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Neuroendocrine Defects in Polycystic Ovary Syndrome (PCOS): Different Phenotypes based on the Levels of Gonadotropins (FSH and LH), and Body Mass Index

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is a genetically complex disorder associated with abnormal follicular growth, hyperandrogenism and subfertility or infertility. There are untimely high levels of luteinizing hormone (LH) and expression of the LH receptor in PCOS women; however, these defects are not part of the criteria for the diagnosis of PCOS. Young women with PCOS require advanced IVF procedures to conceive, but they have a low rate of successful pregnancies.

Aims: To understand the variations in gonadotropin levels in women with PCOS.

Methods: We hypothesized that PCOS women may have differences in the neuroendocrine defects that may ultimately lead to PCOS symptoms. Here, we report different PCOS phenotypes where both follicle stimulating hormone (FSH) and LH levels were elevated, or just LH secretion was higher than normal. In this cohort of PCOS women, 71% had high LH levels.

Result: However, high insulin levels were not associated with either high LH or obesity. Obese PCOS women with high FSH had high insulin levels; however, that could be associated with obesity and not FSH.

Conclusion: The defect in the secretion of FSH, LH, or both leads to the reproductive abnormalities in women with PCOS. With the emerging connection between FSH, LH, and insulin receptor substrates, there may be an increase in the susceptibility of women with PCOS to metabolic disorders due to imbalance in FSH and LH secretion.

Key Words: Luteinizing hormone, Follicle stimulating hormone, Testosterone, Polycystic ovary syndrome, Obesity, Body mass index, Hyperandrogenism

INTRODUCTION

Polycystic ovary syndrome (PCOS), known as Stein and Leventhal syndrome, is characterized by menstrual irregularities or oligomenorrhea, hirsutism or hyperandrogenism, and polycystic ovaries (Dunaif et al. 2012, Kaur et al. 2012, Legro et al. 1998). Women with PCOS have enhanced luteinizing hormone (LH) secretion relative to follicle-stimulating hormone (FSH), leading to reproductive dysfunction, subfertility or infertility; however, the percentage of women with high LH is not reported for this cohort of women with PCOS in India. These features of PCOS were realized long ago however, the role of hormonal disturbances in the aetiology of PCOS has not been completely understood (Rebar et al. 1976, Yen et al. 1970). Circulating FSH levels in women with PCOS vary from a low to high range compared to its levels in normally ovulating women. Further, the increased LH:FSH ratio may not reveal the actual difference in the pulsatile LH release (Taylor et al. 1997). Most women with an imbalance of gonadotropins or sex hormone–binding globulin (SHBG) levels may have abnormal androgen levels (Dunaif et al. 2016, Wild et al. 1983, Azziz et al. 2009). Estradiol levels may vary considerably (normal to high) depending on the constellation of defects in women with PCOS. Symptoms of PCOS such as hirsutism and hyperandrogenism are well described and get further aggravated due to high insulin or mutations in the insulin receptor gene, leading to insulin resistance in women with PCOS and type II diabetes later in their life (Torchen et al. 2014). Previous studies have detected hyperinsulinemia in more than 50% of women with PCOS; however, most young women with PCOS in reproductive age have normal levels of blood glucose.

In a normal menstrual cycle, anterior pituitary derived hormones, LH and FSH regulate ovarian folliculogenesis and

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ovulation (Filatov et al. 2017, Kishi et al. 2017). The release of LH during the follicular phase is at a very low level, however, it is sufficient to produce androgens by the theca cells of the ovarian follicles. Androgens are then converted to estrogen in granulosa cells, and this process is FSH-dependent. Further, LH regulates the process of luteinization and the secretion of progesterone after ovulation. FSH and LH both control oocyte growth and timing of meiosis resumption. FSH is important for the maintenance of meiotic arrest after the birth of females, whereas LH is critical for the resumption of meiosis in oocytes. Gonadotropin releasing hormone (GnRH) is secreted from the hypothalamus and regulates the release of LH and FSH from the pituitary gland. LH is secreted in response to fast GnRH pulses, whereas FSH is secreted when there are slow GnRH pulses. Systemic estrogen and progesterone levels regulate the secretion of GnRH pulses as well as the amount of GnRH secreted per pulse. Previous studies have shown that GnRH secretion is relatively fast in women with PCOS, and there is a loss of the feedback response to estrogen, and progesterone leading to anovulation in these women.

