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A BIVARIATE GENERALIZED EXPONENTIAL MODEL FOR THE EFFECT OF ADMINISTRATION OF HUMAN CHORIONIC GONADOTROPHIN ON NORMAL AND LOW PROGESTRONE GROUPS OF WOMEN

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ABSTRACT

Suppose a system has two components. Each component is subject to individual independent stress say U_1 and U_2 respectively. The system has an overall stress U_3 which has been transmitted to both the components equally, independent of their individual stresses. Therefore, the observed stress at the two components are $X_1=max\{U_1,U_3\}$ and $X_2=max\{U_2,U_3\}$ respectively. Suppose a system has two components and it is assumed that each component has been maintained independently and also there is an overall maintenance. The study in the application part, Luteal phase defect is the best characterized by a defective corpus luteum with insufficient progesterone production. An adequate production of progesterone is dependent on a functioning hypothalamic-pituitary-ovarian axis. In theory, the derangement at any sites of this axis, therefore, may cause luteal phase defect. Based on previously postulated notion of luteal phase stemming from the derangement of follicular growth during the preceding luteal phase, it is postulated that malfunctioning corpus luteum is not normalized by exogenously administrated HCG. To address this issue, investigation was made whether HCG, when given at mid-luteal phase, actually stimulates the progesterone production in women with varying degrees of corpus luteum function. In the mathematical model if (X_1, X_2) ~ BVGE $(\alpha_1, \alpha_2, \alpha_3)$, then the joint probability function of (X_1, X_2) for $x_1>0$, $x_2>0$ is obtained for the LH and FSH variables. Here the mathematical figures concludes that the combined effect of LH and FSH in both the groups after the administration of HCG decreases monotonically and continuously after one hour of administration of HCG. This is same as the medical conclusion that similar suppression of LH concentrations in both groups after HCG administration reduces the likelihood of difference in bio availability of HCG used in this study.

Keywords: *Bivariate Generalized Exponential Distribution, Luteinizing Hormone, Follicle Stimulating Hormone, Human Chorionic Gonadotrophin, Progestrone, Oestrogen.*

AMS classification: *62HXX, 60EXX.*

1. Mathematical model:

Bivariate generalized exponential distribution:

The univariate GE distribution has the following cumulative distribution function (CDF) and probability density function (PDF) respectively for x>0;

$F_{GE}(x; \alpha, \lambda) = (1-e^{-\lambda x})^{\alpha}$, $f_{GE}(x; \alpha, \lambda) = \alpha\lambda e^{-\lambda x}(1-e^{-\lambda x})^{\alpha-1}$

Here $\alpha > 0$, $\lambda > 0$ are the shape and scale parameters respectively. It is clear that for $\alpha = 1$, it coincides with the exponential distribution [1]. From now on a GE distribution with the shape parameter α and the scale parameter λ will be denoted by GE (α, λ). For brevity when $\lambda=1$, we will denote it by GE (α) and for $\alpha=1$, it will be denoted by Exp (λ) [3]. From now unless otherwise mentioned it is assumed that $\alpha_1>0$, $\alpha_2>0$, $\alpha_3>0$, $\lambda>0$. Suppose $U_1 \sim$ GE (α_1, λ), $U_2 \sim$ GE (α_1, λ) and $U_3 \sim$ GE (α_1, λ) and they are mutually independent. Here '~' means follows or has the distribution. Now define $X_1=\max\{U_1,U_3\}$ and $X_2=\max\{U_2,U_3\}$. Then we say that the bivariate vectors (X_1, X_2) has a bivariate generalized exponential distribution with the shape parameters α_1, α_2 and α_3, and scale parameter λ [4]. We will denote it by BVGE (α_1, α_2, α_3, λ). Now for the rest of the discussion for brevity, we assume that $\lambda=1$, although the results are true for general λ also. The BVGE distribution with $\lambda=1$ will be denoted by BVGE (α_1, α_2, α_3). Before providing the joint CDF or the PDF, we first mention how it may occur in practice [6,8]

Suppose a system has two components. Each component is subject to individual independent stress say U_1 and U_2 respectively. The system has an overall stress U_3 which has been transmitted to both the components equally, independent of their individual stresses. Therefore, the observed stress at the two components are $X_1=\max\{U_1,U_3\}$ and $X_2=\max\{U_2,U_3\}$ respectively.

Suppose a system has two components and it is assumed that each component has been maintained independently and also there is an overall maintenance. Due to component maintenance, suppose the life time of the individual is increased by U_i amount and because of the overall maintenance the life time of each component is increased by U_3 amount. Therefore the increased life time of the two components are $X_1=\max\{U_1,U_3\}$ and $X_2=\max\{U_2,U_3\}$ respectively.

