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Comparison of Hormonal Variations Using Mathematical Trivariate Normal Distribution under Placebo and Progesterone Treatments

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Abstract : *The problem of generating Trivariate Normal Distributions from univariate ones is drawing the attention of the reliability analyst. Amongst these approaches the characterisation approach and the modelling approach are very appealing. Infact the characterisation approach is of great interest to both theoreticians and applied workers. Here we have used a Trivariate Normal Distribution for application by extending univariate distribution through characterisation approach. In our application part we have considered post-menopausal women. We have concentrated on a 24 hr profile of Melatonin, TSH , and GH under the treatment with Placebo and with Progesterone. In this respect we have developed a mathematical model which describes the purpose of the present study. The study investigates in post-menopausal women, the effects of a 24-hr profile of progesterone and placebo administration both on sleep architecture and on multiple hormones profile. The protocol allows us to explore the effects of the placebo and progesterone treatment on combined effects of hormones.*

Keywords - *Trivariate Normal Distributions, Melatonin, TSH , GH.*

I. Introduction

Melatonin:

Melatonin is a form of a hormone produced in the brain that helps regulates your sleep and wake cycles. Melatonin is also very effective in treating jet lag, high blood pressure, tumors, low blood platelets, insomnia caused by withdrawal from drug addiction, or anxiety caused by surgery. Melatonin is also known to cure infertility, to control sleep problems caused by shift work, or to enhance athletic performance. Scientists are also looking at other good uses for melatonin, such as,

- Treating seasonal affective disorder (SAD).
- Helping to control sleep patterns for people who work night shifts.[1]
- Preventing or reducing problems with sleeping and confusion after surgery.

GH:

Growth Hormone is a peptide hormone that stimulates growth, development and regeneration. This hormone is made up of amino acids that form a long, single-chain polypeptide. Growth Hormone is organized in the somatotropic cells, which are found in the anterior pituitary gland. These cells are also responsible for storing and releasing the hormone. Growth Hormone is used widely in medicine to help treat growth disorders in children and Growth Hormone deficiency in adults. Growth Hormone encourages growth and development in children and adolescents. It is also responsible to regulate the body fluids, sugar and fat metabolism and maybe even heart function.[3]

TSH:

The thyroid gland helps to perform many important functions in your body, including metabolism. It is managed by the Thyroid-Stimulating Hormone (TSH). A TSH test counts the amount of TSH in your blood. Any doctor may suggest the test if you are showing symptoms of a thyroid disorder. The results of a TSH test can confirm a diagnosis and help your doctor determine an better treatment plan for a certain condition. A thyroid-stimulating hormone (TSH) test counts the amount of TSH in the blood. TSH is produced by the pituitary gland, which is located at the base of your brain.[5]

II. Methods & Results

SUBJECTS:

Postmenopausal women, aged 48–74 yr (mean 57.4 yr), were selected after a careful clinical and biological evaluation. Investigations were performed after natural menopause. Mean age at menopause was

49.4 yr (range, 41–57 yr). The Subjects involved were such that they had never undergone any hormonal therapy. Their body weight was in the normal range for all (body mass index 22.1). In all subjects, Estradiol plasma levels were also normal. FSH plasma levels were under average values. Smokers, shift workers, subjects who had travelled across time zones during the last 2 months, individuals with personal history of drug abuse or with personal or family history of many types of disorders which are highlightened and subjects with current vasomotor symptoms, dieting, or intensive physical exercise were excluded from the study. Each volunteer was examined by one of the authors and had to answer a questionnaire of specific questions concerning her sleep habits. To be included in the study, volunteers had to comply with the following requirements: regular sleep schedules (i.e they sleep from 10 to 12 and 6 to 8), no difficulty to fall asleep, no complaints of awakenings during the sleep period, no snoring, no periodic limb movements, and no daytime fatigue and sleepiness. Written informed consent was obtained from all volunteers.[11][14]