Most studies on PCOS have been on women with a BMI higher than normal women, and these studies conclude that insulin-mediated glucose disposal primarily in skeletal muscle is decreased independent of obesity (Dunaif et al. 1992). Whereas, in certain other studies on non-obese women with PCOS, insulin sensitivity was normal (Ovesen et al. 1993). Studies from our laboratory and others have shown that the defect in insulin responses may be post-receptor activation. Insulin resistance may be a consequence of defects in FSH signaling leading to attenuated synthesis of insulin receptor substrates important for insulin-stimulated responses (Kaur et al. 2012, Anjali et al. 2015, Guedikian et al. 2018). Insulin resistance in women with PCOS is selective, affecting metabolic but not other actions of insulin. Here, we examined the levels of FSH, LH, and insulin in young and adult women with PCOS, with or without obesity, and studied if there is any association between BMI, and levels of hormones such as FSH, LH, and insulin in women with PCOS.

MATERIAL AND METHODS

After clearance from the institutional human ethics committee and informed consent, the hormone levels of 110 women with PCOS who visited Ridge IVF and Gouri hospital Ltd were recruited in this study, and their filed data in the hospital records were analyzed. The Rotterdam diagnostic criteria were used for the selection of the study group of women with PCOS, which included any two of the three features such as oligo- or anovulation, clinical or biochemical signs of hyperandrogenism or polycystic ovary (Rotterdam 2003). The women with PCOS were categorized into four groups based on their hormonal levels (LH, FSH and insulin) and the mean levels were taken to understand the different phenotypes of PCOS in these women. Oligomenorrhea is defined as the menstrual cycle lasting >35 days, and polycystic ovarian morphology was recorded by ultrasonography. Healthy ovulatory women were selected as described in our earlier publications and they had tubal factor or male factor infertility.

Statistical analysis

Analysis of data was done using a Student's t-test and a one-way ANOVA. Statistical analyses were performed using Prism Version 7.0a (GraphPad software Inc. USA). The data is presented as mean ± SD, and the difference between the two means was significant with $P \leq 0.05$.

RESULTS

PCOS phenotypes based on FSH levels:

Women with PCOS enrolled in this study were aged 21.21±2.45 years, and their characteristics were studied. It was observed that PCOS women (n = 95) had three different groups based on FSH levels and BMI (Group 1A: normal FSH and BMI≤23; Group 1B: normal FSH and BMI≥ 24; Group 2A: high FSH and BMI≤23; Group 2B: high FSH and BMI≥ 24; Group 3A: low FSH and BMI≤23; Group 3B: low FSH and BMI≥ 24 (Fig. 1). Among the women with PCOS, 11.69% had normal FSH levels (Group 1A); 22.10% had normal FSH and BMI≥ 24 (Group 1B); 17.9% of lean women had high FSH (Group 2A) and 16.8% had high FSH and BMI≥ 24 (Group 2B); 7.3% of lean women had low FSH levels (Group 3A), whereas significantly higher percentage of women (24.2%) with BMI≥ 24 (Group 3B) had low FSH ($P<0.05$).

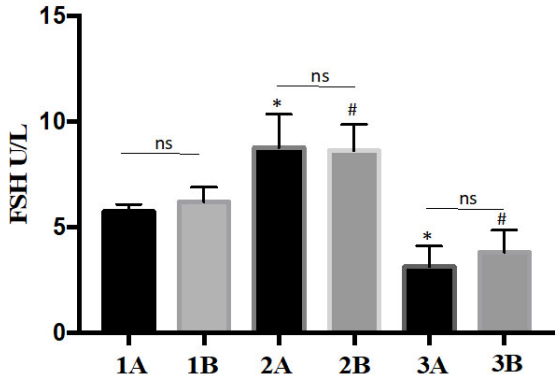

Figure 1: Three phenotypes of PCOS based on the levels of FSH and BMI. *P<0.05 (1A *vs* 2A or 2A *vs* 3A); #P<0.05 (1B *vs* 2B and 2B *vs* 3B).

