A MATHEMATICAL MODEL FOR THE AGE – RELATED ANALYSIS OF INHIBIN A, INHIBIN B AND ACTIVIN A RELATIVE TO THE INTERCYCLE MONOTROPIC FOLLICLE STIMULATING HORMONE RISE IN NORMAL OVULATORY WOMEN

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ABSTRACT

The Beta – Weibull distribution is a highly flexible one and due to its flexibility it can be accommodate the four types of the risk function (increasing, decreasing, unimodal and bathtub). Depending on its parameters it can be used in a variety of problems in modeling survival data. The Log – Beta Weibull (LBW) distribution is defined by the logarithm of the beta Weibull random variable. In this paper the LBW distribution is proposed as the LBW regression model, which is a feasible alternative for modeling the four existing type of failure rate functions. The purpose of the LBW regression model is to find out the likelihood estimator for the Peripheral levels of LH, FSH, estradiol, inhibin A, inhibin B and activin A normalized to the LH surge in the two consecutive cycles (Cycle 1 & Cycle 2) and intercycle FSH peak in older subjects and younger controls. The log – likelihood estimator is find out using the equation (1.10) and the corresponding results are given in the Mathematical Results.

Keywords: Beta Weibull (BW) distribution, Log – Beta Weibull (LBW) distribution, log – Weibull regression, Lutenizing Hormone (LH), Follicle Stimulating Hormone (FSH), inhibin, activin, estradiol.

Mathematics Subject Classification: $60G_{XX}$, $62H_{XX}$, $62P_{XX}$

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1. Mathematical Model

1.1 Log – Beta Weibull Distribution

Most generalized Weibull distributions have been proposed in reliability literature to provide better fitting of criteria data sets than the traditional two and three parameter Weibull models. The BW density function [5] with four parameters $a > 0, b > 0, c > 0$ *and* $\lambda > 0$ is given by for $t > 0$

$$f(t) = \frac{c}{\lambda^c B(a,b)} t^{c-1} \exp\left\{-b\left(\frac{t}{\lambda}\right)^c\right\}\left[1 - exp\left\{-\left(\frac{t}{\lambda}\right)^c\right\}\right]^{a-1} \quad (1.1)$$

where $B(a,b) = [\Gamma(a)\Gamma(b)/\Gamma(a+b)]$ is the beta function and $\Gamma(.)$ is the gamma function. Here, a and b are two additional shape parameters to the Weibull distribution to model the skewness and kurtosis of the data.

The important characteristic of the BW distribution is that it contains, as special sub – models, the EE [8], EW [15] and GR [11] distributions and some other distributions [3]. The survival and hazard rate functions corresponding to (1.1) are

$$S(t) = 1 - \frac{1}{B(a,b)} \int_0^{1-exp\left\{-\left(\frac{t}{\lambda}\right)^c\right\}} w^{a-1}(1-w)^{b-1} dw = 1 - I_{1-exp\left\{-\left(\frac{t}{\lambda}\right)^c\right\}}(a,b)$$

and

$$h(t) = \frac{c\left(\frac{1}{\lambda}\right)^c t^{c-1} exp\left\{-b\left(\frac{t}{\lambda}\right)^c\right\}\left[1-exp\left\{-\left(\frac{t}{\lambda}\right)^c\right\}\right]^{a-1}}{B(a,b)\left[1-I_{1-exp\left\{-\left(\frac{t}{\lambda}\right)^c\right\}}(a,b)\right]}$$

respectively, where $I_y(a,b) = B(a,b)^{-1} \int_0^y \int_0^{1-exp\left\{-\left(\frac{t}{\lambda}\right)^c\right\}} w^{a-1}(1-w)^{b-1} dw$ is the incomplete beta function ratio.

Let T be a random variable having the BW density function (1.1), then the mathematical properties of the LBW distribution defined by the random variable $Y = \log(T)$. The density function of Y, parameterized in terms of $\sigma = c^{-1}$ and $\mu = \log(\lambda)$ can be expressed as

$f(y; a, b, \sigma, \mu)$

$$= \frac{1}{\sigma B(a,b)} exp\left\{\left(\frac{y-\mu}{\sigma}\right) - bexp\left(\frac{y-\mu}{\sigma}\right)\right\}\left\{1 - exp\left[-exp\left(\frac{y-\mu}{\sigma}\right)\right]\right\}^{a-1} \quad (1.2)$$

where $-\infty < Y < \infty, \sigma > 0$ and $-\infty < \mu < \infty$. When refer to the LBW distribution, say $Y \sim LBW(\mu, \sigma, a, b)$, where μ is the location parameter, σ is the dispersion parameter and a, b are shaper parameters. The following result holds, if $T \sim BW(\lambda, a, b, c)$ then $Y = \log(T) \sim LBW(\mu, \sigma, a, b)$. The LBW distribution could also be called the beta extreme value (BEV) distribution, since they are identical. The survival function corresponding to (1.2) is

$$S(Y) = 1 - \frac{1}{B(a,b)} \int_0^{1-exp\left\{\left(\frac{y-\mu}{\sigma}\right)^c\right\}} w^{a-1} (1-w)^{b-1} dw$$

$$= 1 - I_{1-\exp\left[-exp\left(\frac{y-\mu}{\sigma}\right)^c\right]}(a, b) \quad (1.3)$$

