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# A mathematical model by using bivariate normal distribution for changes in prolactin and cortisol levels in women undergoing in vitro fertilization and embryo transfer treatment

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**ABSTRACT**

The normal distribution is a very commonly occurring continuous probability distribution. Normal distributions are extremely important and are used in the natural and sciences related real valued random variables whose distributions are not really known. In this paper the Bivariate Normal distribution is used and the probability density functions for the exponent term q(x,y) are find out. Here Prolactin and Cortisol are considered as bivariate normal and the typical contour for the corresponding quadratic function q(x,y) for the Acupuncture- Prolactin and Cortisol, Control – Prolactin and Cortisol, Prolactin – Acupuncture and Control and Cortisol – Acupuncture and Control cases in the In Vitro Fertilization and Embryo Transfer Treatment days is given in the application part. The PDF obtained for the four cases in the In Vitro Fertilization and Embryo Transfer treatment is a part of an ellipse with the positive correlation.



## Introduction

## Mathematical Model

Let U and V be two random variables, and consider two new random variables X and Y of the form X = aU + bV, Y = cU + dV, where a, b, c, d are scalars. Each one of the random variables X and Y is normal, since it is a linear function of independent normal random variables. Furthermore, because X and Y are linear functions of the same two independent normal variables, their joint PDF takes a special form, known as the bi-variate normal PDF [1]. The bi-variate normal PDF has several useful and elegant properties and for this reason, it is a commonly employed model. In this section we derive many such properties, both qualitative and analytical, culminating in a closed-form expression for the joint PDF.

### The Conditional Distribution of X given Y

We now turn to the problem of estimating X given the value of Y. We assume that both X and Y have positive variance. Let us define

$\widehat{\boldsymbol{X}} = \boldsymbol{\rho}\frac{\sigma_X}{\sigma_Y}\boldsymbol{Y}, \widetilde{\boldsymbol{X}} = \boldsymbol{X} - \widehat{\boldsymbol{X}}, \boldsymbol{where}\ \boldsymbol{\rho} = \frac{E[XY]}{\sigma_X\sigma_Y}$ is the correlation coefficient of X and Y. Since X and Y are linear combinations of independent normal random variables U and V, it follows that Y and $\widetilde{\boldsymbol{X}}$ are also linear combinations of U and V. In particular, Y and $\widetilde{\boldsymbol{X}}$ are jointly normal.

Furthermore,

$$\boldsymbol{E}\left[\boldsymbol{Y}\widetilde{\boldsymbol{X}}\right] = \boldsymbol{E}[\boldsymbol{YX}] - \boldsymbol{E}\left[\boldsymbol{Y}\widehat{\boldsymbol{X}}\right] = \boldsymbol{\rho}\sigma_X\sigma_Y - \boldsymbol{\rho}\frac{\sigma_X}{\sigma_Y}\sigma_Y{}^2 = \boldsymbol{0}$$

Thus Y and $\widetilde{\boldsymbol{X}}$ are uncorrelated and therefore, independent. Since $\widehat{\boldsymbol{X}}$ is a scalar multiple of Y, it follows that $\widetilde{\boldsymbol{X}}$and $\widehat{\boldsymbol{X}}$ are independent.

We have so far decomposed X into a sum of two independent normal random variables namely,

$$\boldsymbol{X} = \widehat{\boldsymbol{X}} + \widetilde{\boldsymbol{X}} = \boldsymbol{\rho}\frac{\sigma_X}{\sigma_Y}\boldsymbol{Y} + \widetilde{\boldsymbol{X}}.$$

We take conditional expectations of both sides, given Y to obtain

$$\boldsymbol{E}[\boldsymbol{X} \mid \boldsymbol{Y}] = \boldsymbol{\rho}\frac{\sigma_X}{\sigma_Y}\boldsymbol{Y}\boldsymbol{E}[\boldsymbol{Y} \mid \boldsymbol{Y}] + \boldsymbol{E}\left[\widetilde{\boldsymbol{X}} \mid \boldsymbol{Y}\right] = \boldsymbol{\rho}\frac{\sigma_X}{\sigma_Y}\boldsymbol{Y} = \widehat{\boldsymbol{X}},$$