There was no significant difference in the level of FSH in lean and overweight or obese women in all three different groups, with FSH levels either normal (Groups 1A and 1B),

higher (Groups 2A & 2B) or lower than normal (Groups 3A and 3B) (Fig. 1)

PCOS phenotypes based on LH levels:

The levels of LH in women with PCOS (n=59) were found to be higher in lean PCOS women with BMI≤23 than among healthy ovulatory women. Whereas, overweight or obese women with PCOS could be divided into two sub-groups with normal or higher than normal LH levels (Fig. 2). Out of the PCOS women, 30.5% were lean, and 69.5% were either overweight or obese. Out of the women with BMI≥ 24, 63.4% of women had higher than normal LH (2. PCOS BMI≥ 24, Fig. 2), and 36.6% had either normal or lower than normal LH (1. PCOS BMI≥ 24, Fig. 2).

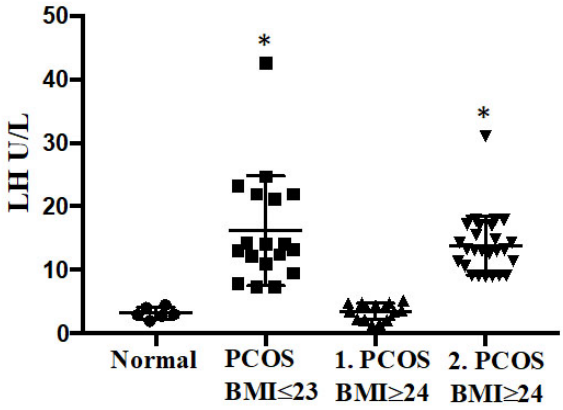

Figure 2: Three phenotypes of PCOS based on the levels of LH and BMI. *P<0.05, normal *vs* PCOS (BMI≤23) and *P<0.05, PCOS group 1 (BMI≥24) vs PCOS group 2 (BMI≥24)

PCOS phenotypes based on LH and insulin levels:

To understand the effect of insulin on gonadotropin levels or vice versa, we studied the levels of LH along with PCOS characteristics and based on different combinations of insulin, LH, and FSH levels. There were predominantly 4 groups of PCOS women (n = 60) based on the levels of FSH, LH, and insulin (Fig. 3A) and each group was subdivided into two groups based on BMI (Fig.3B). The age of PCOS women in these groups was not statistically significant (Group 1: 21±2.51; Group 2: 21±2.45; Group 3: 21±2.38; Group 4: 21±2.53). These PCOS groups have the following characteristics: Group 1A, High FSH and BMI≤23 (21.74±1.67); Group 1B, High FSH and BMI≥24 (31.19±5.48), Group 2A, High LH+High insulin and BMI≤23 (22.26±1.87); Group 2B, High LH+high insulin and BMI≥ 24 (31.21±4.75); Group 3A, normal LH+ high insulin and BMI≤23 (21.57±1.57); Group 3B, normal LH+ high insulin and BMI≥ 24 (30.67±4.88) (Fig.3B); Group 4A, High LH+normal insulin and BMI≤23 (22.03±1.77); Group 4B, High LH+ normal insulin and BMI≥24 (29.88±3.89). Women with PCOS in groups 1, 2, and 4 had significantly more LH than group 3 and LH levels were independent of insulin and BMI (Fig.3). There was no significant difference in the levels of LH in groups 1, 2 and 4 or between BMI≥24 and BMI≤23 in each subgroup or in relation to insulin levels (Fig.3A).

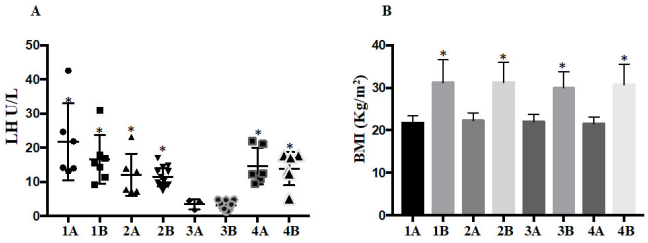

Figure 3: Different phenotypes of PCOS based on the levels of A) LH, FSH, and Insulin, *P<0.05 (3A *vs* other groups) and B) BMI for the groups as in Fig. 3A. *P<0.05, between subgroups.