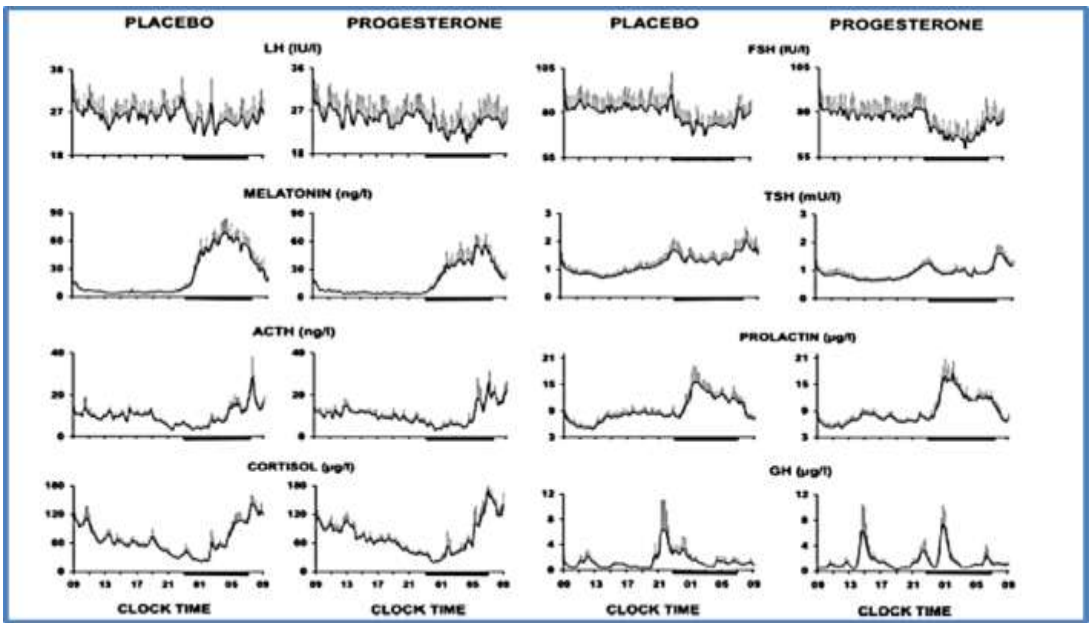

Fig 1:Mean (+ SEM; n = 8, except for Melatonin: n = 6, and for Prolactin: n = 7) 24-hr profiles of Plasma LH,

FSH, Melatonin, ACTH, Cortisol, TSH, Prolactin, and GH under Placebo and Progesterone Treatment. Black bars indicate scheduled Sleep Periods.

Classic postmenopausal gonadotropins profiles were observed in both conditions. Mean 24-h LH levels, pulse frequency, duration, and amplitude were similar in both conditions. Each type of values under progesterone correlated positively with corresponding values under placebo for pulse frequency, duration, and amplitude. Mean 24-h FSH levels were slightly but significantly lower under progesterone than under placebo. FSH pulse characteristics were similar in both conditions.

- Findings from Placebo and Progesterone Treatment: Reference Fig. 1
  - Melatonin:

Melatonin profiles were obtained in six subjects. In both conditions, classic profiles with stable, low daytime values, an evening circadian rise, and a return to low values in the morning were observed. The 24-h levels and the timings of onset and offset of the circadian rise in both conditions were not significantly different from each other. However, over the24 hr period profile, melatonin levels were decreased by more than 40%, compared with placebo (P _ 0.03).

  - TSH:

In both conditions, TSH concentrations followed the expected pattern, with relatively constant daytime levels, followed by an early evening circadian rise, a nocturnal decrease, and a transient rebound after final morning awakening. The timings of the onset of the circadian rise and of the peak were similar in both conditions. However, TSH concentrations were 25–30% lower under progesterone than under placebo over the 1500–2300 h and 2300– 0700 h periods (P _ 0.05), resulting in a mean 24% decrease over the 24-h period (P _ 0.07). [18]

- GH:

Daytime GH secretion was similar in both conditions. In contrast, night time GH secretion was 50% higher under progesterone than under placebo (P _ 0.05). A trend for an increase in IGF-I values was detectable (P _ 0.09).[12][18]

Mathematical Model

- Mathematical Model for Trivariate Normal Distribution
- The Multivariate Normal Distribution

The moment-generating function defined byX1,...,Xn[also called the moment-generating function of the random vector (X1,... ,Xn)] is defined by

$M(t_1,\dots,t_n) = E[\exp(t_1X_1 + \cdots + t_nX_n)]$.