where we have made use of the independence of and $\widetilde{\boldsymbol{X}}$ to set $\boldsymbol{E}\left[\widetilde{\boldsymbol{X}} \mid \boldsymbol{Y}\right] = \boldsymbol{0}$. We have therefore reached the important conclusion that the conditional expectation $\boldsymbol{E}[\boldsymbol{X} \mid \boldsymbol{Y}]$ is a linear function of the random variable Y. Using the above decomposition, it is now easy to determine the conditional PDF of X. Given a value of Y, the random variable $\widehat{\boldsymbol{X}} = \boldsymbol{\rho}\frac{\sigma_X}{\sigma_Y}\boldsymbol{Y}$ becomes a known constant, but the normal distribution of the random variable $\widetilde{\boldsymbol{X}}$ is unaffected, since $\widetilde{\boldsymbol{X}}$ is independent of Y [ 4 ]. Therefore, the conditional distribution of X given Y is the same as the unconditional distribution of $\widetilde{\boldsymbol{X}}$, shifted by $\widehat{\boldsymbol{X}}$. Since $\widetilde{\boldsymbol{X}}$ is normal with mean zero some variance $\boldsymbol{\sigma_{\widetilde{X}}{}^2}$, we conclude that the conditional distribution of X **also** is normal with mean $\widehat{\boldsymbol{X}}$ and the same variance $\boldsymbol{\sigma_{\widetilde{X}}{}^2}$ [ 11, 12 ]. The variance of $\widetilde{\boldsymbol{X}}$ can be found with the following calculations:

$$\boldsymbol{\sigma_{\widetilde{X}}{}^2} = \boldsymbol{E}\left[\left(\boldsymbol{X} - \boldsymbol{\rho}\frac{\sigma_X}{\sigma_Y}\boldsymbol{Y}\right)^2\right]$$

$$= \boldsymbol{\sigma_X{}^2} - \boldsymbol{2\rho}\frac{\sigma_X}{\sigma_Y}\boldsymbol{\rho}\sigma_X\sigma_Y + \boldsymbol{\rho}^2\frac{\sigma_X{}^2}{\sigma_Y{}^2}\sigma_Y{}^2$$

$$\boldsymbol{\sigma_{\widetilde{X}}{}^2} = (\boldsymbol{1} - \boldsymbol{\rho}^2)\boldsymbol{\sigma_X{}^2},$$

where we have made use of the property $\boldsymbol{E}[\boldsymbol{XY}] = \boldsymbol{\rho}\sigma_X\sigma_Y$.

### The form of the Bivariate Normal PDF:

Having determined the parameters of the PDF of $\widetilde{\boldsymbol{X}}$ and of the conditional PDF of $\widetilde{\boldsymbol{X}}$, we can give explicit formulas for these PDFs. We keep assuming that X and Y have zero means and positive variances. Furthermore, to avoid the degenerate where $\widetilde{\boldsymbol{X}}$is identically zero, we assume that $|\boldsymbol{\rho}| < \boldsymbol{1}$ [ 9, 10].

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We have $f_{\tilde{X}}(\tilde{x}) = f_{\tilde{X}|Y}(\tilde{x} \mid y) = \frac{1}{\sqrt{2\pi}\sqrt{1-\rho^2}\sigma_X} e^{-\frac{\tilde{x}^2}{2\sigma_{\tilde{X}}^2}}$

and $f_{X|Y}(x \mid y) = \frac{1}{\sqrt{2\pi}\sqrt{1-\rho^2}\sigma_X} e^{-\left(x-\rho\frac{\sigma_X}{\sigma_Y}y\right)^2 / 2\sigma_{\tilde{X}}^2}$,

where $\sigma_{\tilde{X}}^2 = (1-\rho^2)\sigma_X^2$.

Using also the formula for the PDF of Y,

$f_Y(y) = \frac{1}{\sqrt{2\pi}\sigma_Y} e^{-\frac{y^2}{2\sigma_Y^2}}$ and the multiplication rule

$f_{X,Y}(x,y) = f_Y(y) f_{X|Y}(x \mid y)$, we can obtain the joint PDF of X and Y. This PDF is of the form $f_{x,y}(x,y) = ce^{-q(x,y)}$, where the normalizing constant is $c = \frac{1}{2\pi\sqrt{1-\rho^2}\sigma_X\sigma_Y}$.