Out of all PCOS women, 27.6% had high FSH, 46.8% had high LH and insulin, 27.6% had normal LH and high insulin, and 25.5% had high LH and normal insulin. Groups 2B, and 3B (BMI≥24) had significantly higher percentages of women (34.0% and 21.3% respectively) than in groups 2A and Group 3A with BMI23 (12.7% and 6.3%) respectively. Groups 1 (1A, 12.7% vs 1B, 14.89%) and 4 (4A, 12.7% vs 4B, 12.7%) had no difference in the percentage of women suffering with the characteristics earmarked for these groups.

Insulin levels in different PCOS phenotypes:

Insulin levels were analyzed in 4 groups of PCOS women, as described in Figs 3A and 3B. There were significantly higher insulin levels in women with PCOS, high FSH, and BMI≥ 24 than the women with high FSH and BMI≤23 and women with normal insulin in group 4 (Fig.4). There were no differences in the levels of insulin in the three groups of women with PCOS (1B, 2A, 2B, 4A, and 4B), and high insulin levels were independent of obesity in women with PCOS (Fig.4). A total of 56.5% of women with PCOS had both high insulin and BMI≥24.

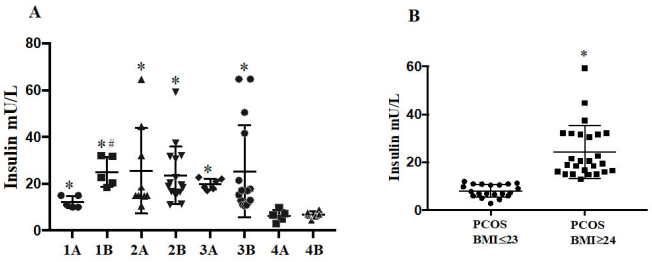

Figure 4: Insulin levels in different phenotypes of PCOS based on the levels of A) LH, FSH, and insulin *P<0.05 (4A *vs* other groups) B) groups based on insulin and BMI. *P<0.05

DISCUSSION

Here, we show four different phenotypes of PCOS based on the levels of gonadotropins, FSH and LH. A cohort of women with PCOS, lean as well as obese, had high FSH levels, indicating either a defect in the FSH receptor (FSHR), FSH binding, or activation of FSHR. Overweight or a obese PCOS women with high FSH had higher level of insulin than the lean women with PCOS, indicating a common pathway being affected by these two hormones, however as per the earlier reports, high insulin is more associated with obesity. LH and insulin levels were high in PCOS women independent of obesity, indicating genetic or epigenetic causes in the neuroendocrine axis. In this study, women with PCOS who had high FSH also had high LH, indicating hypersecretion of both gonadotropins in this phenotype. The reason of the hypersecretion of both the gonadotropins from the pituitary is not known. However, high levels of FSH and LH may contribute to the high secretion of androgens such as testosterone, resulting in abnormalities in neuroendocrine regulation through the impairment of feedback mechanisms. Gonadotropin imbalance results in anovulation, relative deficiencies of progesterone, leading to either the absence of menstrual periods or oligoamenorrhea in women with PCOS (Engmann et al. 2017, Dewailly et al. 2014). Further, high levels of insulin aggravate the symptoms of PCOS, such as hyperandrogenism, acne, glucose intolerance, and anovulation.

PCOS was described more than 65 years ago however, we still do not understand its aetiology (Amsterdam ESHRE/ASRM 2012, Welt et al., 2006, Dokras et al 2017). Three of the most probable causes of PCOS are related to 1. abnormal neuroendocrine regulation and higher secretion of pituitary hormones; 2. abnormal levels of male hormones or androgen in women with PCOS; and 3. Epigenetic changes, which support that the exposure of female infants to male hormones during gestation leads to PCOS upon reaching adulthood. PCOS has complex traits, and it has been suggested to be polygenic (Boyle et al 2017). Epigenetic variations due to obesity and lifestyle may contribute to the complexity of PCOS (Frazer et al. 2009). After the initial GWAS, the genetic skyline of PCOS includes several gene loci; however, we still need to understand the effect of the susceptibility loci on different phenotypes in women with PCOS (Gallagher et al. 2018).

