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Mixture Pareto Distribution of the Circadian Variation in AMH with PCOS Differs Significantly from Normally Ovulating Women

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Abstract

The Pareto distribution plays an important role in various areas of research. A new mixture Pareto distribution generated from logit of the weighted two-component mixture distribution which is mixed between a Pareto and a length biased Pareto distributions. We have derivation of the mixture Pareto types II, III, IV and hazard rate. Also, we apply a mathematical model to PCOS condition by examining the circadian variation and relationship between Anti Mullerian hormone, gonadotropins in PCOS patients compared to normally ovulating and menstruating women it shows that the mixture Pareto distribution gives a better fit than other important lifetime models; a Weibull, length biased pareto distribution and the Pareto distribution.

Keywords: Pareto distribution, length biased Pareto distributions, new mixture Pareto distribution, probability density function, hazard rate function, Follicle Stimulating Hormone(FSH), Polycystic ovary syndrome (PCOS), Luteinizing Hormone (LH), Anti-Mullerian Hormone(AMH).

INTRODUCTION

The family of the Pareto distribution is well known in the literature for its capability in modelling the heavy-tailed distributions that are mostly common in data on income distribution [23], city population size [2, 38], and size of firms [12, p. 151]. Newman [32] also provided many other quantities measured in the physical, biological, technological and social systems of various kinds, where the Pareto law has been found to be an appropriate fit. The application of extreme value theory to the study of environmental time series was studied by Smith[39],who presented are view of the statistical concepts in formulating air-quality standards. The distribution of wealth in the society was investigated by Levy and Levy [25].They showed, among other results, that general wealth accumulation process in the high wealth range with homogeneous investment talent leads to the Pareto distribution. The paper by Aban et al. [1] contains a detailed list of important areas where heavy-tailed distributions are found applicable. Some of these areas are in finance, physics, hydrology and engineering. There are also recent applications of the Pareto distribution in data sets on earthquakes, forest fire areas, fault lengths on Earth and Venus, and on oil and gas fields sizes [8]. Recently, attempts have been made to define new families of probability distributions that extend well-known families of distributions and at the same time provide great flexibility in modeling data in practice. One such class of distributions generated from the two-component mixture model of random variable which extends the original distribution with the length biased distribution provide powerful and popular tools for generating flexible distributions with attractive statistical and probabilistic properties see McLachlan and Peel [28]. The two-component mixture model method is employed in many vocations. For example, Hall and Zhou [19] proposed nonparametric estimation for a mixture of two distributions in a multivariate mixture model. In addition, estimates of the mixing proportions, locations and variances for the components of a finite univariate mixture model were introduced by Cruz-Medina and Hettmansperger [9].

Furthermore, two real location parameters and the mixing proportion were presented by Bordes et al. [6]. Moreover, the problem of parameter estimation in finite mixtures is proposed by Hunter et al. [21], when comparing their method with the method of maximum likelihood using normal components, their method produces higher standard error estimates in the case where the components are truly normal. Their method dramatically outperforms the normal method when the components are heavy-tailed. Moreover, several aspects of the mixture inverse Gaussian distributions are useful for modeling positive data that the empirical fit of the mixture inverse Gaussian distributions to the data is very good, introduced by Balakrishnan et al. [3]. Recently, Vandekerkhove [42] introduced the mixture of regression models which are generalization of the semi parametric two-component mixture model.

In this paper, we suggest a mixture Pareto (MP) distribution by method of the two-component mixture distribution. The main reasons for introducing it since its flexibility in accommodating mixture between original and length biased distributions. The MP distribution is an important model that can be used in a variety of problems in modeling lifetime data.

