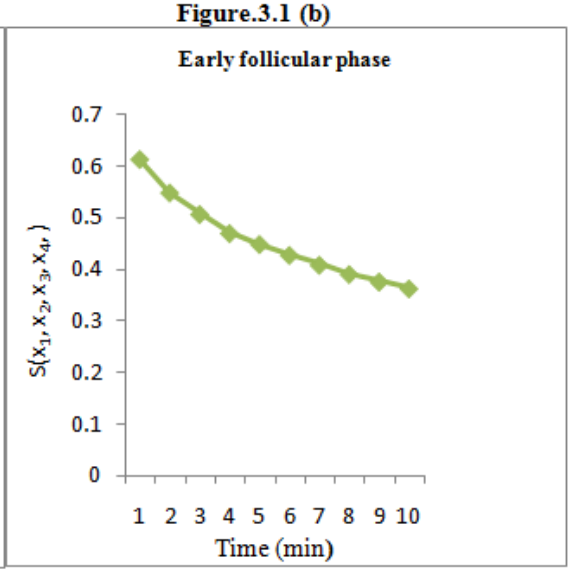


Figure. 3.1(d)

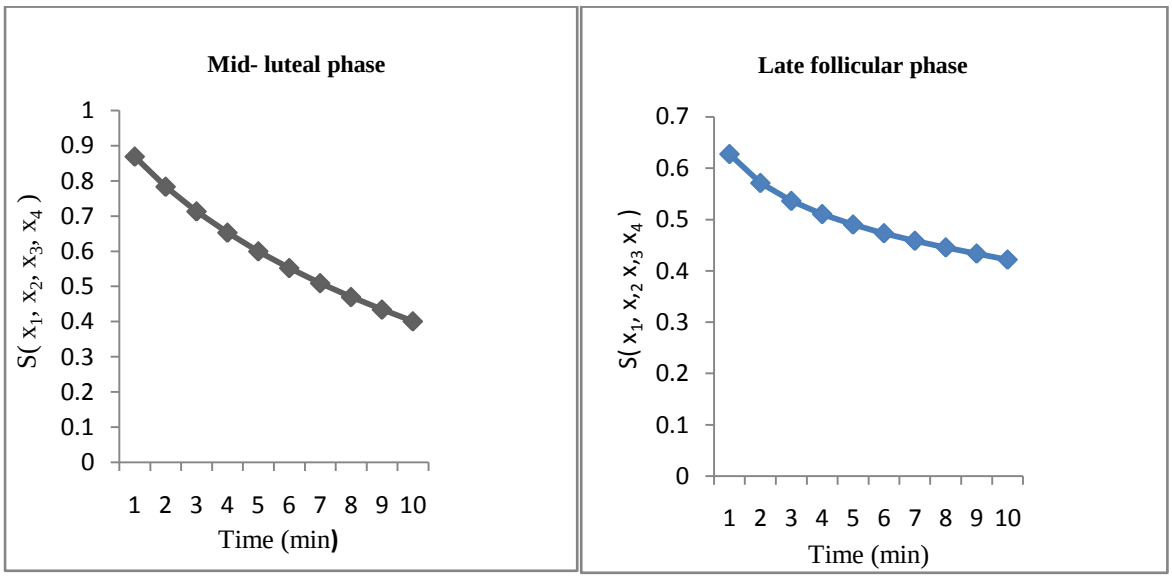
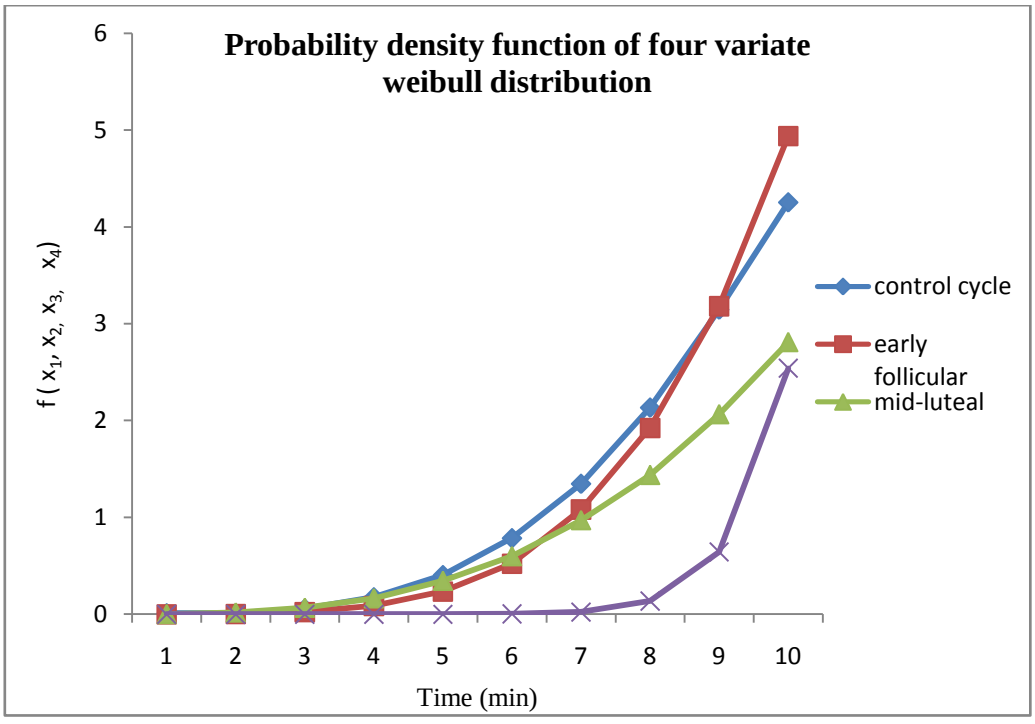


Figure 3.2



IV. CONCLUSION

The present experimental conditions of an acute injection of ghrelin to normal women, basal and GnRH-induced LH and FSH secretion were not affected. We suggest that ghrelin does not play a major physiological role in gonadotrophin secretion in women. Survival function of four variate Weibull distribution of early follicular of control cycle, early follicular phase, mid-luteal phase, late follicular phase of cycle1are given in the figure 2.1.1 by using the equation (1) is given in the figure 3.1 (a), 3.1(b),3.1(c), 3.1(d) respectively and the curve is suddenly decreased in Mid-luteal phase compare with other phases. Pdf of early follicular of control cycle, early follicular phase, mid-luteal phase, late follicular phase are given in the figure 2.1.1 by using the equation (3) is given in the figure3.2. Pdf of the curve is suppressed in late follicular phase and it will be increased at the time of 7min. Pdf for early follicular phase of control cycle is increased from 3min. Also Pdfcurve for early follicular phase and mid-luteal phase with ghrelin administration are also increased at the time of 4 and 3 minutes respectively.

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