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Quantum Chemical Computational Method for Finding Energy deficiency in Women aged 25-40 years in terms of Estrogen and Progestrone

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ABSTRACT

The problem of generating bivariate life distributions from univariate ones is drawing the attention of the reliability analysts for quite long. Several approaches have been developed for generalizing univariate laws. Amongst those approaches, the characterization approach and the modeling approach are very appealing. Here Bivariate Inverse Exponential Distribution is used in the application part. This study aims to test the hypothesis that moderate exercise training combined with caloric restriction would produce significant menstrual disturbances and alterations in ovarian steroids in premenopausal women. Sedentary premenopausal women (25–40 years; body mass index: 23.6±0.6 kg/m2) assigned to either a light conditioning (LC, n = 9) or an exercise combined with caloric restriction group (EX + CR, n = 24) were studied for one screening, one baseline and four intervention periods equivalent to the length of subjects' menstrual cycles. In conclusion, the results of this study suggest that a moderate aerobic exercise training program combined with modest weight loss in accordance with recommended guidelines produces significant reductions in ovarian steroid exposure without disrupting menstrual cyclicity in premenopausal women of advanced gynecological age.

Introduction

1. Mathematical Model

The problem of generating bivariate life distributions from univariate ones is drawing the attention of the reliability analysts for quite long. Several approaches have been developed for generalizing univariate laws. Amongst those approaches, the characterization approach and the modeling approach are very appealing[10,14]. In fact, characterization approach is of interest to both theoreticians and applied workers. The characterization results are distribution dependent and have limited appeals. The other important approach is the modeling approach. It uses functional equations to determine a multivariate distribution from univariate marginal distribution. Thus a need for developing a general approach may be felt so that one can suitably eliminate the limitations of earlier approaches. To this end we present a combined procedure, a characterized model.

2. Characterization of the Model

Let us denote by X= (X_1, X_2) two nonnegative component lives, X_1 and X_2. Let $F_i(x_i)$ be the marginal distribution function of X_i, and $f_i(x_i)$ be the density function, i= 1,2. By definition, the Reversal Hazard Rate (RHR), $a_i(x_i)$, and the cumulative RHR, $A_i(x_i)$ are

$$a_i(x_i) = \frac{f_i(x_i)}{F_i(x_i)}, A_i(x_i) = \int_{x_i}^{\infty} a_i(u_i)du_i \quad (2.1)$$

Therefore,

$$F_i(x_i) = \exp\{-A_i(x_i)\}, \frac{d}{dx_i} A_i(x_i) = -a_i(x_i), i = 1,2. \quad (2.2)$$

Making use of these marginal distributions of X_1 and X_2 let us present a Characterized Extension Model (CE Model) based on the following [8].

At the time of extending a univariate life distribution to a higher dimension one must retain the basic features of the original life distributions. Since the concept of RHR plays an important role in reliability theory, as may be seen from the works of [4,16], we would like to incorporate in the bivariate model the retention of univariate RHR structure. Thus, functional forms of $a_1(x_1)$ and $a_2(x_2)$ are the two basic structures that one should retain in the bivariate system and this retention should logically be in terms of the corresponding bivariate RHRs. Let $F(x_1,x_2)$ be the distribution function of X=(X_1, X_1). We propose that the corresponding bivariate RHRs be defined by

$$a_i(x_1,x_2) = -\frac{\delta}{\delta x_i} A(x_1,x_2), \text{i=1,2.} \quad (2.3)$$

Where

$$A(x_1,x_2) = -logF(x_1,x_2) \quad (2.4)$$

is a bivariate cumulative RHR function.

Thus $a_i(x_1,x_2)$ must retain the structure of $a_i(x_i)$ i= 1,2,. In otherwords $a_i(x_1,x_2)$ must be locally proportional to $a_i(x_i)$ where the constant of proportionality, $c_i(x_{3-i})$, may depend only on x_{3-i}. The following theorem establishes that this above consideration uniquely determines a model which will be referred as CE model for our subsequent discussion.