Pareto Type I Distribution

The Probability density function of the Pareto type I (P) distribution is given by

$$f(t) = \alpha\beta^{\alpha}t^{-(\alpha+1)}, \quad t > \beta. \tag{1.1.1}$$

The cumulative density function is given by

$$F(T) = 1 - \left(\frac{\beta}{t}\right)^{\alpha}, \quad t > \beta \tag{1.2.1}$$

The survivor function is given by

$$S(T) = \left(\frac{\beta}{t}\right)^{\alpha}, t > \beta \qquad (1.3.1)$$

The hazard rate function is given by

$$h(T) = \frac{\alpha}{t}, \quad t > \beta \qquad (1.4.1)$$

The Cumulative hazard rate function is given by

$$H(T) = -\alpha(\ln(\beta) - \ln(t)), \ t > \beta \qquad (1.5.1)$$

This distribution is a special form of the Pearson Type VI distribution. Since the P distribution has a reversed-J PDF shape and a decreasing hazard rate function (hrf), it may sometimes be in sufficient to model data. Generally, practical problems require a wider range of possibilities for the medium risk, for example when the lifetime data present a bathtub-shaped hrf, such as human mortality and machine life cycles. For this reason, researchers developed various extensions and modified forms of the P distribution to obtain a more flexible model with different numbers of parameters.

Length biased Pareto distribution

Patil and Rao [36] presented a length biased Pareto (LP) distribution by concept of a weighted distribution. If X is Pareto random variable with PDF (1.1.1), then the PDF for the length biased distribution of random variable X is

$$g_{Lp}(x) = \frac{(\alpha-1)}{\beta}\left(\frac{x}{\beta}\right)^{-\alpha}, x \geq \beta, \alpha > 1, \beta > 0 \qquad (1.2.1)$$

The cumulative distribution function of the LP distribution is

$$G_{Lp}(x) = 1 - \left(\frac{x}{\beta}\right)^{-(\alpha-1)} \qquad (1.2.2)$$

A NEW MIXTURE PARETO DISTRIBUTION

The probability density function and cumulative distribution function

Definition 2.1.1:

Let $g_p(x) and\ g_{Lp}(x)$ are the pdf and length biased pdf of the random variable X. If ω is mixing parameter 0 ≤ ω ≤ 1, then the weighted two-component mixture distribution produced by the mixture between $g_p(x) and\ g_{Lp}(x)$ is defined by

$$f(x) = (1-\omega)g_p(x) + \omega g_{Lp}(x) \quad , \quad x > 0 \qquad (2.1.1)$$

Theorem 2.1.1: Let X ~ MP (α,β,ω) , then the PDF and CDF of random variable X , are respectively

$$f(x) = \frac{1}{\beta}\left(\frac{x}{\beta}\right)^{-(\alpha+1)}\left[(1-\omega)\alpha + \frac{\omega(\alpha-1)x}{\beta}\right], \quad x \geq \beta, \alpha > 1, \beta > 0, 0 \leq \omega \leq 1 \qquad (2.1.2)$$

$$F(x) = 1 - \omega\left(\frac{x}{\beta}\right)^{-(\alpha-1)} - (1-\omega)\left(\frac{x}{\beta}\right)^{-\alpha} \qquad (2.1.3)$$

Proof: We then say that a random variable X follows the MP distribution with parameters α,β and ω, if its pdf is obtain by substitute (1.1.1) and (2.1.1) in Definition 2.1.1, can be obtained as

$$f(x) = (1-\omega)\left[\frac{\alpha}{\beta}\left(\frac{x}{\beta}\right)^{-(\alpha+1)}\right] + \omega\left[\frac{\alpha-1}{\beta}\left(\frac{x}{\beta}\right)^{-\alpha}\right]$$

$$= \left(\frac{x}{\beta}\right)^{-(\alpha+1)}\left[\frac{(1-\omega)\alpha}{\beta} + \frac{\omega(\alpha-1)x}{\beta^2}\right]$$

$$= \frac{1}{\beta}\left(\frac{x}{\beta}\right)^{-(\alpha+1)}\left[(1-\omega)\alpha + \frac{\omega(\alpha-1)x}{\beta}\right]$$