Just as in the one-dimensional case, the moment-generating function determines the density uniquely. The random variables X1,... ,Xn are said to have the multivariate normal distribution or to be jointly Gaussian (we also say that the random vector (X1,... ,Xn) is Gaussian) if

$$M(t_1,\dots,t_n) = \exp(t_1\mu_1 + \cdots + t_n\mu_n)\exp\left(\frac{1}{2}\sum_{i,j=1}^{n} t_i a_{ij} t_j\right)$$

where the tiandμj are arbitrary real numbers, and the matrix A is symmetric and positive definite. [6]

Let us indicate the notational scheme we will be using. Vectors will be written with an underbar, and are assumed to be column vectors unless otherwise specified. If a column vector say t with defined componentst1,... ,tn, then to save space we write t =(t1,... ,tn)'. The row vector with these components is the transpose of t, written t'. The moment-generating function of jointly Gaussian random variables has the form

$$M(t_1,\dots,t_n) = \exp(\underline{t}'\underline{\mu})\exp\left(\frac{1}{2}\underline{t}'A\underline{t}\right).$$

Theorem

Joint Gaussian random variables arise from non singular linear transformations on independent normal random variables. [7]

Proof. Let X1,... ,Xn be independent, with Xi normal (0,λi), and let X =(X1,... ,Xn)'. Let Y= BX+μwhere B is nonsingular. Then YisGaussian, as can be seen by computing the moment-generating function of Y:

MY(t) = E[exp(t'Y)] = E[exp(t'BX)] exp(t'μ).

But

$$E[\exp(\underline{u}'\underline{X})] = \prod_{i=1}^{n} E[\exp(u_iX_i)] = \exp\left(\sum_{i=1}^{n}\lambda_i u_i^2/2\right) = \exp\left(\frac{1}{2}\underline{u}'D\underline{u}\right)$$

whereD is a diagonal matrix with λi' s down the main diagonal. Set u= B't,u'= t'B; then

$$M_{\underline{Y}}(\underline{t}) = \exp(\underline{t}'\underline{\mu})\exp\left(\frac{1}{2}\underline{t}'BDB'\underline{t}\right)$$

andBDB'is symmetric since D is symmetric. Since t'BDB't= u'Du, which is greater than 0 except when u= 0(equivalently when t= 0because B is nonsingular), BDB'is positive definite, and consequently Yis Gaussian.

On the otherhand,if the moment-generating function of Y is exp(t'μ) exp[(1/2)t'At)] where A is symmetric and positive definite. Let L be an orthogonal matrix such that L'AL = D, where D is the diagonal matrix of eigenvalues of A. Set X= L(Y− μ), so that Y= μ+ LX. The moment-generating function of Xis

E[exp(t' X)] = exp(−t'μ)E[exp(t'L'Y)]

The last term is the moment-generating function of Ywitht'replaced by t'L', or equivalently, treplaced by Lt. Thus the moment-generating function of Xbecomes

$$\exp(-\underline{t}'L'\underline{\mu})\exp(\underline{t}'L'\underline{\mu})\exp\left(\frac{1}{2}\underline{t}'L'AL\underline{t}\right)$$

$$\exp\left(\frac{1}{2}\underline{t}'D\underline{t}\right) = \exp\left(\frac{1}{2}\sum_{i=1}^{n}\lambda_i t_i^2\right).$$

Therefore the Xi are independent, with Xi normal (0,λi). [8]

A Geometric Interpretation:

Assume for simplicity that the random variables Xi have zero mean. If E(U) = E(V) =0 then the covariance of U and V is E (UV), which can be regarded as an inner product. Then Y1 −μ1,... ,Yn − μn span an n-dimensional space, and X1,...,Xn is an orthogonal basis for that space. Oorthogonality is equivalent to independence. (Orthogonality means that the Xi are uncorrelated, i.e., E(XiXj) = 0 for I = j

Theorem:

Let Y = μ + LXand let A be the symmetric, positive definite matrix appearing in the moment-generating function of the Gaussian random vector Y . Then E(Yi)= μi for all i, and furthermore, A is the covariance matrix of the Yi, in other words, aij =Cov(Yi,Yj) (and aii =Cov(Yi,Yi)=VarYi).[6][9]

It follows that the means of the Yi and their covariance matrix determine the moment-generating function, and therefore the density.[8][10]

Proof. Since the Xihave zero mean, we have E(Yi)= μi. Let K be the covariance matrix of the Yi. Then K can be written in the following peculiar way:

$$K = E\left\{ \begin{bmatrix} Y_1 - \mu_1 \\ \vdots \\ Y_n - \mu_n \end{bmatrix} (Y_1 - \mu_1, \dots, Y_n - \mu_n) \right\}.$$

Note that if a matrix M is n by 1 and a matrix N is1by n, then MN is n by n. In this case, the ij entry is E[(Yi −μi)(Yj −μj)] = Cov (Yi,Yj). Thus

$$K = E[(\underline{Y} - \underline{\mu})(\underline{Y} - \underline{\mu})'] = E(L\underline{X}\underline{X}'L') = LE(\underline{X}\underline{X}')L'$$

since expectation is linear. [For example, E(MX)= ME(X) because E(∑j mijXj) = ∑j mijE(Xj).]. But E(XX') is the covariance matrix of the Xi, which is D. Therefore K = LDL'= A (because L'AL= D).