The following results will provide the joint CDF, joint PDF and conditional PDF.
Theorem 1.1:

If (X_1, X_2) ~ BVGE (α_1, α_2, α_3) then the joint CDF of (X_1, X_2) for $x_1 > 0$, $x_2 > 0$ is
$F_{X_1X_2}(x_1, x_2) = (1-e^{-x_1})^{\alpha_1}(1-e^{-x_2})^{\alpha_2}(1-e^{-Z})^{\alpha_3}$ where $Z=\min\{x_1,x_2\}$.

Corollary 1.1:
The joint CDF of the BVGE (α_1, α_2, α_3) can also be written as

$F_{X_1X_2}(x_1, x_2) = F_{GE}(x_1;\alpha_1) F_{GE}(x_2;\alpha_2) F_{GE}(z;\alpha_3)$

$= F_{GE}(x_1;\alpha_1 + \alpha_3)\, F_{GE}(x_2;\alpha_2)$ if $x_1 < x_2$

$= F_{GE}(x_1;\alpha_1)\, F_{GE}(x_2;\alpha_2 + \alpha_3)$ if $x_2 < x_1$

$= F_{GE}(x;\alpha_1 + \alpha_2 + \alpha_3)$ if $x_1 = x_2 = x$

Theorem 1.2

If (X_1, X_2) ~ BVGE $(\alpha_1, \alpha_2, \alpha_3)$ then the joint PDF of (X_1, X_2) for $x_1 > 0, x_2 > 0$ is

$f_{X1,X2}(x_1, x_2) = f_1(x_1,x_2)$ if $0 < x_1 < x_2 < \infty$

$= f_2(x_1,x_2)$ if $0 < x_2 < x_1 < \infty$

$= f_0(x)$ if $0 < x_1 = x_2 < \infty$

where $f_1(x_1,x_2) = f_{GE}(x_1;\alpha_1 + \alpha_3)\, f_{GE}(x_2;\alpha_2)$

$= (\alpha_1 + \alpha_3)\, \alpha_2\, (1-e^{-x_1})^{\alpha_1+\alpha_3-1}(1-e^{-x_2})^{\alpha_2-1}\, e^{-x_1-x_2}$

$f_2(x_1,x_2) = f_{GE}(x_2;\alpha_2 + \alpha_3)\, f_{GE}(x_2;\alpha_1)$

$= (\alpha_2 + \alpha_3)\, \alpha_1\, (1-e^{-x_2})^{\alpha_2+\alpha_3-1}(1-e^{-x_1})^{\alpha_1-1}\, e^{x_1-x_2}$

$f_0(x) = \frac{\alpha_3}{\alpha_1+\alpha_2+\alpha_3} f_{GE}(x;\alpha_1 + \alpha_2 + \alpha_3)$

$= \alpha_3\, (1-e^{-x})^{\alpha_1+\alpha_2+\alpha_3-1}\, e^{-x}$

Proof:

The expression for $f_1(.,..)$ and $f_2(.,..)$ can be obtained simply by taking $\frac{\partial^2 F_{X_1,X_2}(x_1,x_2)}{\partial x_1 \partial x_2}$ for $x_1 < x_2$ and $x_2 < x_1$ respectively.

But $f_0(.,.)$ cannot be obtained in the same way. Using the fact that

$$\int_0^\infty \int_0^{x_2} f_1(x_1,x_2)\, dx_1 dx_2 + \int_0^\infty \int_0^{x_1} f_2(x_1,x_2)\, dx_2 dx_1 + \int_0^\infty f_0(x)\, dx = 1$$

$$\int_0^\infty \int_0^{x_2} f_1(x_1,x_2)\, dx_1 dx_2 = \alpha_2 \int_0^\infty (1-e^{-x})^{\alpha_1+\alpha_2+\alpha_3} e^{-x} dx$$

$$\int_0^\infty \int_0^{x_1} f_2(x_1,x_2)\, dx_2 dx_1 = \alpha_1 \int_0^\infty (1-e^{-x})^{\alpha_1+\alpha_2+\alpha_3} e^{-x} dx$$

$$\int_0^\infty f_0(x)\, dx = \alpha_3 \int_0^\infty (1-e^{-x})^{\alpha_1+\alpha_2+\alpha_3} e^{-x} dx = \frac{\alpha_3}{\alpha_1+\alpha_2+\alpha_3}$$

Therefore the results follows:

2. Application

Introduction

Luteal phase defect is the best characterized by a defective corpus luteum with insufficient progesterone production. An adequate production of progesterone is dependent on a functioning hypothalamic-pituitary-ovarian axis. In theory, the derangement at any sites of this axis, therefore, may cause luteal phase defect.