Let F(x) denote the CDF of a random variable X. The CDF for a generalized class of distribution, as defined by Definition 2.1.1, is generated by applying the CDF to the MP random variable to obtain

$$F(x) = (1-\omega)G_p(x) + \omega G_{Lp}(x) \qquad (2.1.4)$$

Hence obtain by substitute 1.2.1 and 1.2.2 in (2.1.4) can be written as

$$F(x) = (1-\omega)\left[1 - \left(\frac{x}{\beta}\right)^{-\alpha}\right] + \omega\left[1 - \left(\frac{x}{\beta}\right)^{-(\alpha-1)}\right]$$

$$= 1 - \omega - (1-\omega)\left(\frac{x}{\beta}\right)^{-\alpha} + \omega - \omega\left(\frac{x}{\beta}\right)^{-(\alpha-1)}$$

$$= 1 - \omega\left(\frac{x}{\beta}\right)^{-(\alpha-1)} - (1-\omega)\left(\frac{x}{\beta}\right)^{-\alpha}$$

Corollary2.1.1: Where ω = 0, the MP distribution reduces to the Pareto distribution with parameters α and β is given by (1.1.1).

Corollary2.1.2: Where ω = 1, the MP distribution reduces to the LP distribution as (1.2.2).

OTHER TYPES

Various types of the Pareto distribution other than the Pareto density in (1.1.1) were discussed by Nadarajah [30]. The density in (1.1.1) is called the Pareto type I. The CDF of Pareto types II, III and IV are, respectively, defined as

$$G_{II}(x) = 1 - \left(1 + \frac{x}{\beta}\right)^{-\alpha}, \quad x > 0, \alpha, \beta > 0$$

$$G_{III}(x) = 1 - \left[1 + \left(\frac{x-\mu}{\beta}\right)^{\frac{1}{\lambda}}\right]^{-1}, x > \mu; \ \beta, \lambda > 0$$

$$G_{IV}(x) = 1 - \left[1 + \left(\frac{x-\mu}{\beta}\right)^{\frac{1}{\lambda}}\right]^{-\alpha}, x > \mu; \ \alpha, \beta, \lambda > 0$$

Note that, the Pareto types II also known as a Lomax distribution. The mixture distribution for the random variable X, as Definition 2.1.1, the pdf of the MP distribution in (2.1.2) is originated

$$f(x) = \left\{1 - \omega\left[1 - \frac{x}{E(x)}\right]\right\} g(x) \qquad (2.3.1)$$

By applying $G_{II}(x), G_{III}(x) and\ G_{IV}(x)$ in (2.3.1), the corresponding types of MP density functions can be written, respectively, as

$$f_{II}(x) = \frac{\alpha}{\beta}\left(1+\frac{x}{\beta}\right)^{-\alpha-1}\left\{1-\omega\left[1-\frac{x(\alpha-1)}{\beta}\right]\right\}$$

$$f_{III}(x) = \frac{1}{\lambda\beta}\left(\frac{x-\mu}{\beta}\right)^{\frac{1}{\lambda}-1}\left[1+\left(\frac{x-\mu}{\beta}\right)^{\frac{1}{\lambda}}\right]^{-2}\left\{1-\omega\left[1-\frac{x}{\beta T(1-\lambda)\Gamma(1+\lambda)}\right]\right\}$$

$$f_{IV}(x) = \frac{\alpha}{\lambda\beta}\left(\frac{x-\mu}{\beta}\right)^{\frac{1}{\lambda}-1}\left[1+\left(\frac{x-\mu}{\beta}\right)^{\frac{1}{\lambda}}\right]^{-\alpha-1}\left\{1-\omega\left[1-\frac{x\Gamma(\alpha)}{\beta\Gamma(\alpha-\alpha\lambda)\Gamma(1+\lambda)}\right]\right\}$$

Hazard rate

By definition, the hazard rate (or failure rate) of a random variable X with PDF f(x) and

CDF F(x) is

$$h(x) = \frac{f(x)}{1-F(x)} \qquad (2.4.1)$$

Using (2.1.2) and (2.1.3), the hazard rate of the MP distribution may be expressed as

$$h(x) = \frac{\alpha\beta+\omega(\alpha x-x-\alpha\beta)}{\beta x+\omega(x^2-\beta x)} \qquad (2.4.2)$$

It is noted that by setting ω = 0 in (2.4.2), we have the hazard rate of the Pareto distribution. In the like manner, by setting ω =1, we have the hazard rate of the LP distribution. More generally, when modeling data with monotone hazard rate, right tail, high threshold and no mode in the probability density, the original distribution may be an initial choice because of its density shapes. However, in countering the phenomenon with non-monotone failure rate, it does not provide a reasonable parametric fit.