1.2 Properties of the LBW distribution

Here, some properties of the LBW distribution are to be noted and for the standardized LBW random variable defined by $Z = (Y - \mu)/\sigma$. The density function Z reduces to

$\pi(z; a, b)$

$$= \frac{1}{B(a,b)} exp[z - bexp(z)] \left\{1 - exp\left[-exp\left(\frac{y-\mu}{\sigma}\right)\right]\right\}^{a-1}, -\infty < z < \infty \quad (1.4)$$

The associated cumulative distribution function (cdf) is $F_Z(z) = 1 - I_{1-\exp[-\exp(z)]}(a, b)$. The basic exemplar a = b = 1 corresponds to the standard extreme – value distribution.

1.2.1 Linear Combination

By expanding the binomial term in (1.4) it can be written as,

$$\pi(z; a, b) = \frac{1}{B(a,b)} \sum_{j=0}^{\infty} (-1)^j \binom{a-1}{j} exp[z - (b+j)\exp(z)] \quad (1.5)$$

The density function $h_b = b\,exp[z - b\exp(z)]\ for\ b > 0$ gives the Kumaraswamy extreme value (Kum EV) distribution [3] with parameters one and b. its associated cumulative function is $H_a(x) = 1 - [1 - exp(-e^z)]^a$. Thus,

$$\pi(z; a, b) = \sum_{j=0}^{\infty} \mathcal{W}_j h_{b+j}(z)$$

where the coefficients are,

$$\mathcal{W}_j = \frac{(-1)^j \binom{a-1}{j}}{(b+j)B(a,b)}.$$

So, the LBW density function can be expressed as a linear combination of KumEV densities. For a = 1, the LBW distribution reduces to the Kum EV distribution with parameters one and b. For b = 1, it becomes the log exponentiated Weibull, which is a new model defined here. The LBW random variable Z can be generated directly from the beta variate V with parameters $a > 0, b > 0\ by\ Z = log[-\log(1 - V)]$.

1.2.2 Moments

The s[th] ordinary moment of the LBW distribution (1.4) is

$$\mu'_s = E(Z^s) = \frac{1}{B(a,b)} \int_{-\infty}^{\infty} z^s\, exp[z - bexp(z)] \left\{1 - exp\left[-exp\left(\frac{y-\mu}{\sigma}\right)\right]\right\}^{a-1} dz.$$

By expanding the binomial term and setting $\mathcal{W} = e^z$, we obtain

$$\mu'_s = \frac{1}{B(a,b)} \sum_{j=0}^{\infty} (-1)^j \binom{a-1}{j} \int_0^{\infty} log(\mathcal{W})^s\ exp[-(b+j)\mathcal{W}] d\mathcal{W}.$$

The above integral can be calculated from Purnidkov et al. [18] and [6] as

$$I(s,j) = \left(\frac{\partial}{\partial p}\right)^s [(b+j)^{-p}\Gamma(p)]|_{p=1}$$

and then $$\mu'_s = \frac{1}{B(a,b)} \sum_{j=0}^{\infty} (-1)^j \binom{a-1}{j} I(s,j) \qquad (1.6)$$

Equation (1.6) gives the moments of the LBW distribution.

Mean Deviation

The amount of scatter in Z is evidently measured to some extent by the totality of deviations from the mean μ_1' and median m. These are known as the median deviations about the mean and the median defined by

$$\delta_1(Z) = \int_{-\infty}^{\infty} |x-\mu|\,\pi(z;a,b)dz \;\; and \;\; \delta_2(Z) = \int_{-\infty}^{\infty} |x-m|\,\pi(z;a,b)dz$$

respectively. From (1.6) with s = 1, we obtain

$$\mu_1' = E(Z) = \frac{1}{B(a,b)} \sum_{j=0}^{\infty} \frac{(-1)^{j+1}\binom{a-1}{j}}{(b+j)} [\gamma + \log(b+j)]$$

where γ is Euler's constant. The median m is calculated from the nonlinear equation $I_{1-\exp[-\exp(m)]}(a,b) = 1/2$. The measures $\delta_1(Z)$ and $\delta_2(Z)$ can be expressed as