The exponent term q(x,y) is a quadratic function of x and y,

$$q(x,y) = \frac{y^2}{2\sigma_Y^2} + \frac{\left(x-\rho\frac{\sigma_X}{\sigma_Y}y\right)^2}{2(1-\rho^2)\sigma_X^2}$$

which after some straightforward algebra simplifies to

$$q(x,y) = \frac{\frac{x^2}{\sigma_X^2} - 2\rho\frac{xy}{\sigma_X\sigma_y} + \frac{y^2}{\sigma_y^2}}{2(1-\rho^2)}$$

An important observation here is that the joint PDF is completely determined by $\sigma_X, \sigma_y$ **and** $\rho$.

In the special case where X and Y are uncorrelated (ρ=0), this joint PDF takes the simple form

$f_{X,Y}(x,y) = \frac{1}{2\pi\sigma_X\sigma_Y} e^{-\frac{x^2}{2\sigma_X^2} - \frac{y^2}{2\sigma_Y^2}}$ which is just the product of two independent normal PDFs. We can get some insight into the form of this PDF by considering its contours. i.e., sets of points at which the PDF takes a constant value. These contours are described by an equation of the form

$$\frac{x^2}{\sigma_X^2} + \frac{y^2}{\sigma_Y^2} = \textbf{constant}$$

and are ellipses whose two axes are horizontal and vertical.

In the more general case where X and Y are dependent, a typical contour is described by

$\frac{x^2}{\sigma_X^2} - 2\rho\frac{xy}{\sigma_X\sigma_Y} + \frac{y^2}{\sigma_Y^2} = \textbf{constant}$, and is again an ellipse, but its axes are no longer horizontal and vertical.

**Application**

Recent studies have demonstrated how stress affects pregnancy rates. Women with functional chronic anovulation had higher serum Cortisol and cerebrospinal fluid corticotrophin – releasing hormone concentrations than healthy controls. This CORT hypersecretion has been reported in women undergoing In Vitro Fertilization and Embryo Transfer Treatment who fail to achieve implantation. Moreover, a significant correlation between low adaptation to cognitive stress and poor outcomes has been reported in couples. There was a significant positive correlation between urinary adrenaline concentrations at baseline and day of ET and the scores on depression at baseline. Women who had successful treatment had a lower concentration of adrenaline at oocyte retrieval and lower concentrations of adrenaline and noradrenaline at ET compared with the unsuccessful women. IVF contains a number of stressful aspects: daily injections, blood draws, ultrasound, laproscopic surgery, and the possibility of failure at any of the various phases. The women were categorized as having good levels of social support systems. Outcomes were interesting: for each unit increase in a woman's chronic negative – effect score on the stress survey, there was a 2% decrease in the number of oocytes retrieved. Similarly, when a woman's chronic negative – effect score was high, one to two fewer embryos were transferred. Stress and anxiety had an effect on successful pregnancies and live births. A 1-point increase in positive affect on the stress scale increased the live – birth delivery rate by 7 percent.

**In Vitro Fertilization and Embryo Transfer Treatment:**

The purpose of this paper is to investigate whether there are changes in the stress hormones (CORT and PRL) that are known to influence reproductive outcomes (i.e., pregnancy rates), in IVF patients treated with Acupuncture. An extra vial of blood was collected on the following days: new patient visit, day 3 blood work, day of down – regulation, days of IVF medication for detection of IVF treatment effects (stimulation days), day of hCG trigger, day 1 post – hCG trigger, and day of pregnancy detection. Each data point represents a normalized number standardized to start of stimulation. Demographic data on all aspects of patients and their partners were collected, and these were used to derive demographic characteristics of patients. Only those patients deemed eligible for IVF were included. All patients completed IVF stimulation, egg retrieval, ET, and resultant pregnancy tests.

Multiple variables can impact serum CORT and PRL levels (e.g., fasting state, medications). To reduce these variables, the following steps were taken: all patients had serum levels checked before 8 a.m and were not fasting; all patients received gonadotrophins, baby aspirin, and GnRH agonist in the standard IVF protocol as stated; control and test patient demographics were consistent and statistically the same over 80 parameters.