Theorem 2.1

Bivariate RHRs are locally proportional to the corresponding univariate RHRs if and only if the bivariate distribution function is of form

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$F(x_1,x_2) = F_1(x_1)F_2(x_2)\exp\{-\gamma(logF_1(x_1))(logF_2(x_2))\}$ for some γ. (2.5)

Proof: Under (2.5) it is very easy to note that

$a_1(x_1,x_2) = \{1 + \gamma A_2(x_2)\}a_1(x_1)$, $a_2(x_1,x_2) = \{1 + \gamma A_1(x_1)\}a_2(x_2)$. (2.6)

Thus bivariate RHRs are locally proportional to the corresponding univariate RHRs.

To prove the converse let bivariate RHRs be locally proportional. With proportionality constants as $c_1(x_2)$ and $c_2(x_1)$ we write

$a_1(x_1,x_2) = c_1(x_2)a_1(x_1)$,

$a_2(x_1,x_2) = c_2(x_1)a_2(x_2)$.

Using the concept of line integration, two equivalent expressions of the underlying distribution function are obtained as

$$F(x_1,x_2) = exp\left\{-\int_{x_1}^{\infty} a_1(u,\infty)du - \int_{x_2}^{\infty} a_2(x_1,v)\,dv\right\}$$

$$F(x_1,x_2) = exp\{-c_1(\infty)A_1(x_1) - c_2(x_1)A_2(x_2)\} \quad (2.7)$$

And

$$F(x_1,x_2) = exp\left\{-\int_{x_1}^{\infty} a_1(u,x_2)du - \int_{x_2}^{\infty} a_2(\infty,v)\,dv\right\}$$

And

$$F(x_1,x_2) = exp\{-c_1(x_2)A_1(x_1) - c_2(\infty)A_1(x_2)\} \quad (2.8)$$

Comparing (2.7) and (2.8) we get for all $x_1,x_2(\geq 0)$

$c_1(\infty)A_1(x_1) + c_2(x_1)A_2(x_2) = c_1(x_2)A_1(x_1) + c_2(\infty)A_1(x_2)$ (2.9)

It may be observed from (2.9) that the left hand side is linear in $A_2(x_2)$. Hence the right hand side of (2.9) must be linear in $A_2(x_2)$. This implies that

$c_1(x_2) = \alpha + \gamma A_2(x_2)$ (2.10)

where $\alpha = c_1(\infty) = 1$ because $A_2(\infty) = 0$. Now, simplifying (2.8) by using (2.10) and using the fact that $c_2(\infty) = 1$, we have

$F(x_1,x_2) = exp\{-A_1(x_1) - A_2(x_2) - \gamma A_1(x_1)A_2(x_2)$ (2.11)

This may ensure (2.5).

It may be noted from the above result that the form of the characterized model given at (2.5) can be used for bivariate extension of univariate distributions retaining univariate structure of RHRs. Let us examine the set of values of γ for which (2.5) is a proper distribution function. The following results provides an answer to this problem by specifying the range of values for γ.

Theorem 2.2

The distribution function $F(x_1,x_2)$ defined through the CE Model at (2.5) is defined if and only if $0 \leq \gamma \leq 1$. The corresponding joint density function is given by

$f(x_1,x_2) = F_1(x_1)\,F_2(x_2)\,a_1(x_1)\,a_2(x_2)[\{1+\gamma A_2(x_2)\}\{1+\gamma A_1(x_1)\}-\gamma]\exp\{-\gamma(\log F_1(x_1))(\log F_2(x_2))\}$

Given theorem 1 and 2, it is easy to verify that (2.9) admits $F_i(x_i)$ as the distribution function of X_i i=1,2. Thus CE model is a suitable model for bivariate extension from univariate distribution. It may also be noted that $\gamma = 0$ implies independence under this model.