$$\delta_1(Z) = 2\mu_1'[FZ(\mu_1') - 1] + 2T(\mu_1') \; and \; \delta_2(Z) - 2T(m) - \mu_1'$$

where $T(q) = \int_q^{\infty} z\,\pi(z;a,b)dz$. We obtain T(q) as

$$T(q) = \frac{1}{B(a,b)} \int_q^{\infty} z\, exp[z - b\exp(z)]\{1 - exp[-\exp(z)]\}^{a-1}$$

$$= \frac{1}{B(a,b)} \sum_{j=0}^{\infty} (-1)^j \binom{a-1}{j} \int_{e^q}^{\infty} \log(\mathcal{W})\; exp[-(b+j)\mathcal{W}]d\mathcal{W}$$

$$K(p,a) = \int_p^{\infty} \log(x)\, e^{-bx}\, dx = b^{-1}[e^{-bp}\log(p) - E_i(-bp)],$$

where $E_i(x) = \int_{-\infty}^{x} t^{-1}e^t dt$ *is the exponential integral, we obtain*

$$T(q) = \frac{1}{B(a,b)} \sum_{j=0}^{\infty} \frac{(-1)^j \binom{a-1}{j}}{(b+j)} \left[qe^{-(b+j)e^q} - E_i(-b+j)e^q\right]$$

This equation for T(q) can be used to determine Bonferroni and Lorenz curves that have applications in economics to study income and poverty, reliability, demography, insurance and medicine and other fields. They are defined by

$$B(p) = \frac{\mu'_1 - T(q)}{p\mu'_1} \quad and \quad L(p) = \frac{\mu'_1 - T(q)}{\mu'_1}$$

respectively, where $q = F^{-1}(p)$ can be calculated for given p from the quantile function.

1.3 Log – Beta Weibull Regression Model

In many practical applications the lifetimes are affected by explanatory variables such as the cholesterol level, blood pressure, weight and many others. Parametric models to estimate univariate survival functions and for censored data regression problems are widely used. A parametric model that provides a good fit to lifetime data tends to yield more precise estimates of interest. Based on the LBW density function, we propose a linear location – scale regression model linking the response variable y_i and the explanatory variable vector $x_i^T = (x_{i1}, x_{i2}, \dots\dots\dots x_{ip})$ as follows

$$y_i = x_i^T\beta + \sigma z_i, i = 1,2, \dots\dots\dots\dots\dots, n \qquad (1.7)$$

where the random error z_i has density function (1.4), $\beta = (\beta_1, \beta_2, \dots\dots\dots \beta_p)^T, \sigma > 0,$

$a > 0$ and $b > 0$ are unknown parameters. The parameter $\mu_i = x_i^T\beta$ is the location of y_i. The location parameter vector $\mu = (\mu_1, \mu_2, \dots\dots\dots, \mu_n)^T$ is represented by a linear model $\boldsymbol{\mu = X\beta}$ where $\boldsymbol{X} = (\boldsymbol{x_1}, \boldsymbol{x_2}, \dots\dots\dots, \boldsymbol{x_n})^{\boldsymbol{T}}$ is a known model matrix. The LBW model (1.7) opens new possibilities for fitting many different types of data. It contains as special sub – models the following well – known regression models. For $a = b = 1$ the classical Weibull regression model is obtained [12]. If $\sigma = 1$ and $\sigma = 0.5$ in addition to $a = b = 1$, it coincides with the Rayleigh regression models, respectively. For b = 1, it reduces to the log – exponentiated Weibull regression model [2,9,17]. If $\sigma = 1$, in addition to b = 1, the LBW model yields the log – ecponentiated exponential regression. If $\sigma = 0.5$, in addition to b = 1, it becomes the log – generaliazed Rayleigh regression model. For $\sigma = 1$, we have a new model called the log – beta exponential regression model.

Consider a sample $(y_1, x_1), (y_2, x_2), \ldots\ldots\ldots, (y_n, x_n)$ of n independent observations, where each random response is defined by $y_i = min\{log(t_i), log(c_i)\}$. Assume non – informative censoring such that the observed lifetimes and censoring times are independent, let F and C be the sets of individuals for which y_i is the log- lifetime and log – censoring, respectively. The log – likelihood function for the vector of parameters

$\theta = (a, b, \sigma, \beta^T)^T$ from model (1.7) has the form $l(\theta) = \sum_{i\in F} log[f(y_i)] + \sum_{i\in C} log[S(y_i)]$,

where $f(y_i)$ is the density function (1.2) and $S(y_i)$ is the survival function (1.3) of Y_i. The log – likelihood function for θ reduces to

$$l(\theta) = -r\, log\{log(\sigma) + log[B(a,b)]\} + \sum_{i\in F} z_i - \sum_{i\in F} exp(z_i)$$

$$+(a-1)\sum_{i\in F} log\{1 - exp[-exp(z_i)]\}$$

$$+\sum_{i\in C} log\left\{1 - I_{1-\exp[-\exp(z_i)]}(a,b)\right\} \qquad (1.8)$$

where r is the number of uncensored observations (failures) and $z_i = \frac{(y_i - x_i^T\beta)}{\sigma}$.