This prospective cohort clinical trial of IVF patients was based on the following principles: All new infertility patients signed informed consent forms to be a part that required a blood draw, all samples of blood were frozen for later analysis, data were collected, stored, and then analyzed after all patient's birth outcomes were recorded, approximately 12 months from start of study, data represent completed IVF cycle. The primary outcomes were detection of CORT and PRL serum levels at various stages of IVF medication stimulation with comparisons between controls (IVF alone, n = 33) and treated patients (IVF plus Ac, n = 34). This does not assume that every patient has Ac on the same days of the stimulation cycles. The secondary study outcomes were pregnancy rates, miscarriage rates (spontaneous abortion), ectopic pregnancies, multiple pregnancy rates, and births per pregnancies.

Patients are treated with the electrostimulation procedure (nine treatments) before egg retrieval and are treated with the pre – ET Ac within 24 hours before and 1 hour after ET. The strict criteria are defined as nine electrostimulation Ac treatments before egg retrieval and one pre – and one post – ET Ac treatment – for a total of 11 treatments.

This study demonstrates biochemical differences in serum levels of CORT and PRL in patients receiving Ac along with their IVF treatments. It is observed that the increased pregnancy rates in Ac – treated IVF patients and hypothesize that the increase in pregnancies is the result of impact of Ac on PRL and CORT levels during the gonadotropins stimulation in the IVF treatment cycle. This study supports one possible mechanism of action of Ac on IVF outcomes that is, Ac induced biochemical changes in CORT and PRL during the gonadotropins stimulation in the IVF treatment cycle.

There have been reports on how stress levels across stages of the IVF treatment cycle vary between pregnant and non pregnant women [2]. Osaki et al. [6] studied the relationship between PRL and prognosis for pregnancy in IVF – ET patients. Their study specifically addressed midluteal PRL levels and found that lowered PRL levels at this point in an IVF cycle

resulted in early pregnancy loss in those patients who became pregnant with IVF. This reduction in miscarriage rates in consistent with our studies that revealed a lower miscarriage rate in those patients treated with Ac. In this study, Ac enhances PRL levels (above normal) before hCG trigger in an IVF treatment cycle (Figure 2.1A PRL), and there were no differences in serum PRL levels after hCG trigger (Figure 2.1A) although few data points were available and the information was averaged). It is noted that PRL suppresses the immune response and that T – cell immune competence is maintained with PRL. It is also noted that PRL is detected in the endometrium after day 23 of the menstrual cycle and that it increases with additional decidualization of the cavity, which roughly corresponds to the time at which implantation normally would occur.

Merari et al. [5] addressed the issues of psychological find hormonal changes in the course of IVF and believed both PRL and CORT were indicators of stress. By testing serum levels on day 3, day of retrieval and day of ET it is observed that CORT levels were unchanged at these three points, and there were no differences in conception cycles versus nonconception cycles. On day 3 of stimulation and certainly on the day of ET there were similar, insignificant differences, in CORT levels. However, on the day of retrieval, there were significant elevations in CORT levels in the Ac group. It is found that significant improvements in IVF outcomes when patients were treated with Ac, but whether they were attributed to PRL or CORT levels is hard. With regard to PRL. Merari et al. found no differences at the time points measured. A slightly lower, not significant, reduction in PRL in the conception group was found. It was also found that the conception group was characterized by a negative significance for the states of anxiety and depression with both PRL and CORT. However, there remains the observation is that significantly lower levels of CORT were observed in controls.

In this study, those Ac – treated patients with PRL levels greater than those of controls during the stimulation phase of their IVF cycles had significantly higher pregnancy rates. It is important to note that, the PRL levels observed in the Ac – treated patients after the start of stimulation and before the time of hCG trigger demonstrated no differences from controls; it was note that at the time of their IVF cycle, the patients would have had on average over nine Ac treatments. There may be a cumulative effect of Ac on IVF outcomes and this may explain the consistency in improved reproductive outcomes in patients with the Cridennda/Magrelli protocol, consisting of 11 Ac treatments, nine before hCG plus pre and post ET.

