Original Article

Is Weight Gain the Precipitating Factor for Polycystic Ovarian Syndrome? A Hypothesis Based on a Retrospective Study

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Abstract

Objective: To evaluate if weight gain is a risk factor for the development of polycystic ovarian syndrome (PCOS) in a genetically susceptible patient, irrespective of the BMI.

Study design: A retrospective study. Study Group: Female patients who presented to our infertility clinic and fulfilled the inclusion criteria.

Study Setting: Department of Reproductive medicine, Chettinad Super Speciality Hospital.

Study period: January 2014 - December 2014.

Results: A total of 172 patients were included in this study, among whom 107 patients had PCOS and the rest had other causes of infertility. The patients were distributed in the BMI categories of normal, overweight and obese. Out of the 107 patients who had PCOS, 104 (97.2%) had a history of minimum 4.5% gain in weight from their earlier weight after adolescence, following which they developed oligo (or) anovulation or clinical hyperandrogenism. The association between weight gain and PCOS was assessed by plotting the data in a 2x2 contingency table and p value was calculated using a Chi-Square test, which showed a significant association (Chi square test - 72.629 with 1 degree of freedom, p value - <0.0001).

Conclusion: From the above observation, we arrive at a hypothesis that weight gain could probably be the major precipitating factor for development of polycystic ovarian syndrome in genetically susceptible women, irrespective of their BMI.

Key Words: Polycystic ovarian syndrome (PCOS), BMI, Weight gain, Oligo/anovulation, Hyperandrogenism, Polycystic ovarian morphology.

Introduction

PCOS is a heterogeneous disorder which results from interaction of multiple genes along with environmental factors. Body weight plays a pivotal role in reproductive neuroendocrinology. Both significant weight gain and weight loss affects the reproductive axis. Ovulatory dysfunction is responsible for subfertility in 20-40% of women[1]. Polycystic ovarian syndrome (PCOS) is the commonest ovulatory disorder accounting for 60-85% of anovulatory patients and the commonest endocrinopathy in women of reproductive age group[2,3].

Polycystic ovarian morphology in an ultrasound is seen in 20-33% of normal women[4]. Therefore, the presence of polycystic ovaries alone is not significant, and the diagnosis is made by the Rotterdam's criteria[5].

The European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in 2003 laid down the criteria for diagnosing PCOS - the Rotterdam criteria. At least 2 of the following 3 features should be present: Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea. Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess). Polycystic ovaries as defined on ultrasonography (12 or more follicles, each measuring 2-9mm in diameter, ovarian volume >10cm^3).

There are various theories regarding the pathophysiology of this multisystem disorder, as depicted in Figure 1, and newer factors are identified regularly, claiming to play a role in its etiopathogenesis.

The coexistence of obesity and PCOS is commonly seen, but the exact pathogenesis involved in patients with low and normal BMI with PCOS is yet to be identified[6]. Studies have proposed genetic disorder of insulin action and abnormalities of insulin secretion as the cause for PCOS in these patients[7,8]. The purpose of this study is to propose that weight gain is the major precipitating factor for polycystic ovarian syndrome, in all categories of BMI, because it is becoming a common trend to see non-obese women with PCOS in our daily practice.