The MLE $\hat{\theta}$ of the vector θ of unknown parameters can be calculated by maximizing the log – likelihood (1.8). Initial values for σ and β can be taken from the fit of the log- Weibull (LW) regression model with a = b = 1. The fitted LBW model gives the estimated survival function of Y for any individual with explanatory vector x

$$S(y; \hat{a}, \hat{b}, \hat{\sigma}, \hat{\beta}^T) = 1 - I_{1-\exp\left[-\exp\left(\frac{y - x^T\hat{\beta}}{\hat{\sigma}}\right)\right]}(\hat{a}, \hat{b})$$

The invariance property of the MLEs yields the survival function for $T = \exp(Y)$

$$S(t; \hat{a}, \hat{b}, \hat{c}, \hat{\lambda}) = 1 - I_{1-exp\left[-exp\left(\frac{y - x^T\hat{\beta}}{\hat{\sigma}}\right)\right]}^{(\hat{a}, \hat{b})} \qquad (1.9)$$

where $\hat{c} = 1/\hat{\sigma}$ and $\hat{\lambda} = exp(x^T\hat{\beta})$

Under conditions that are fulfilled for the parameter vector θ in the interior of the parameter space but not on the boundary, the asymptotic distribution of $\sqrt{n}(\hat{\theta} - \theta)$ is multivariate normal

$N_{p+3}(0, K(\theta)^{-1})$ where $K(\theta)$ is the information matrix. The asymptotic covariance matrix $K(\theta)^{-1}$ of $\hat{\theta}$ can be approximated by the inverse of the $(p+3) \times (p+3)$ observed information matrix $\ddot{L}(\theta) = \{L_{r,s}\}$.

The approximate multivariate normal distribution $N_{p+3}(0, \ddot{L}(\theta)^{-1})$ for $\hat{\theta}$ can be used in the classical way to construct approximate confidence regions for some parameters in θ. We can use the likelihood ratio (LR) statistic for comparing some special sub – models with the LBW model. We consider the partition $\theta = (\theta_1^T, \theta_2^T)^T$, where θ_1 is a subset of parameters of interest and $\theta_2$is a subset of the remaining parameters. The LR statistic for testing the null hypothesis $H_0: \theta_1 = \theta_1^{(0)}$ versus the alternative hypothesis $H_1: \theta_1 \neq \theta_1^{(0)}$ is given by $w = 2\{l(\hat{\theta}) - l(\theta)$, where θ and θ are the estimates under the null and alternative hypotheses, respectively. The statistic w asymptotically (as $n \to \infty$ distributed as χ_k^2, where k is the dimension of the subset θ_1 of parameters of interest.

Iterative maximization of the logarithm of the likelihood function ( ) starts with initial values for β *and* σ taken from the fit of the LW regression model with a = b = 1. The LR statistic for testing the hypotheses $H_0: a = b = 1$ *versus* $H_1: H_0$ is not true to compare the LW and LBW regression models, which gives favorable indications toward to the LBW model. The LBW model involves two extra parameters which gives it more flexibility to fit the data. The fitted LBW regression model indicates that all explanatory variables are significant at 5%.

Let $R(t_i)$ be the set of individual at risk at time t_i. Conditionally on the risk sets, the required likelihood $L(\beta)$ can be expressed as

$$L(\beta) = \prod_{i=1}^{n} \left[\frac{\exp(x_i^T \beta)}{\sum_{j \in R(t_i)} \exp(x_i^T \beta)} \right]^{\delta_i} \qquad (1.10)$$

2.Application

Human ovarian senescence is a continuous process that begins many years before the event of menopause, which marks the cessation of normal ovarian function. To understand the etiology of human ovarian aging, it is prudent to study the ovarian aging at its earliest stages. The most consistent endocrine change observed in ovulatory women as they enter into the period of diminished ovarian function is the monotropic rise in FSH [20,21]. To date, the underlying

factors responsible for this monotropic rise in FSH have not been completely elucidated. Recent studies have suggested that decreased follicular and / or luteal production of the inhibin protein hormones [1, 4, 16] and / or an increase in activin levels may accompany the monotropic rise in FSH. Although an age – related decrease in early follicular phase inhibin B has been consistently reported, whether inhibin A and activin are critical modulators of the early follicular phase monotropic FSH rise remains unclear.