APPLICATION

Introduction

Polycystic ovary syndrome (PCOS), anovulation and clinical or biochemical hyperandrogenism, are phenotypically heterogenic endocrine disorders, affecting women of reproductive age with a prevalence of 6–10% [41]. Obesity, insulin resistance and the metabolic syndrome may also be related to PCOS. Polycystic ovaries as a central feature of PCOS are secondary to follicular arrest interfering with normal folliculogenesis, including follicle recruitment, follicle dominance and ovulation. Although there is no consensus as to an explanation of the biological mechanisms behind PCOS, the condition seems to be at least two- factorial [22]. Firstly, the intra-ovarian hyperandrogenism promotes early follicular growth and leads to an excess in follicles measuring from 2–5 mm. Secondly, a low aromatase activity caused by insufficient Follicle Stimulating Hormone [15] activity impairs estrogen synthesis interfering with the selection and growth of a dominant follicle [13]. Insulin resistance, secondary to both genetic and lifestyle related factors as e.g. overweight is associated with anovulation, but is probably not the primary cause of PCOS [14,16,20,40]. Androgen production is driven by Luteinizing Hormone (LH)-stimulated steroid genesis in theca interna cells [18] and hyperandrogenism may have both an extra- and intra-ovarian origin. An increased pituitary output of LH secondary to an altered Gonadotropin Releasing Hormone (GnRH) pulse [4] may be reinforced by other PCOS related factors like hyperinsulinemia, triggering a reduction of SHBG levels and enhanced bioavailability of free testosterone. Actually, insulin has been reported to increase LH secretion secondary to altered GnRH-neurone activity in both animals and in normally menstruating women [28], but this issue is debated due to surveys of insulin-infusion in PCOS-women not confirming this effect [11,24,26,30]. If present, both mechanisms would promote an increase in the androgen synthesis [31, 10] which may further deteriorate the regulation of the folliculogenesis.

A study reported with a significant circadian variation in AMH levels and a significant positive correlation between AMH and LH levels in normally menstruating women [7]. In order to improve our understanding of the biology of the PCOS condition and since AMH and LH seem closely linked to hyperandrogenism and anovulation in PCOS, it would be of interest to examine whether the pattern of co-variation between AMH and LH, seen in normally ovulating women, is preserved in those patients suffering from PCOS. Therefore, the aim of this study was to explore the circadian variation and relationship between AMH, gonadotropins and ovarian steroids in PCOS patients compared to normally ovulating and menstruating women.

Interventions

Eight normal-weighted young, an ovulatory PCOS woman as study group and ten normal menstruating and ovulating women as controls. Observational prospective study of the circadian variation in AMH, gonadotropins, sex steroids and androgens in a study and a control group. A circadian profile was performed in each study and control subject during a 24-h period by blood sampling every second hour, starting at 8:00 a.m. and continuing until 8:00 a.m. the following day.

Results

Circadian variation in AMH

A significant difference in mean AMH levels between the groups was observed, the highest values being seen in the PCOS group. With 8 am values on the first day of investigation as a reference, the mean concentrations in the study group revealed a statistically significant variation throughout the sampling period. Unlike the control group, where significantly lower AMH values were seen in the early morning, the study group revealed no such uniform pattern with subjects having nadir values at different time points of the diurnal period (Fig. 3.3.2.1).

The relative median (range) maximum intra-individual variation in AMH concentration through the 24 hours period was 29% (13–63%) in the study group and 23% (10–230%) in

the control group; this difference was not statistically significant.

Circadian variation in gonadotropins

A significant difference in mean FSH levels between the groups was observed, the lowest values being found in the PCOS group (Fig. 3.3.2.1). The mean difference was 2,7 IU/L (95% CI: 23,2; –2,2 IU/L).The circadian variation in FSH in the PCOS group showed no significant variation over the 24-h period, similar to findings of the control group. The control group had a period of statistically significantly suppressed levels at 2 a.m., 4 a.m. and 6 a.m. while the study group showed significant nadir values at 2 a.m.