The corpus luteum is anatomically derived from the post ovulatory follicle. Thus, the events prior to ovulation may be responsible for the malfunctioning of the corpus luteum. Consistent with this idea is the evidence we have provided that luteal phase defeat is associated with impaired follicular growth and/or abnormal LH surge, suggesting that luteal phase defeat is not a disease occurring after the formation of the corpus luteum, but a disorder consequent upon the derangement of the hypothalamic-pituitary-ovarian axis during the luteal phase [2]

Based on previously postulated notion of luteal phase stemming from the derangement of follicular growth during the preceding luteal phase, it is postulated that malfunctioning corpus luteum is not normalized by exogenously administrated HCG. To address this issue, investigation was made whether HCG, when given at mid-luteal phase, actually stimulates the progesterone production in women with varying degrees of corpus luteum function.

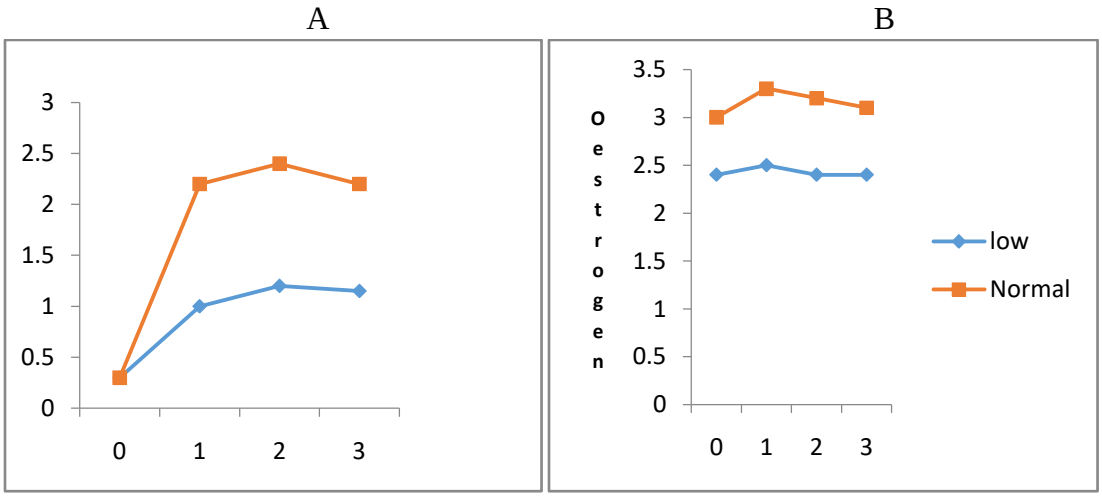


Figure A: The response of progesterone concentrated after human chorionic gonadotrophin (HCG) injection in normal progesterone group and low progesterone group. The mean percentage charge in progesterone concentration from the initial concentration in normal progesterone and low progesterone groups are shown in the Figure A. Blood samples were taken before and 1,2 and 3 h after HCG (5000 IU i.m.) . Serum progesterone concentrations were measured with AxSYM.

Figure B: The concentrations of oestradiol after human chorionic gonadotrophin(HCG) injection in normal progesterone and low progesterone and low progesterone groups. Blood samples were taken before and 1,2 and 3 h after HCG (5000 IU i.m.). Serum oestrodiol concentrations were measured with AxSYM..

C D

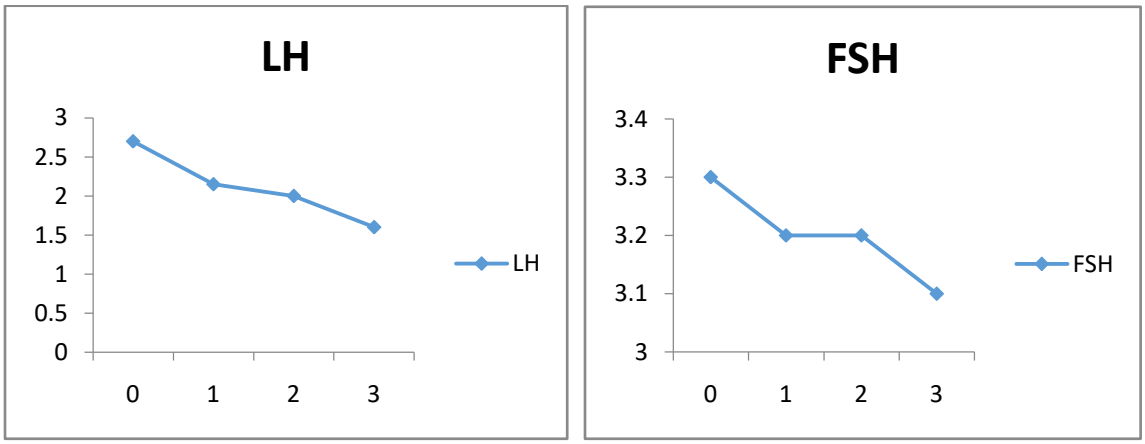


Figure C & D: The serum luteinizing hormone (LH)(panel A) and follicle stimulating hormone (FSH)(panel B) concentration after human chorionic gonadotrophin (HCG) injection. Blood samples were taken before and 1, 2 and 3 h after HCG (5000 IU i.m.). Serum LH and FSH concentrations were measured with AxSYM.