During the normal menstrual cycle, FSH begins to rise in the late luteal or early follicular phase, reaches a peak in the early follicular phase [13] and subsequently falls throughout the remainder of the follicular phase in response to negative feedback from ovarian steroids and / or inhibin. The monotropic FSH elevation observed in older women is present throughout the menstrual cycle; however, it is most pronounced in the early follicular phase. In older women with regular menses, the early follicular phase FSH peak occurs earlier in the cycle and reaches a greater magnitude.

Thus, the objectives of this study were to determine whether reproductive aging in normal ovulatory women is associated with changes in circulating levels of inhibin A, inhibin B, and / or activin A during this critical intercycle period.

As a part of a series of clinical studies to examine the normal reproductive aging process, the healthy and ovulatory women were recruited under the age of 40 – 45 years for the participation in this study. All participants were required to have regular menstrual cycles, normal body mass index (18 – 24 kg/m^2), absence of medical or reproductive disorders and midluteal serum levels of prolactin less than 20pg/ml, progesterone more than 10 nmol/liter, and testosterone less than 3 nmol/liter in a prestudy cycle. Women who engaged in greater than 5 h/wk of aerobic exercise were excluded. For the duration of the study, all participants were either sexually abstinent or used nonhormonal methods of contraception.

Daily blood samples were collected during one complete menstrual cycle and continued throughout the subsequent follicular phase in all volunteers. All serum samples were analyzed in duplicate in the same assay to minimize effects of interassay variability. In addition, participants underwent daily transvaginal ultrasound monitoring of dominant follicle development beginning in the midfollicular phase and continuing until follicle collapse was observed.

Results

The first of the two menstrual cycles for each subject was selected arbitrarily for d 3 and follicular phase comparisons. Older women had higher levels of FSH on cycle d 3, lower levels of inhibin B, and shorter follicular phase length compared with the younger control group. The FSH elevation was most pronounced in the intercycle phase between the two cycles. There was no significant differences in cycle d 3 estradiol levels or luteal phase length (first cycle). All participants developed a dominant follicle with ultrasound demonstration of ovulation noted after the LH surge.

Figure 2.1 depicts levels of FSH, LH, estradiol, progesterone, inhibin A, inhibin B, and activin A across the menstrual cycle when normalized to the LH surge. Again, as expected, FSH was elevated throughout the initial cycle and the subsequent follicular phase in the older group. There were no significant differences in LH, activin A, or in luteal – phase progesterone levels. There was a trend toward higher activin A in the older group, consistent with previous reports, although this trend did not reach statistical significance and was diminished when data were normalized to the early follicular phase FSH peak (Figure 2.2). Estradiol was significantly elevated in the older women, most apparently in the follicular phase during dominant follicle development. There was also a trend toward higher levels of inhibin A, whereas inhibin B was significantly lower in the older participants.

Figure 2.2 depicts levels of FSH, estradiol, inhibin A, inhibin B, and activin A, examined in the intercycle phase (the 5 d immediately surrounding and including the early follicular phase FSH peak). When data were normalized to the early follicular phase FSH peak, the older women had significantly lower levels of inhibin B and similar levels of estradiol and activin A. In contrast, inhibin A levels were significantly greater in the older subjects than in the younger controls.

Discussion

The monotropic FSH rise in older reproductive – age women has been well documented and recognized for many years. When it became clear that this rise precedes any significant decline in ovarian steroid secretion, attention turned to inhibin as the most likely candidate ovarian hormone to account for FSH elevation. It is shown that total immunoreactive inhibin, as well as its free subunits and precursors, confirmed that inhibin levels fall with advancing age and

rising FSH, ultimately becoming detectable after menopause. After development of assays for dimeric inhibin A and B [7], it became evident that the two hormones exhibited very different patterns across the menstrual cycle. Inhibin A, the predominant inhibin product of the dominant follicle and corpus luteum, has a pattern in the follicular phase that is similar to estradiol, rising and reaching a peak with maturation of the dominant follicle. It falls transiently with ovulation and then rises and remains elevated throughout the luteal phase. Inhibin B is the predominant inhibin in the small antral follicles, rising in the early to midfollicular phase, then falling throughout the late follicular phase and remaining low for the duration of the luteal phase.

Using assays specific for dimeric inhibin, it is found that inhibin B is low in the follicular phase of older women exhibiting a monotropic FSH elevation [14, 16, 19]. Inhibin B levels inversely correlate with the number of small antral follicles present by transvaginal ultrasound. It is likely that this decrease in inhibin B concentration is the result of fewer primordial and early antral follicles remaining in the ovaries of older women. In this study there was no evidence that inhibin A is deficient in early stages of reproductive aging after the onset of the monotropic FSH rise. The fact that overall inhibin A secretion appears to be higher in the older women suggests that it is inhibin B and not inhibin A that is responsible for the monotropic FSH rise. This is consistent with the evidence that inhibin A is not a major determinant of the early follicular phase FSH rise in normal reproductive age women. It is also found that inhibin A was normal in older women without FSH elevation but was decreased in older participants who demonstrated a monotropic FSH rise. It appears that inhibin B but not A declines in the earliest stages of reproductive aging, in contrast to the decrease in inhibin A levels [1,4].