Regarding the specific applications of the CE model we consider bivariate generalization of inverse exponential distribution, which is of special importance in RHR analysis. This distribution function of an inverse exponential variable, X, is $F(x) = exp(-\gamma/x)$ so that {1/X} follows an exponential distribution. For two marginal inverse exponential distribution, we note that cumulative RHRs are (λ_1/x_1) and (λ_2/x_2). Then, from Theorem 1 we get the Bivariate Inverse Exponential Distribution as the following:

$$F(x_1,x_2) = \exp\left\{\frac{-\lambda_1}{x_1} - \frac{-\lambda_2}{x_2} - \gamma\frac{\lambda_1}{x_1}\frac{\lambda_2}{x_2}\right\} \quad (2.12)$$

Similarly, one may generalize the Inverse Rayleigh, Inverse Weibull distributions.

3. Application

3.1 Introduction

Ovarian steroids play important and diverse roles in physiological processes independent of their primary role in the reproductive function. For example, the importance of estradiol in the maintenance of optimal bone health [2], and the promotion of breast cancer tumorigenesis [11] has been established. Alterations in circulating steroids are believed to be important mediators of the impact that diet and exercise have on breast cancer risk [3,5] and bone density [6,13]. Menstrual disturbances and concomitant changes in circulating estradiol and progesterone occur with a greater frequency in exercising women than in non-exercising women [7]. However, the effects of physical stress of exercise per se are unlikely to explain these changes, as prospective studies that employed exercise training in the absence of weight loss have produced only mild disruptions of menstrual cyclicity [17]. In contrast, several laboratory-based studies which demonstrate that reductions in circulating ovarian steroids and gonadotrophins occur predominantly when exercise energy expenditure is higher than energy from food intake, illustrate the importance of negative energy balance in the suppression of reproductive hormones with exercise [12]. However, age-related changes have been suggested to alter the responsiveness of the reproductive axis to exercise perturbations. To date, no prospective studies have been performed in premenopausal women aged 25 –40 years to test the impact of exercise combined with caloric restriction on menstrual cyclicity. Prospective laboratory based studies are needed to test whether, and to what degree, older (>25 years) premenopausal women who are also gynecologically older than subjects in previous studies, are susceptible to the impact of lifestyle interventions on menstrual cyclicity. The purpose of this study was to test the hypothesis that moderate exercise training combined with caloric restriction would produce significant changes in menstrual cyclicity and ovarian steroids in premenopausal women aged 25 –40 years. A secondary goal was to describe the time course of changes in these factors and the magnitude of energy deficit associated with these changes.

3.2 Baseline

During baseline subjects completed a 3-day diet log during Days 1 – 7 and underwent testing to determine body weight, body composition, baseline energy needs (see Assessment of baseline energy needs and energy balance during the intervention) and aerobic capacity (see Assessment of baseline energy needs and energy balance during the intervention). Daily urine collections and menstrual calendars were collected, and subjects underwent serial blood sampling for the determination of serum estradiol, and testing for sex hormone binding globulin (SHBG).

3.3 Effects of the intervention on menstrual cyclicity

The effects of the intervention on menstrual cyclicity were found. No significant changes in the average menstrual cycle length, follicular phase length or luteal phase length

were observed in either the EX + CR or the LC groups. There was also no significant impact of the intervention in either group upon the incidence of menstrual disturbances of any type. The most frequent menstrual disturbance was the occurrence of a short (<10 days) luteal phase. There were two subjects during the baseline cycle that had short (<10 days) luteal phases (8%), and short luteal phases were observed in four subjects during intervention 1 (17%), two subjects during intervention 2 (8%), four subjects during intervention 3 (17%) and two subjects during intervention 4 (8%) in the EX + CR group. Only one subject out of 24 in the

EX + CR group experienced an anovulatory cycle in intervention 4 (4%) which was preceded by an inadequate luteal phase in intervention 3 (4%). No other anovulatory cycles were observed and no other inadequate luteal phases were observed in the EX + CR group. Oligomenorrheic cycles, defined as longer than 36 days, occurred very infrequently, with two subjects in the EX + CR group experiencing this disturbance in the intervention 4 cycle (8%).