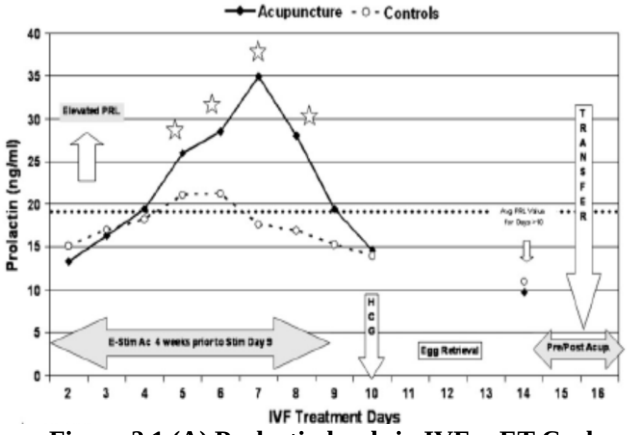


**Figure 2.1 (A) Prolactin levels in IVF - ET Cycles**

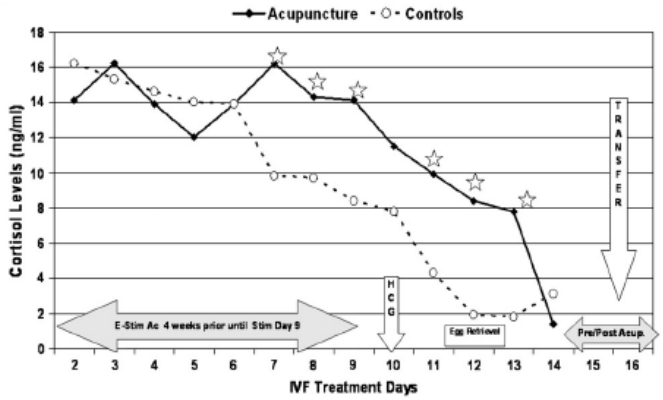


**Figure 2.1(B) Cortisol levels in IVF - ET Cycles**

Changes in serum levels of PRL (A) and CORT (B) associated with Ac (Solid diamonds) in women undergoing COH for IVF – ET. Acupuncture was associated with a significant increase in PRL levels (Solid diamonds) on stimulation days 4, 5, 6 and 7. On the other hand, CORT levels were significantly higher on stimulation days 7, 8, 9 and 11, 12, 13 in association with the Ac treated group. All patients are IVF patients who underwent IVF medication stimulation, egg retrieval, and ECT. Cridennda / Magarelli Ac protocol: electrostimulation Ac (nine treatments) occurred usually 4 weeks before the day of hCG. Pre - / Post – Ac occurred within 24 hours before ET (one treatment) and 1 hour after ET (one treatment). (IVF timings vary from patient to patient, and the figure illustrates the typical timing of events) Each data point represents a normalized number standardized to start of stimulation. Data represent the completed IVF cycle.

Levels of PRL and $E_2$ were found and correlate with improved polar body extrusion and overall improvements in oocyte maturity, fertilization, and embryo development. Mature follicles that produced fertilizable oocytes were found to contain higher follicular fluid PRL levels. In Ac – treated patients, the serum levels of PRL just before hCG administration were statistically higher (Figure 2.1A). Although not a direction correlation to follicular levels, PRL is not formed in the follicles and would thereby require serum elevations to result in follicular increases. Clomiphene citrate (CC) was used to stimulate controlled ovarian hyperstimulation (COH) in IVF cycles. In the CC – treated patients there were significantly diminished serum PRL levels at the time of hCG trigger compared with in the hMG – treated group. The average number of follicles developed and number of eggs retrieved demonstrated a twofold improvement in the hMG – treated patients for average number of follicles and a 137% increase for the number of eggs retrieved. This study suggest that PRL level suppression may not be beneficial in IVF patients or conversely that elevations in PRL levels in the weeks just before egg retrieval may play a beneficial role. PRL appears to exert a regulatory influence upon the estrogen – androgen metabolism in granulose cells within the developing follicle, specifically on the aromatase enzyme [7,8]. The recent advent of aromatase inhibitors for the treatment of infertility suggests that inhibition of aromatase during folliculogenesis may result in improved pregnancy outcomes in low – responder patients.