Activin A has been shown to increase with age in both men and women and does not correlate with FSH levels in either gender. Furthermore, mRNA for activin subunits is expressed in a number of extragonadal tissues, is present predominantly in a bound (and therefore inactive) form in the circulation, and does not vary across the menstrual cycle despite marked variability in FSH levels. Although our current understanding of activin physiology is limited by the lack of available assays for other activin forms to date there is little evidence to support an endocrine role for activin in FSH regulation.

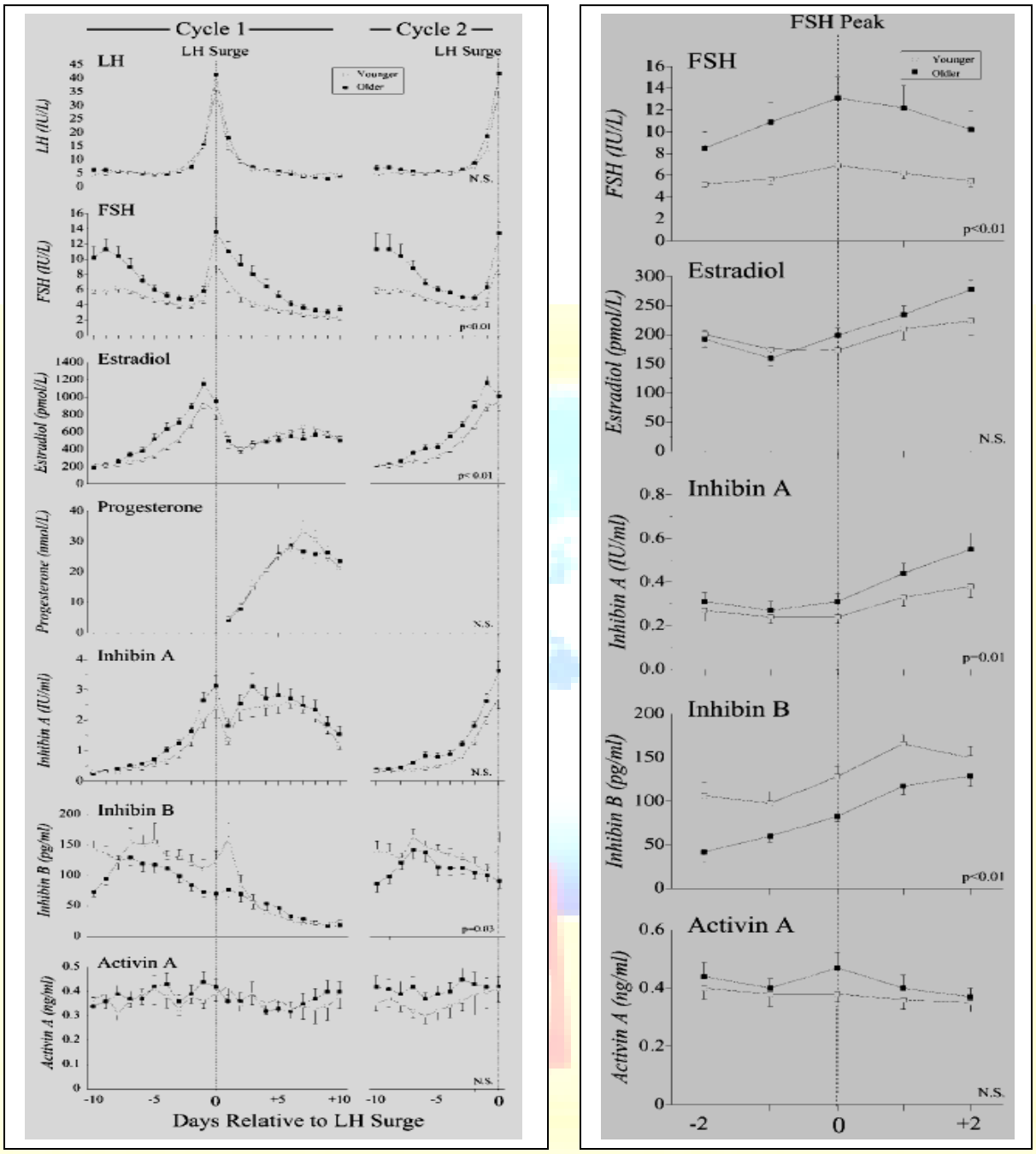


Figure 2.1*Peripheral levels of LH, FSH, estradiol, progesterone, inhibin A, inhibin B, and activin A normalized to the LH surge in the two consecutive cycles in older subjects (40 – 45 yr, n= 16) and younger controls (20 – 25 yr, n = 13).*