A significant difference in mean LH levels between the groups was observed, the highest values being found in the PCOS group with a mean difference between groups of 8,0 IU/L (95% CI: 6,7; 9,0 IU/L).LH showed no variation by time in the PCOS group and no nadir nocturnal values unlike the control group which varied significantly throughout the 24 hour period displaying significantly lower values at 2 a.m., 4 a.m. and 6 a.m.

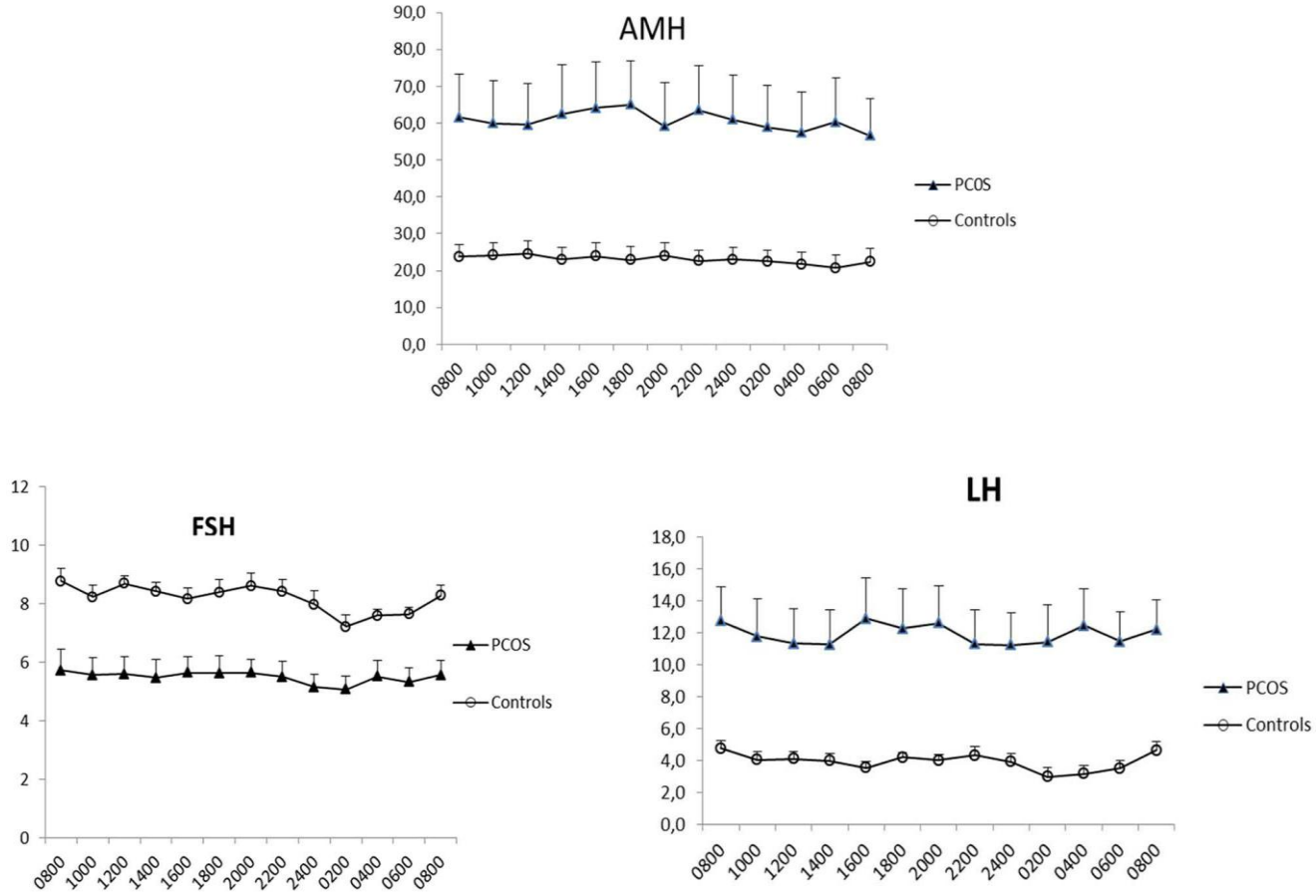


Figure 3.3.2.1. *Circadian variation in AMH (pmol/L), LH (IU/L) and FSH (IU/L). Figures illustrate the mean values + SEM for PCOS and controls*