**CORT in the form of an elevated CORT:**

Hydrocortisone ratio in follicular fluid improves the rate fo implantation leading to pregnancy. The Ac group demonstrated elevations of CORT from 4 days before hCG administration, and the remained higher than controls throughout the retrieval process (Figure 2.1B CORT), although the levels remained in

the normal range for morning values. The need for psycho – therapeutic counseling in IVF patients refers to reports that PRL and CORT correlate to higher stress levels in women who actually undergo the IVF stimulation versus those who receive oocyte donation.

Although there does not appear to be an adequate body of knowledge to speculate on the actual impact of CORT and PRL on IVF outcomes based on changes during the menstrual cycle, we believe that the demonstrated changes in PRL and CORT may be one mechanism of action for the effects. It is also noted that contrary to natural cycle conception in which pathologic elevations of PRL have been shown to decrease reproductive outcomes and improved reproductive outcomes in Ac – treated COH cycle patients and they were associated with elevated PRL during the gonadotropin phase of the IVF treatment cycles. The CORT data would seem to suggest that suggests that changes in the levels that start with the gonadotropins phase and continue into the post – hCG and retrieval phase results in improved reproductive outcomes in Ac – treated groups.

Acupuncture may "correct" the negative effects of IVF medications on PRL as well as the adrenal response, and these effects may reduce stress as perceived by the patient. There has been much controversy regarding the reported beneficial and potentially harmful impact of Ac on IVF outcomes. Some investigators believe that the number and acupoints as well as the timing and geographical location of the Ac treatments may explain the differences in outcomes observed [3]. The patients receiving Ac weeks before the stimulation medications (usually 4 weeks at two treatments per week until day of retrieval) and in the times before egg retrieval and ET (as is the standard in our protocol, no patients receive electrostimulation Ac after egg retrieval) may benefit more than those patients treated just pre-/post – ET. This also supports that it may be the changes in the PRL levels during the gonadotropin phase of the IVF treatment (days 0 – 10) that most influence reproductive outcomes in patients treated with Ac. This hypothesis also supports the addition of additional Ac treatments before ET since the PRL levels only differed during the gonadotropin phase of the IVF treatment cycle and returned to physiologic levels that were equivalent to those of the control patients at the time of hCG (Figure 2.1A).

The strength of Ac is that they restore balance or return the body to homeostasis. It may be that Ac neither increases nor decreases hormone levels but simply returns the body to its natural state (note a significantly elevated PRL level in the Ac – treated group, however, above normal nonstimulated levels). The effects of Ac on PRL and CORT levels were noted even in the environment of extreme ovarian hyperstimulation as seen in typical IVF patients.

**Mathematical Results**

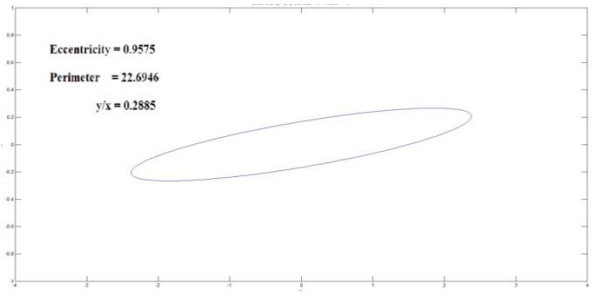


**Figure 3.1. A contour of the Bivariate Normal PDF of the Prolactin and Cortisol for the Acupuncture case with positive correlation in the IVF treatment days form a part of an ellipse**

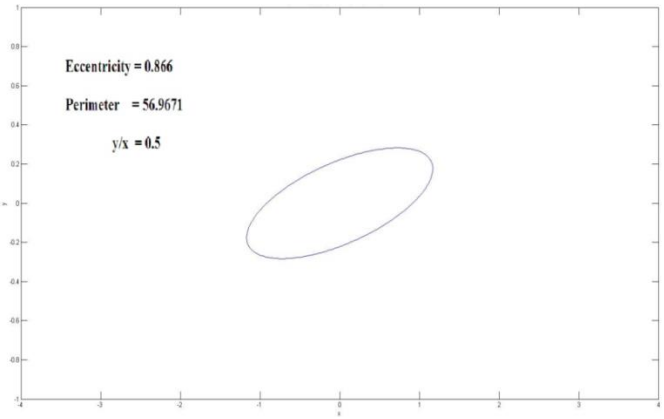


**Figure – 3.2 A contour of the Bivariate Normal PDF of the Prolactin and Cortisol for the Control case with positive correlation in the IVF treatment days form a part of an ellipse**