In LC subjects, the most commonly observed menstrual disturbance was, again, the presence of short luteal phases. Short luteal phases were observed in one LC subject during baseline (11%), four subjects during intervention 1 (44%), three during intervention 2 (33%), three during intervention 3 (33%) and two during intervention 4 (22%). Inadequate luteal phases were observed in one LC subject during baseline (11%), one during intervention 1 (11%) and one subject during intervention 3 (11%). There were no anovulatory cycles observed in the LC group (0%) although there were three oligomenorrheic cycles, i.e., one during Intervention 1 (11%), one during Intervention 2 (11%), and one during Intervention 4 (11%). Overall, there are no differences in the incidence of any type of menstrual disturbance during any intervention cycle when the EX + CR and LC groups are compared with each other. In addition, there was no significant incidence of any type of menstrual disturbance across the intervention cycles when EX + CR and LC subjects were compared with the baseline.

3.4 Effects of the intervention and ovarian steroid exposure

In EX + CR subjects, urinary E1G AUC exhibited a progressive decline (time effect F= 4.110; P = 0.004) with a significant decline noted by intervention cycle 4 (Figure.3.1). Figure.4.3 illustrates a composite representation of E1G data for all EX + CR subjects during the baseline cycle and intervention cycles. An additional analysis of the change from baseline in E1G AUC during the luteal phase (defined as the day after the day of ovulation until the day before the next menses) revealed that the AUC during the luteal phase was largely responsible for the decline observed in the total cycle AUC (time effect F =3.445; P =0.012). A similar result was observed for estrogen AUC as calculated using serum 17-β estradiol. The total AUC (representing the entire menstrual cycle) calculated using the 10 serum samples for serum estradiol obtained during the baseline cycle and then during the intervention 4 cycle declined significantly from the baseline cycle to intervention 4 cycle (from 2596$\pm$144 to 2060$\pm$163 pg/ ml×day) (t = 3.194; P =0.004) in the EX + CR group. In the EX + CR group, the change in urinary E1G AUC was significantly correlated with the overall study energy deficit (R = 0.61; P = 0.003), but not correlated with the change in body weight. The latter correlation was also significant (R = 0.39; P = 0.037) when the LC group is included. Urinary PdG AUC across the menstrual cycle declined significantly over time in the EX + CR group (time effect F = 3.46; P = 0.011) from 160$\pm$15 ng/ml×day during the baseline cycle to 139$\pm$10 ng/ml×day during intervention cycle 4 (Figure. 3.3). In LC subjects no changes were observed in urinary E1G, serum 17-β estradiol or urinary PdG over time (Figure. 3.1). At baseline, BMI was negatively correlated with SHBG (R = 20.42; P = 0.020) when all the subjects were considered. Similarly, percent body fat was inversely correlated with SHBG (R = 20.40; P = 0.03). The intervention produced a biphasic response in SHBG such that concentrations in the EX + CR group significantly increased by intervention 2 and intervention 3 and then decreased somewhat by intervention 4 (time effect F = 3.921; P = 0.003).

Figure.3.1 shows the changes in SHBG in comparison with those in E1G and PdG AUC. In the EX + CR group, a significant increase in SHBG during intervention 2 preceded the significant decline in E1G observed at intervention 4. No changes in SHBG were noted in the LC group. The results of our study challenge the notion that reductions in ovarian steroid exposure in response to an exercise and diet intervention occur in association with significant disruptions in menstrual cyclicity. Our results suggest that modest disruptions in ovarian synthesis and/or secretion of estradiol can occur in the absence of significant disruptions in ovulation, significant suppression of folliculogenesis such that follicular length is increased, and without a significant impact on corpus luteum function as is usually indicated by a shortening of luteal phase length or inadequate luteal phases. The reductions in estrogen and progesterone exposure occurred in the absence of significant alterations in menstrual cycle, follicular or luteal phase length, and without severe disturbances in the menstrual cycle such as anovulation or oligomenorrhea. Our results, combined with other reports of associations between estradiol and body composition [9,18] in premenopausal women with normal cycle lengths, may suggest that menstrual disturbances represented by changes in cycle length are not a prerequisite for varying estradiol concentrations. As the mechanism for the observed reduction in estrogen exposure in the present investigation is unclear, our results underscore the need for more studies in peak reproductive aged women, including women older than our subjects, i.e. those entering the perimenopausal years, where comprehensive measures of estrogen exposure across the menstrual cycle in response to exercise and diet interventions are employed. The observed decline in estrogen exposure was associated with a transient increase in SHBG, suggesting that the bioavailability of estrogen was further reduced during that time. Others have reported higher SHBG in association with exercise alone or exercise combined with caloric restriction [1,15,13].