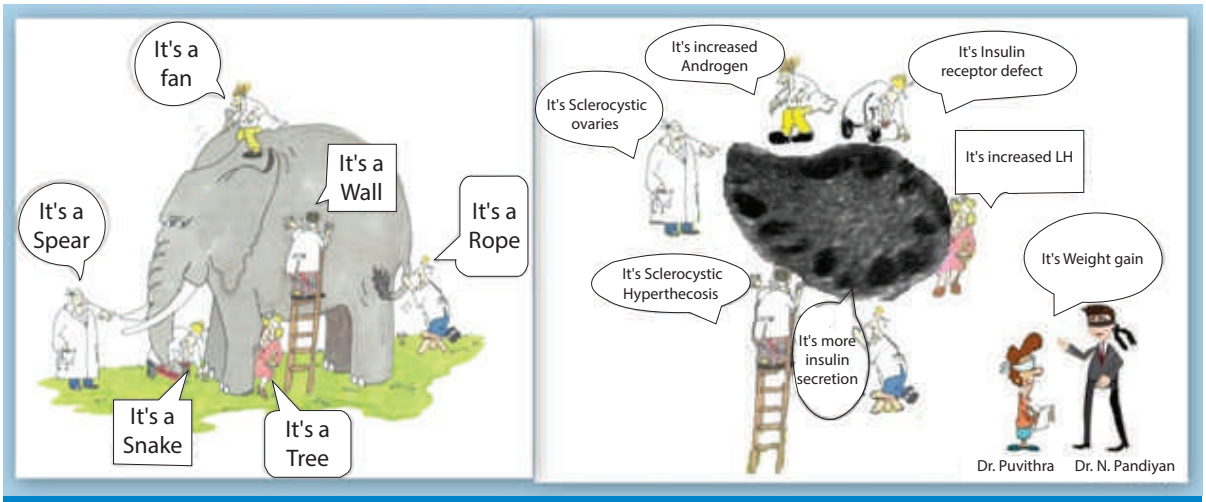

Fig 1 - Pictorial representation of various theories proposed

The treatment is primarily based on the symptom the woman presents with, like ovulation induction for anovulation and infertility. The concern is that the primary pathology is left untreated, and the hyperinsulinemia and hyperandrogenemia in these women prevail during pregnancy and is attributed to numerous pregnancy and neonatal complications.

Studies have shown that 5–10% weight loss causes significant clinical benefits improving psychological outcomes, reproductive features (menstrual cyclicity, ovulation and fertility) and metabolic features (insulin resistance and risk factors for CVD and T2DM)[9]. Therefore, the converse that weight gain could trigger the development of these symptoms, maybe applicable too.

Materials and Methods

In this retrospective study, data was collected from the records of subfertile women who attended the Department of Reproductive Medicine, Chettinad Super Speciality Hospital, from January 2014 to December 2014.

During primary evaluation, a detailed menstrual history and history of weight gain and duration was obtained from all patients who presented to our department. These details are recorded in the case sheet. Patients who were uncertain about their weight gain were excluded from the study. Routine gynecological examination was done and their BMI noted. Clinical evidence of hyperandrogenism noted, if present. Most of the patients undergo a basal ultrasound examination on Day 2 of their menstrual cycle, and presence of polycystic ovaries documented. Those who did not have an ultrasound examination in our department were excluded from the study. Women were considered to have PCOS if they fulfilled the Rotterdam's criteria.

Women who had a previous term pregnancy were excluded from the study, as the normal weight gain during pregnancy can interfere with the results. Those who had other confounding factors like alternative causes of anovulation (eg. hypothyroidism or hyperprolactinemia), recent laparoscopy and ovarian drilling, recent treatment with Metformin or long term intake of hormonal pills until recent past were also excluded from the study.

Results

A total of 172 patients were included in this study, among whom 107 patients had PCOS and the rest had other causes of infertility, like unexplained or male factor infertility. It was possible to obtain the weight gain pattern in the non-PCOS group also, as it was practiced as a routine to elicit the history and include it in the case records.

Figure 2a shows the educational qualification of all women included in the study. As seen in the figure, all patients are educated and were therefore able to elaborate on their weight gain pattern. Figure 2b shows the occupation of the women in the PCOS group.

They were divided into groups as shown in Table 1, and the same was plotted in a 2x2 contingency table. It is appreciable from the tables that majority of women in the study group had gained weight after adolescence, and thereafter developed PCOS. The minimum weight gain observed in the study was 4.5%, at a given point of time. Out of the 107 women with PCOS, 104 (97.2%) had a history of weight gain after adolescence. The BMI of women in all groups were comparable, and there was no predilection towards higher BMI noted in PCOS patients.

Group	Age	BMI	Number
Weight gain - Present PCOS - Present	26.42 ± 3.54	26.69 ± 3.73	104
Weight gain - Present PCOS - Absent	29.95 ± 4.91	25.74 ± 2.60	22
Weight gain - Absent PCOS - Present	23.33 ± 3.51	25.20 ± 7.05	3
Weight gain - Absent PCOS - Absent	28.88 ± 4.11	25.94 ± 5.98	43

Table 1 - Distribution of women in the groups and their baseline characteristics

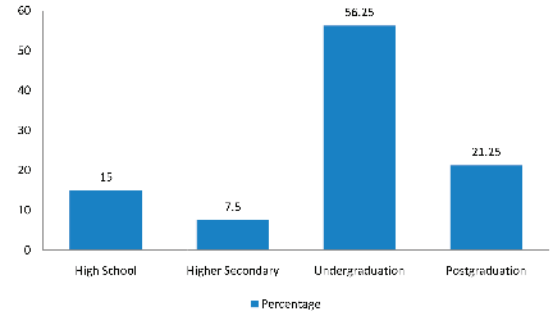

Fig 2a - Educational Status

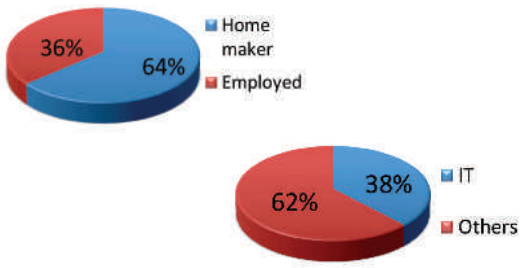

Fig 2b - Occupation of women in PCOS group

The patients in the study group were classified into different BMI categories, according to the WHO criteria - normal BMI, overweight and obese, as shown in Figure 2c. Out of the 126 women who gained weight 82.5% developed PCOS, which suggests a probable genetic predisposition to PCOS in those 104 patients.