Discussion

The study was a difference in the circadian variation pattern of AMH and LH between PCOS patients and normal controls. Unlike controls, a uniform pattern of variation in serum levels of AMH and LH without significant nadir late-night values was seen in the PCOS group. A significant positive co-variation between AMH and LH was seen in both groups. The study subjects included in this study revealed differences in their endocrine profile. Thus, the significantly higher level of AMH, LH in the study group compared to the controls, as well as a reduced FSH is all findings characteristic of a PCOS cohort. The study revealed no significant variation in LH in the circadian profile of PCOS women. In contrast, the control group had a significant late night hour reduction in LH levels, in accordance with earlier reports describing low follicular phase GnRH pulses in ovulatory women while PCOS subjects had constant and rapid pulses [43]. Such persistently rapid GnRH pulse favour the synthesis and secretion of LH over FSH and probably depicts an insufficiency in the negative feedback systems necessary to suppress the GnRH-pulse generator rather than representing an acceleration of the pulse generator [5]. The findings of a non-significant variation in

LH are in accordance with more rapid GnRH-pulses producing a high LH level without significant variation and nadir values throughout the night.

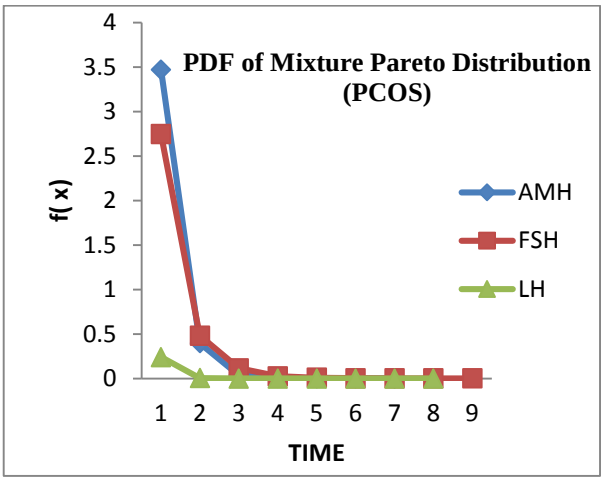
We found a significantly lower FSH level in PCOS compared to controls, but no co-variation between AMH and FSH was noticed in the groups. Available reports on the relationship between AMH and FSH are inconsistent. It has been postulated that the relationship between AMH and gonadotropins depends on the size of the ovarian reserve [35], based on a strong correlation between LH and AMH in young women with normal FSH and excess ovarian reserve while in subjects with high FSH marking reduced ovarian reserve, AMH and FSH was correlated [17,33,34,36]. This is well in accordance with the findings in a previously published study based on a normal ovulatory population of different ages [7], in whom a significant co-variation between AMH and LH but not AMH and FSH was found.

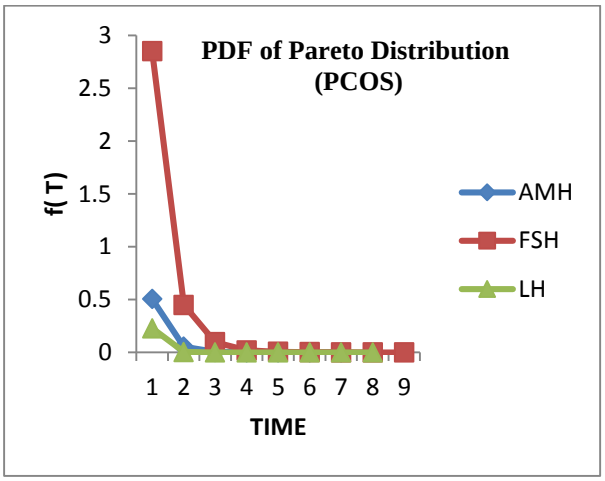
In the previous study [7] we were unable to conclude whether the variation in AMH levels drives the fluctuations in LH or vice versa, and as a third option we suggested a joint factor regulating the secretion of both hormones. In the present study, PCOSwomen had high, non-fluctuating diurnal levels of LH and AMH, indicating an increased activity in the GnRH pulse generator.