Finding The Density:

From Y= μ+LXwe can calculate the density of Y. The Jacobian of the transformation from XtoYisdetL= ±1, and

$$f_{\underline{X}}(x_1, \dots, x_n) = \frac{1}{(\sqrt{2\pi})^n} \frac{1}{\sqrt{\lambda_1 \cdots \lambda_n}} \exp\left(- \sum_{i=1}^{n} x_i^2 / 2\lambda_i \right).$$

We have $\lambda_1 \cdots \lambda_n = \det D = \det K$ because $\det L = \det L' = \pm 1$. Thus

$$f_{\underline{X}}(x_1, \dots, x_n) = \left| \frac{1}{(\sqrt{2\pi})^n \sqrt{\det K}} \exp\left(- \frac{1}{2} \underline{x}' D^{-1} \underline{x} \right) \right.$$

But $\underline{y} = \underline{\mu} + L\underline{x}$, $\underline{x} = L'(\underline{y} - \underline{\mu})$, $\underline{x}' D^{-1} \underline{x} = (\underline{y} - \underline{\mu})' L D^{-1} L' (\underline{y} - \underline{\mu})$, and $K = LDL'$, $K^{-1} = LD^{-1}L'$. The density of $\underline{Y}$ is

$$f_{\underline{Y}}(y_1, \dots, y_n) = \frac{1}{(\sqrt{2\pi})^n \sqrt{\det K}} \exp\left[- \frac{1}{2} (\underline{y} - \underline{\mu})' K^{-1} (\underline{y} - \underline{\mu}) \right].$$

Individually Gaussian Versus Jointly Gaussian

If X1,... ,Xn are jointly Gaussian, then each Xi is normally distributed , but not conversely. For example, let X be normal (0,1) and flip an unbiased coin. If the coin shows head then, set Y = X, and if the coin shows tail, set Y = −X. Then Y is also normal (0,1) since

P{Y ≤y}=1/2 *P{X ≤y}+ ½ *P{−X ≤y}= P{X ≤y}

because −X is also normal (0,1). Thus FX = FY . But with probability 1/2, X+Y =2X, and with probability 1/2, X+ Y = 0. Therefore P{X+ Y =0}=1/2. If X and Y were jointly Gaussian, then X+ Y would be normal. We conclude that X and Y are individually Gaussian but not jointly Gaussian. [7]

Theorem:

If X1,...,Xn are jointly Gaussian and uncorrelated (Cov (Xi,Xj) = 0 for all i=j), then the Xi are independent.

Proof. The moment-generating function of X =(X1,... ,Xn) is

MX(t) = exp(t'μ) exp (1/2 t'Kt)

whereK is a diagonal matrix with entries σ12,σ22,... ,σ2down the main diagonal, and 0's elsewhere. Thus

$$M_{\underline{X}}(\underline{t}) = \prod_{i=1}^{n} \exp(t_i \mu_i) \exp\left(\frac{1}{2} \sigma_i^2 t_i^2\right)$$

which is the joint moment-generating function of independent random variables X1,... ,Xn, wheeXiis normal (μi,σ2).

Conditional Density:

Let X1,... ,Xn be jointly Gaussian. We find the conditional density of Xn given X1,... ,X_{n-1}:

$$f(x_n|x_1,\dots,x_{n-1}) = \frac{f(x_1,\dots,x_n)}{f(x_1,\dots,x_{n-1})}$$

with

$$f(x_1,\dots,x_n) = (2\pi)^{-n/2}(\det K)^{-1/2}\exp\Big[-\frac{1}{2}\sum_{i,j=1}^{n} y_i q_{ij} y_j\Big]$$

where $Q = K^{-1} = [q_{ij}]$, $y_i = x_i - \mu_i$. Also,

$$f(x_1,\dots,x_{n-1}) = \int_{-\infty}^{\infty} f(x_1,\dots,x_{n-1},x_n)\,dx_n = B(y_1,\dots,y_{n-1}).$$