Medical Curves

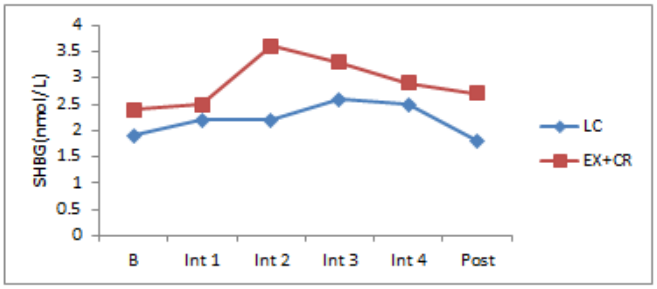

Figure 3.1. Effects of Ex+CR and Light Conditioning for each cycle in all subjects across the intervention.

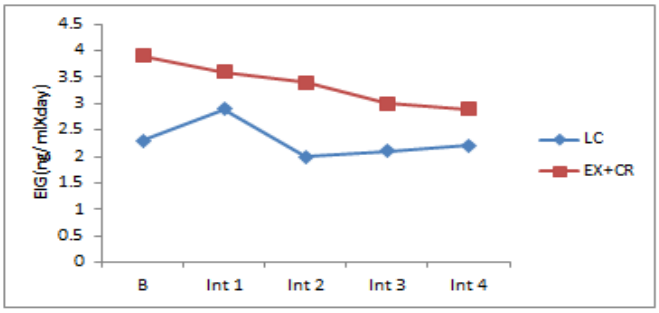

Figure 3.2. Effects of Ex+CR and Light Conditioning for each cycle in all subjects across the intervention.

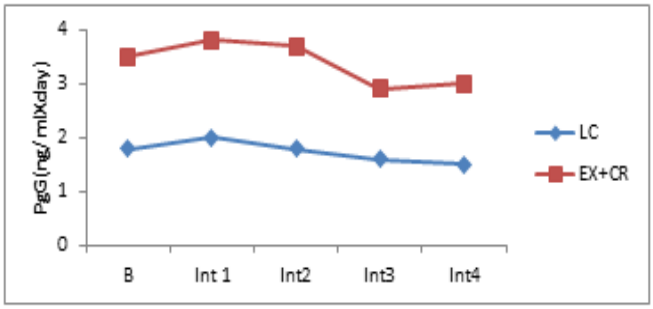

Figure 3.3 Effects of Ex+CR andLightConditioning for each cycle in all subjects across the intervention.

Hepatic production of SHBG is regulated by many factors including but not limited to insulin, thyroid hormone, sex steroids and dietary factors. As insulin has been shown to inhibit SHBG synthesis [14], it is possible that the observed increase in SHBG in our study was secondary to a decline in circulating insulin.

4. Mathematical Curves

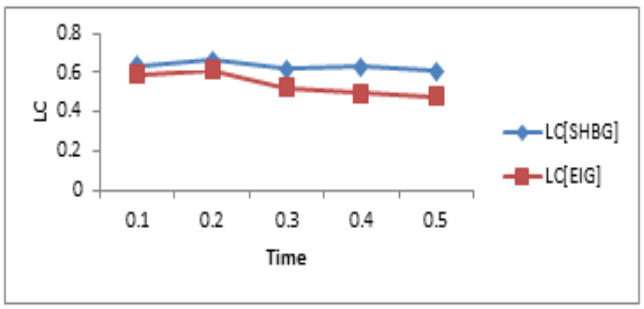

Fig 4.1. Combined graphs of SHBGS ,EIG and PdG.