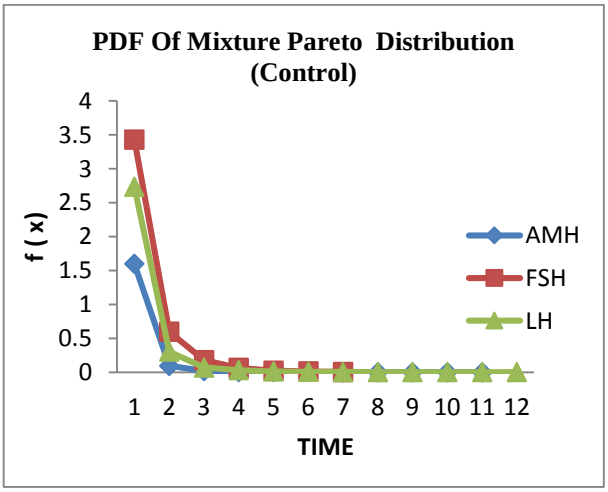
The weakness of the present study is the relatively limited number of study subjects fulfilling the inclusion criteria (age, hormonal status, clinical symptoms and BMI). On the other hand, the statistically significant associations found seem to be of a sufficient magnitude to draw conclusions even though the sample size is small. Moreover, the strength of the study is the frequent sampling throughout a 24 hour period in a PCOS study group.

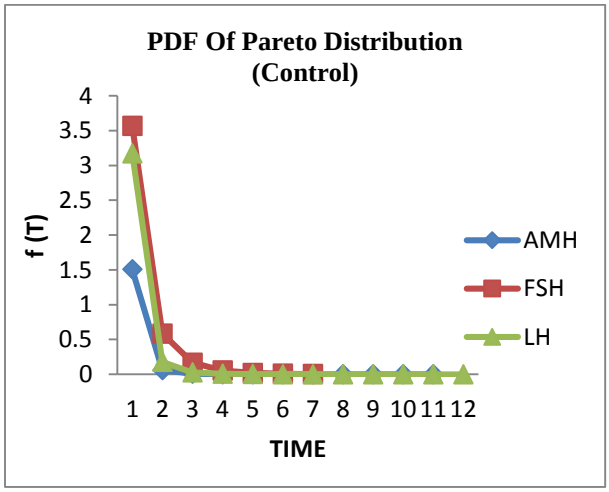
In conclusion, we found a significant difference in the circadian secretion of LH and AMH in PCOS women compared to normally ovulating women. This may be explained by an increased GnRH pulse, creating high and constant LH serum concentrations. Moreover, a significant co-variation between LH and AMH was seen, suggesting LH as a possible factor involved in the control of AMH secretion. Future studies in PCOS women with different phenotypes are needed to validate our findings.