Now

$$\sum_{i,j=1}^{n} y_i q_{ij} y_j = \sum_{i,j=1}^{n-1} y_i q_{ij} y_j + y_n \sum_{j=1}^{n-1} q_{nj} y_j + y_n \sum_{i=1}^{n-1} q_{in} y_i + q_{nn} y_n^2.$$

withC =(1/2)qnn,D =∑ j=1 qnjyj =∑ i=1 qinyi since Q= K−1 is symmetric. The conditional density may now be expressed as [15]

$$\frac{A(y_1,\dots,y_{n-1})}{B(y_1,\dots,y_{n-1})}\exp[-(Cy_n^2 + D(y_1,\dots,y_{n-1})y_n]$$

We conclude that
givenX1,... ,Xn−1,Xn is normal.

The conditional variance of Xn (the same as the conditional variance of Yn = Xn −μn) is [16]

$$\frac{1}{2C} = \frac{1}{q_{nn}} \quad \text{because} \quad \frac{1}{-\sigma^2} = C, \sigma^2 = \frac{1}{2C}.$$

Thus

$$\boxed{\mathrm{Var}(X_n|X_1,\dots,X_{n-1}) = \frac{1}{q_{nn}}}$$

and the conditional mean of Yn is

$$-\frac{D}{2C} = -\frac{1}{q_{nn}}\sum_{j=1}^{n-1} q_{nj} Y_j$$

So the conditional mean of Xnis[17]

$$\boxed{E(X_n|X_1,\dots,X_{n-1}) = \mu_n - \frac{1}{q_{nn}}\sum_{j=1}^{n-1} q_{nj}(X_j - \mu_j).}$$

E(Y|X) is the best estimate of Y based on X, in the sense that the mean square error is minimized. In the joint Gaussian case, the best estimate of Xn based on X1,... ,Xn−1 is linear, and it follows that the best linear estimate is in fact the best overall estimate. This has important practical applications, since linear systems are usually much easier than nonlinear systems to implement and analyse. A multivariate normal distribution in three variables. It has probability density function,

$$P(x_1, x_2, x_3) = \frac{e^{-w/\left[2\left(\rho_{12}^2+\rho_{13}^2+\rho_{23}^2-2\,\rho_{12}\,\rho_{13}\,\rho_{23}-1\right)\right]}}{2\sqrt{2}\,\pi^{3/2}\sqrt{1-\left(\rho_{12}^2+\rho_{13}^2+\rho_{23}^2\right)+2\,\rho_{12}\,\rho_{13}\,\rho_{23}}},$$

Where

$$w = x_1^2\left(\rho_{23}^2-1\right)+x_2^2\left(\rho_{13}^2-1\right)+x_3^2\left(\rho_{12}^2-1\right)+$$
$$2\left[x_1 x_2\left(\rho_{12}-\rho_{13}\,\rho_{23}\right)+x_1 x_3\left(\rho_{13}-\rho_{12}\,\rho_{23}\right)+x_2 x_3\left(\rho_{23}-\rho_{12}\,\rho_{13}\right)\right].$$

The standardized trivariate normal distribution takes unit variances. The quadrant probability in this special case is then given analytically by

$$P(x_1 \le 0, x_2 \le 0, x_3 \le 0)$$
$$= \int_{-\infty}^{0}\int_{-\infty}^{0}\int_{-\infty}^{0} P(x_1, x_2, x_3)\,dx_1\,dx_2\,dx_3$$
$$= \frac{1}{8} + \frac{1}{4\pi}\left(\sin^{-1}\rho_{12} + \sin^{-1}\rho_{13} + \sin^{-1}\rho_{23}\right)$$

III. Mathematical Results

- **COMPARISON OF COMBINED EFFECTS ON HORMONES WITH PLACEBO & PROGESTERONE TREATMENT**

For different values of shape and Scale parameters we have the following figures for the application part.