Figure 2.2 ***Peripheral levels of LH, FSH, estradiol, progesterone, inhibin A, inhibin B, and activin A normalized to the intercycle FSH peak in older subjects (40 – 45 yr, n= 16) and younger controls (20 – 25 yr, n = 13).***

Similar to the elevated estradiol [10] and normal progesterone levels observed in older women demonstrating a monotropic FSH rise, normal or increased inhibin A may be a result of FSH elevation. In 45 – yr – old ovulatory women, the normal follicular fluid concentrations of steroids and inhibin are found. Together with normal peripheral levels of estradiol and inhibin A, these findings suggest that, under the influence of FSH elevation, the dominant follicle is fully functional in terms of its secretory capacity. Thus, FSH elevation may represent a compensatory mechanism in response to declining inhibin b secretion from a diminishing follicle pool, sufficient in early stages to maintain normal dominant follicle development and ovulation. By recruiting only women who reported very regular menstrual cycles, we selected women who were in a relatively early stage of reproductive aging. Cross sectional and longitudinal study reports suggest that inhibin A levels eventually decline as women approach the menopausal transition, which represents a more advanced stage of reproductive aging [22].

Previous studies of inhibin secretion have been limited by sampling during only one menstrual cycle. Due to the dynamic interactions of hormones across the menstrual cycle, comparisons between groups require normalizing data to a specific point in the cycle (traditionally, the midcycle LH surge). Relative to the menstrual period, older reproductive age women have an earlier onset of the monotropic FSH rise and shorter follicular phase length such that normalization to the LH surge does not allow for comparison of hormones in the early follicular phase. The onset of menses is an end – organ response to falling ovarian steroids and as such, is a crude and inaccurate indicator of the beginning of the follicular phase. Therefore, to study the relationship between inhibin and FSH, it was important to examine the entire intercycle phase so that the intercycle FSH peak could be identified and the associated hormonal patterns compared relative to this important physiological time point.

In summary, this study more precisely characterizes the role of the inhibin and activin glycoprotein hormones in early reproductive aging. The finding of an isolated inhibin B deficiency in the face of normal estradiol, activin A, and inhibin A supports the notion that inhibin B may be the primary mediator of the monotropic rise in FSH. Thus, a decline in inhibin B may a sensitive marker of the earliest stages of ovarian senescence.

3. Mathematical Results

The log - likelihood estimator for the Peripheral levels of LH, FSH, estradiol, inhibin A, inhibin B and activin A normalized to the LH surge in the two consecutive cycles (Cycle 1 & Cycle 2) and intercycle FSH peak in older subjects and younger controls.

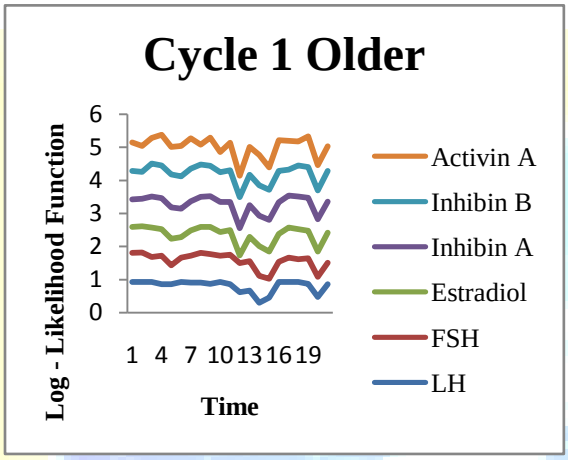


Figure 3.1

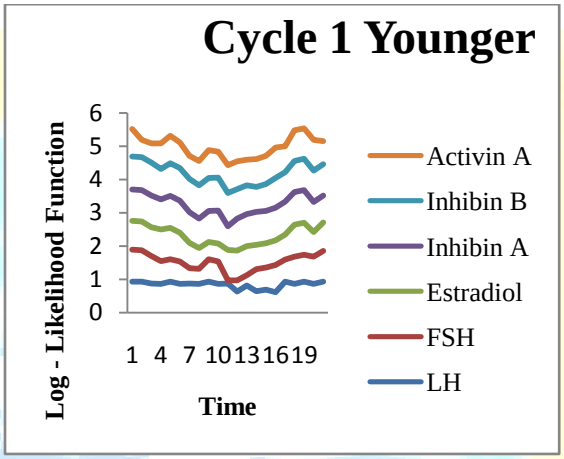
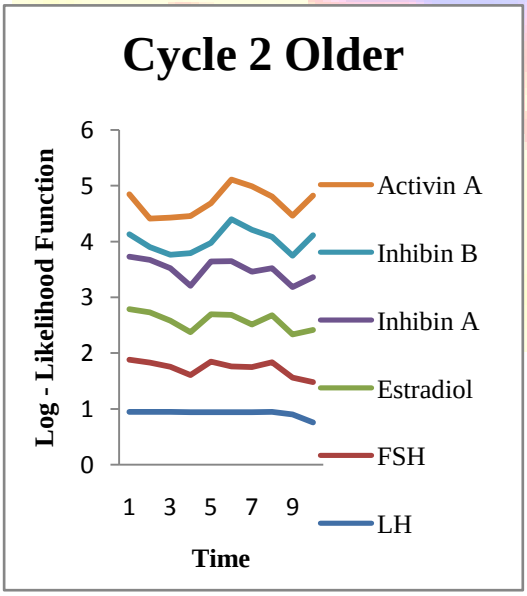