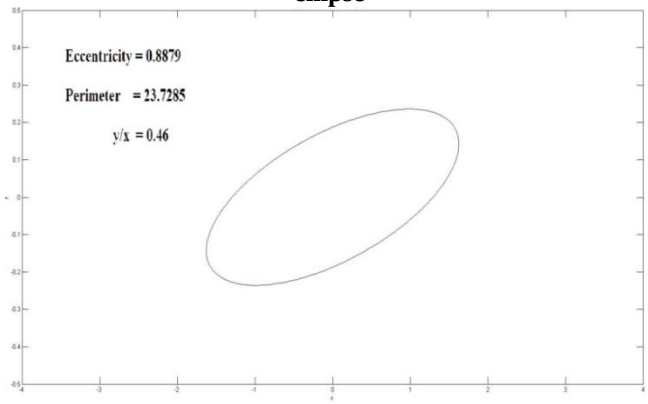


**Figure 3.3 A contour of the Bivariate Normal PDF of the Prolactin level of Acupuncture and control case with positive correlation in the IVF treatment days form a part of an ellipse**

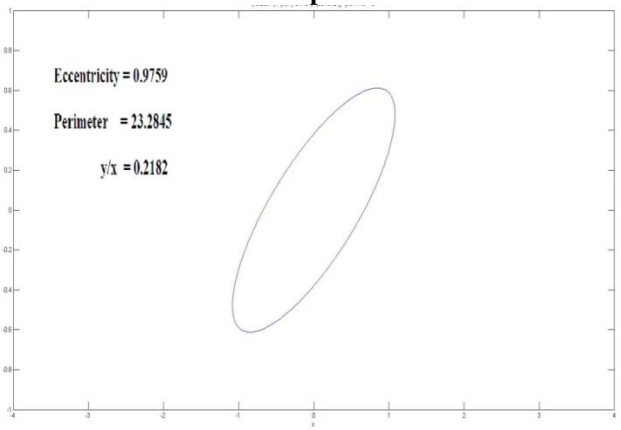


**Figure 3.4. A contour of the Bivariate Normal PDF of the Cortisol level of Acupuncture and control case with positive correlation in the IVF treatment days form a part of an ellipse**

**Conclusion**

The purpose of this paper is to investigate whether there are changes in the stress hormones (Cortisol and Prolactin) that are known to influence reproductive outcomes (i.e., pregnancy rates), in Vitro Fertilization patients treated with Acupuncture. There have been reports on how stress levels across stages of In Vitro Fertilization treatment cycle vary between pregnant and non – pregnant women. In the mathematical part by using the correlation for the following four cases: i.) Acupuncture case for Prolactin and Cortisol, ii.) Control case for Prolactin and

Cortisol, iii.) Prolactin level for Acupuncture and Control cases, iv.) Cortisol level for Acupuncture and Control cases in the In Vitro Fertilization and Embryo Transfer Treatment the quadratic function q(x,y) is find out and the contours for the above four cases have been obtained which are clearly explained in the figures 3.1, 3.2, 3.3, 3.4.

From figure3.1 the ellipse drawn for Acupuncture case for Prolactin and Cortisol in IVF treatment is more flattened if we compare it with the ellipse drawn for the Control case for Prolactin and Cortisol in figure 3.2. From figure 3.3 the Prolactin level for Acupuncture and Control case and Cortisol level for Acupuncture and Control cases in IVF treatment are also obtained. In the medical conclusion the study supports that one possible mechanism of action of Acupuncture on IVF outcomes, that is, induced biochemical changes in Cortisol and Prolactin during the gonadotropins stimulation in the IVF treatment cycle. Thus the Acupuncture treatments improve reproductive outcomes in IVF patients.

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