- **Melatonin, GH, TSH**

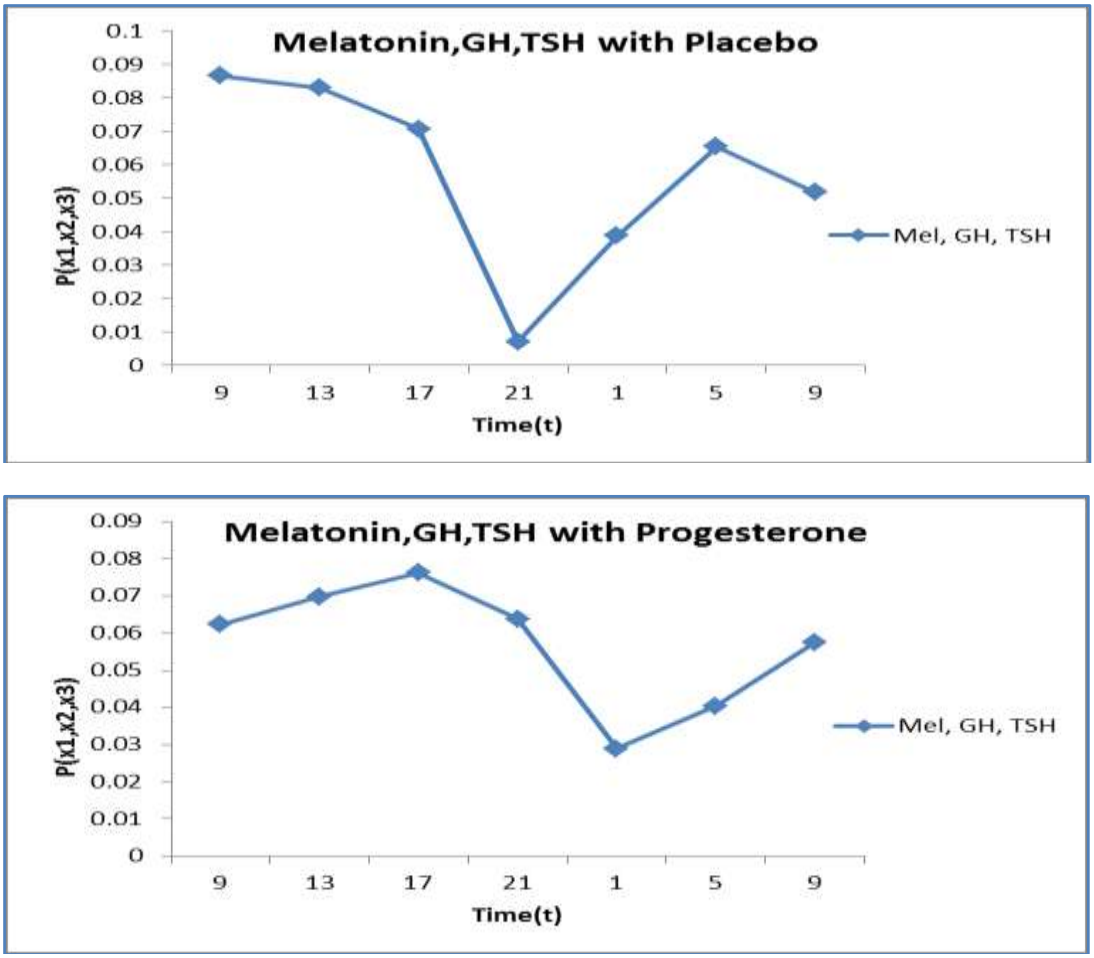

Fig A: The function P(Melatonin, GH, TSH) varing with Time (t)

IV. Conclusion

- **Mathematical Conclusion**

We have shown the comparison of characterizing hormones with respect to Placebo and Progesterone treatments. The following observations are made:

- **Figure A :**The function P(Melatonin, GH, TSH) varying with Time (t)

In Both Treatments,Melatonin,GH,TSH concentrations followed the desired way,with relatively constant daytime levels followed by an early nocturnalrise in the concentration levels. The timings in the rise of the nocturnal peak showed avary of three hours more in the progesterone treatment. Thus showing progesterone treatment more effective in the case of combined effects of the hormones in a 24-hr time profile for classic post-menopausal subjects. The Function P(x1,x2,x3) representing the levels of concentrations of Melatonin,GH,TSH shows a hike in the Progesterone treatment as compared to the Placebo one thus giving a good conclusion to the medical professionals.

In this direction we have developed a Trivariate Mathematical Normal Distribution Model to analyse a data set of various hormones and compare the combined effects of the hormones in a 24 hr. time profile under Placebo and Progesterone treatments. Here the model concludes that the level of concentrations of respective hormones shows a hike in the Progesterone treatment as compared to the Placebo Treatment. Thus giving a good conclusion to the Medical Professionals.

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