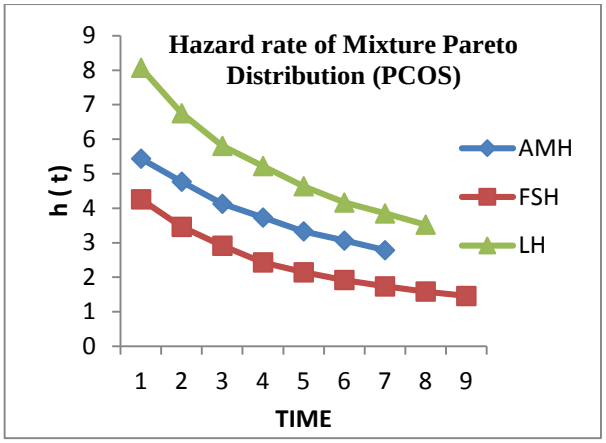
MATHEMATICAL RESULT

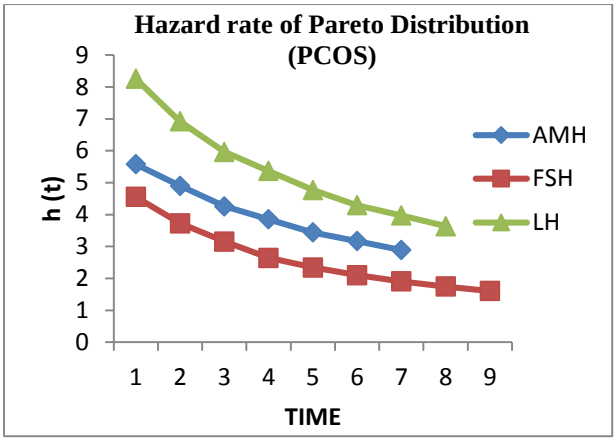


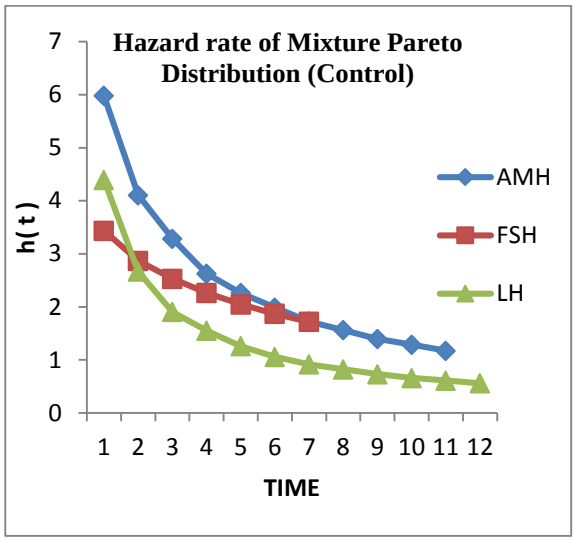


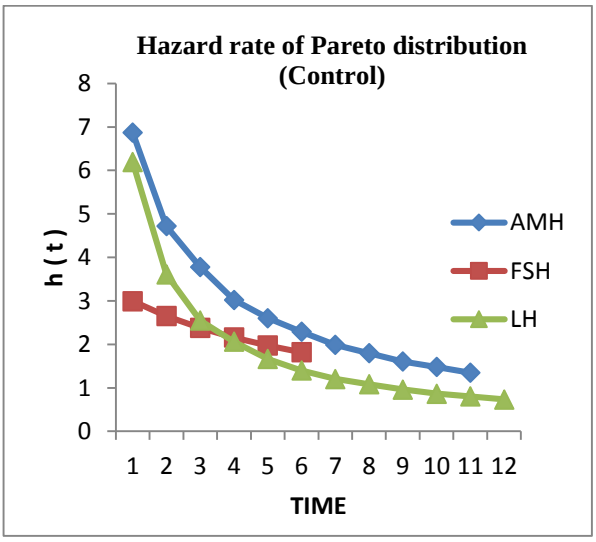












CONCLUSION

New two-component mixture distributions called a mixture Pareto distribution has some special sub-models, such as the Pareto, exponential, chi-square and the mixture Pareto types II, III, IV distributions. We have derived various mathematical properties of the mixture Pareto distribution. The mixture Pareto distribution provides a rather general and flexible framework for statistical analysis. We hope that the mixture Pareto distribution may attract wider application in lifetime data. In medical part, A difference in the circadian secretion of LH and AMH in PCOS women compared to normally ovulating women indicate an increased GnRH pulse, creating high and constant LH serum concentrations. A co-variation between LH and AMH may suggest LH as a factor involved in the control of AMH secretion. In mathematical part, when using Pareto distribution and Mixture Pareto distribution the hazard rate of AMH, LH are higher whereas FSH value is lower in PCOS group. The hazard rate decreases with time fastly in control subject than PCOS in AMH case when using Pareto distribution. This is similar in LH case also. The similar result follows for AMH, LH when using mixture Pareto distribution. A difference in AMH levels between the groups was observed, the highest values are seen in the PDF of mixture Pareto distribution in PCOS group. The result for AMH and LH are very clear when using mixture Pareto distribution rather than Pareto distribution.

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