3. Discussion

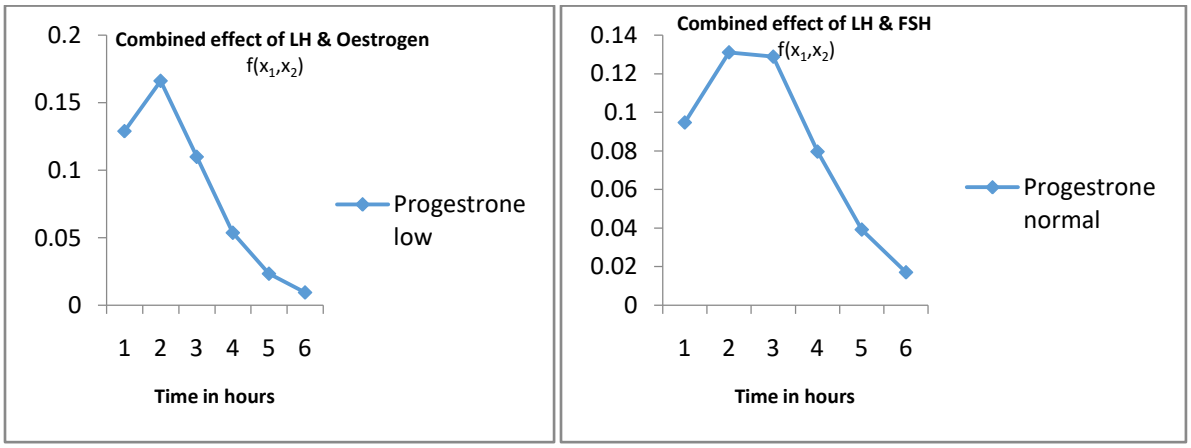
The present study provides that the stimulatory effect of HCG on the production of progesterone in mid-luteal phase is dependent on the functional state of the corpus luteum. More specifically, HCG readily stimulated progesterone production in women with normal corpus luteum function, where as the stimulatory effect of HCG was less pronounced in women lower progesterone levels, putative luteal phase defect. The present data are also in support of the previous findings that luteal phase defect is the consequence of the derangement of follicular growth and/or ovulation, and not a disorder after the formation of the corpus luteum due to inadequate stimulation of gonadotrophin. Hence, it seems logical to postulate that treatment of luteal phase defect is targeted to correct the process of follicular growth and ensuing ovulation.

The main purpose of this study was to see whether luteal phase defect is impart, casually related to insufficient gonadotrophin stimulation. To test this, 5000IU of HCG at the mid-luteal phase to observe changes in progesterone concentrations upto 3 hr after the injection. The response of progesterone may be different if HCG is given earlier after ovulation. In addition, it also remains a possibility that a longer follow-up time after HCG administration or a lower dose of HCG may yield the same results as where shown here. Thus the conclusion that HCG has no therapeutic benefit should be tempered.

An interesting finding in this study is the apparent suppression of LH concentrations after HCG administration. One may speculate that elevated progesterone concentrations may negatively regulate the LH release. However, this possibility is unlikely because LH concentrations where equally suppressed, even in women with low progesterone concentrations. HCG has been shown to inhibit the release of GnRH, when administered to castrated women [7], furthermore, HCG down-regulates the expression of the GnRH receptor

gene in a neuronal cell line [5]. Thus, the likely explanation is that HSG acts directly on the hypothalamo-pituitary system without mediated by ovarian steroid hormones.

4. **Mathematical Results**:



From the above mathematical figures the bivariate function $f(x_1,x_2)$ decreases continually and monotonically after one hour administration of HCG.

5. Conclusion

In medical conclusion HCG with low bio availability is supposed to cause an empty follicle syndrome, if used for ovarian stimulation [9]. However this is not the case in this study because serum concentrations of HCG after its injection were essentially the same between the low progesterone group and the normal progesterone group (data not shown).

The mathematical model concludes in these mathematical figures that the combined effect of LH and FSH in both the groups after the administration of HCG decreases monotonically and continuously after one hour of administration of HCG. This is same as the medical conclusion that similar suppression of LH concentrations in both groups after HCG administration reduces the likelihood of difference in bio availability of HCG used in this study.

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