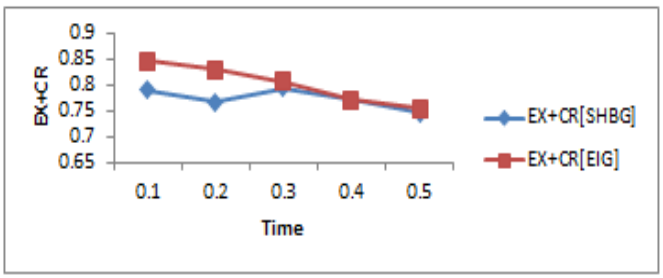

Fig 4.2. Combined Effects of SHBG, EIG and PdG.

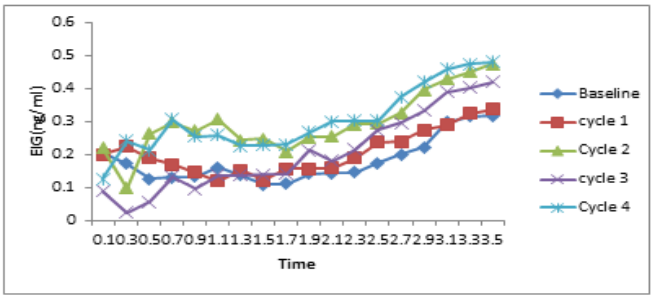

Figure 4.3. Effects of Exercise Training on EIG during Baseline and Intervention Cycles.

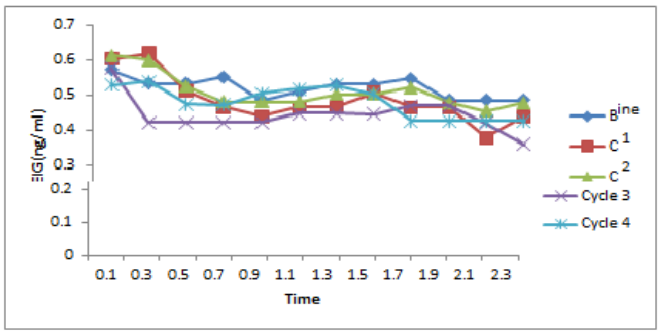

Figure 4.4. Effects of Caloric Restriction on EIG during Baseline and Intervention Cycles.

4. Conclusion

In conclusion, the results of this study suggest that a moderate aerobic exercise training program combined with modest weight loss in accordance with recommended guidelines produces significant reductions in ovarian steroid exposure without disrupting menstrual cyclicity in premenopausal women of advanced gynecological age. A combined mathematical curves [Figure 4.1] of LC for SHBG, EIG and PdG was done and found that the curves are monotonically decreasing function. Also a combined mathematical curves [Figure 4.2] of EX+CR for SHBG, EIG and PdG was done and found a drastic decreasing curves. This shows that the effects of exercise training and caloric restriction(EX+CR) and light conditioning (LC) on SHBG, AUC and PdG for each cycle was monotonically decreasing. The mathematical curves in Figure 4.3 shows that the exercise training has monotonically increasing effect and in Figure 4.4 shows that the caloric restrictions on EIG AUC in all the intervention cycles and the baseline has a monotonically decreasing effect. Thus the CE model has many advantages over the standard model available in the literature.

In Medical conclusion, the results of the study suggest that a moderate aerobic exercise training program combined with modest weight loss in accordance with recommended guidelines produces significant reductions in ovarian steroid exposure without disrupting menstrual cyclicity in premenopausal women of advanced gynecological age. These results are obtained from our Mathematical curves along with time. Although larger studies using more precise measures of energy balance are required to confirm this finding, in future studies the change in estrogen exposure may be more related to daily fluctuations in energy balance than longer term changes in body weight or body fat.

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