Figure 3.2



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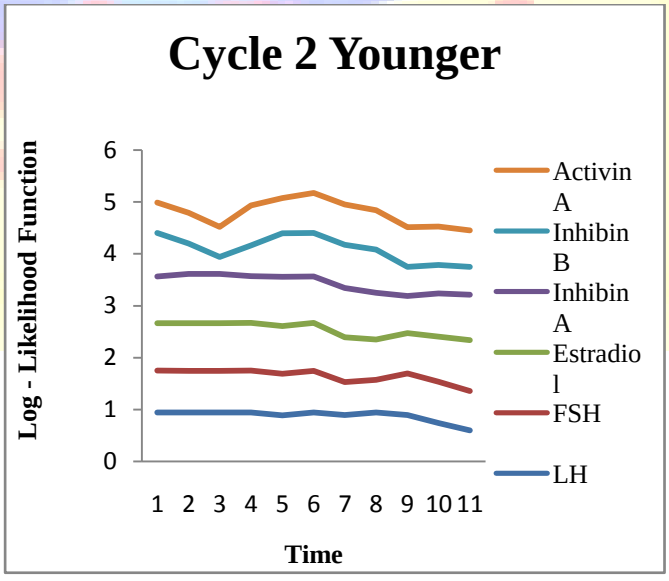
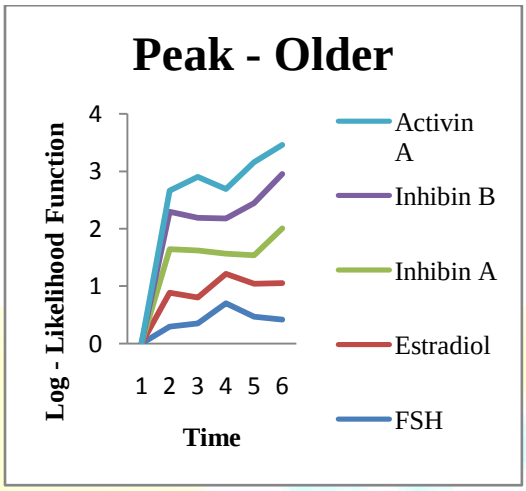


Figure 3.4



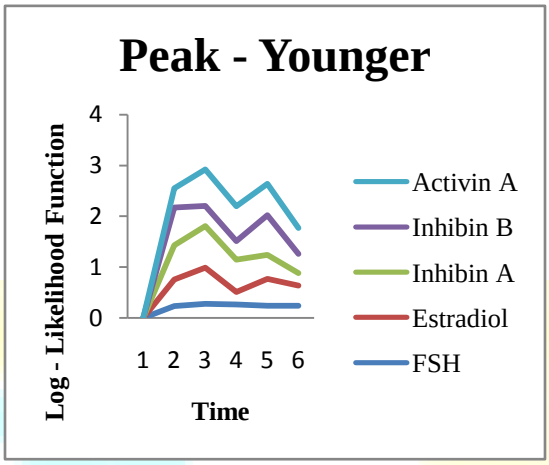


Figure 3.5 **Figure 3.6**

4. Conclusion

. The Log – Beta Weibull (LBW) distribution is defined by the logarithm of the beta Weibull random variable. In this paper the LBW distribution is proposed as the LBW regression model, which is a feasible alternative for modeling the four existing type of failure rate functions. The purpose of the LBW regression model is to find out the likelihood estimator for the Peripheral levels of LH, FSH, estradiol, inhibin A, inhibin B and activin A normalized to the LH surge in the two consecutive cycles (Cycle 1 & Cycle 2) and intercycle FSH peak in older subjects and younger controls. Medical result concluded that overall inhibin A secretion appears to be higher in the older women and that inhibin B and not inhibin A is responsible for the monotropic FSH rise. Our Mathematical results show that both inhibin A and inhibin B are responsible for FSH rise and inhibin A secretion appears to be higher both in younger and older women.

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