Further, there is an increase in the risk of adverse pregnancy outcomes in women with PCOS, and therefore, it is important to understand the cause and effect of the complex traits connected to PCOS (Roos et al. 2011, Bu et al. 2013). Obesity and overweight have been associated with negative outcomes of assisted reproductive technologies in women with PCOS (Roos et al. 2011, Bu et al. 2013, Sheng et al. 2017). Bellver et al. 2010 showed that obesity in women with PCOS impairs the outcome of in vitro fertilization even in the presence of good quality embryos. Our studies and those of others indicate that there are metabolic defects due to the imbalance of gonadotropins, which adversely impact the nutritional status of the oocyte. Nongonadal receptors of LH in the endometrium may further influence the implantation of the oocyte after fertilization.

The enhanced release of LH in women with PCOS is due to an increase in the frequency and amplitude of pulsatile GnRH secretion (Waldstreicher et al. 1988, Marshall et al. 1999, Eagleson et al. 2000). However, how hypothalamic dysregulation affects the release of FSH is not well documented for Indian women (Marshall et al. 1999). Hyperandrogenism affects the sensitivity of the hypothalamic GnRH pulse generator, and the feedback mechanisms of estradiol and progesterone are adversely affected (Eagleson et al. 2000). LH stimulates theca cells in the follicles, and the testosterone thus produced gets aromatized to estradiol by FSH action (Filatov et al. 2017, Kishi et al. 2017). However, in women with PCOS, FSH responses may be abnormal (Ehrmann et al. 1995, Franks et al. 2000, Anjali et al. 2015). Several intra-ovarian and neuroendocrine factors may contribute to the inhibition of granulosa cell aromatase activity in some women with PCOS, while several others may have a normal to high response to FSH in terms of expression of the aromatase enzyme or actual levels of estrogen. Increases in androgen production in theca cells have been observed in both ovulatory and anovulatory women with PCOS (Gilling-Smith et al., 1994). Women with PCOS have several arrested follicles at the mid-antral stage compared with normal ovaries (Hughesdon et al. 1982, Webber et al. 2003). PCOS women have increased expression of LH receptors in granulosa cells early in the follicular phase, and that causes aberrant responsiveness to LH (Mason et al. 1994, Willis et al. 1998). However, during IVF, those women with PCOS may respond to FSH after pituitary desensitization. The gonadotropin therapy produces normal follicular maturation and ovulation in many of the PCOS women, but they may have a negative pregnancy outcome (Franks et al. 2008, Erickson et al. 1992, White et al. 1996). The present study differentiates between the biochemical phenotypes of PCOS, and in each group, women may require a different IVF therapy with recombinant gonadotropins for successful ovulation and oocyte maturation.

However, this study has limitations with regard to the data on androgens and estrogen levels in PCOS women, especially in the case of lean women. The variability in the lifestyle of PCOS women was not reported, and the drugs taken before or at the time of blood sampling in overweight or obese women were not available in the records of many women with PCOS. Therefore, we selected very young women diagnosed with PCOS to avoid the long-term effects of drugs on their hormonal parameters. However, to make the study

conclusions robust, we need to analyse the hormonal data of a large cohort of PCOS women in each subgroup based of hormone levels and BMI.

CONCLUSION

This study demonstrates the variability in the gonadotropin levels in women with PCOS and distinguished four phenotypes indicating that there is neuroendocrine defect in the secretion of FSH, LH, or both leading to reproductive abnormalities in women with PCOS. With the emerging connection between FSH, LH, and insulin receptor substrates, there may be an increase in the susceptibility of women with PCOS to metabolic disorders, and subfertility. Based on our data, it is important to identify each PCOS women with a specific phenotype so that an appropriate gonadotropin therapy can be given for successful conception after natural process or IVF.

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Ethical Clearance:

The study was conducted after approval from the Ethical Board of Gouri hospital, Ridge IVF and University of Delhi. The PCOS patients and normal women participants provided their informed consent to participate in this study.

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Conflicts of interest: Nil

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