There was no lean woman with PCOS in this group. As seen in the figure, 31.73% of these women had a normal BMI, 49.04% were overweight and only 19.23% were obese, contradicting the general presumption that PCOS is commonly seen in obese women.

Statistical analysis was done using Chi-square test with Yates correction (72.629 with 1 degree of freedom). There was a significant association between weight gain and PCOS (p value - <0.0001).

Another interesting observation was that, among those who gained weight, a considerable number had gained weight after marriage, during a minimum duration of 1 year and the rest during college days, as shown in Figure 2d.

In another study done at our department, we observed that 79.5% of women who presented to our department, had gained weight after marriage, irrespective of the weight of male partner[10].

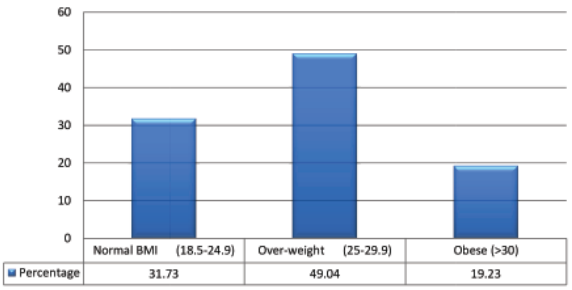

Figure 2c - BMI distribution of women who had weight gain and PCOS

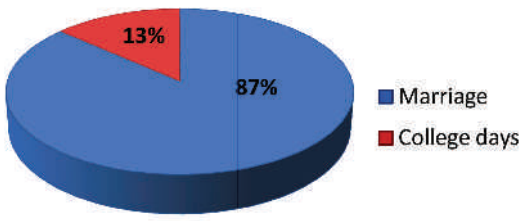

Figure 2d - Period when weight gain occurred

Discussion

Body weight of an individual is determined at conception (genetic) and in-utero (external influences). Studies have shown that environmental influences account for about 25% of the birth weight variance and genetic influences account for 38–80% birth weight variance[11]. When there is a change in this predestined weight, the human metabolic and endocrine systems try to acclimatize to this change by producing more or less hormones and enzymes which contribute to the development of metabolic syndrome.

Burghen GA et al, identified the presence of hyperinsulinemia and thereby suggested the presence of insulin resistance in patients with PCOS[12]. It is considered as the fundamental metabolic alteration which leads to the heterogeneous disorder. The same study showed the concurrent presence of hyperandrogenism in these patients. This hyperinsulinemia could have been an indirect consequence of hyperglycemia due to the sedentary life style or inappropriate dietary habits in these patients. Barker's hypothesis on fetal origin of adult diseases was followed by the thrifty phenotype hypothesis, where it was suggested that poor nutrition in early life leads to permanent changes in glucoseinsulin metabolism[13,14]. Similarly, studies have shown that when small for gestational age children try to catch-up growth by increasing their growth velocity above the 50th percentile, they are at higher risk of developing obesity, Type 2 diabetes and cardiovascular complications[15,16].

In this study, 31.73% of women had a normal BMI, 49.04% were overweight and only 19.23% were obese, contradicting the general presumption that PCOS is commonly seen in obese women. The salient occurrence in all these women was weight gain after adolescence. With these observations and related studies mentioned above, it is apparent that an individual's weight is programmed in-utero, and the relative gain in weight is responsible for the metabolic derangements, which leads to PCOS (Figure 3,4). In the sequence of events, Leptin is also found to play a role. Leptin is secreted primarily from white adipose tissue, although it is present at several other sites, including the ovary[17]. Leptin stimulates LH secretion, as ascertained by correction of LH pulses following Leptin administration in women with fasting-induced HPO axis dysfunction[18]. Therefore, an increase in adipose tissue, increases the circulating Leptin levels and thereby alters the HPO axis. Leptin also exerts direct effect in all ovarian cells and seems to have a physiological regulatory effect in folliculogenesis[19].

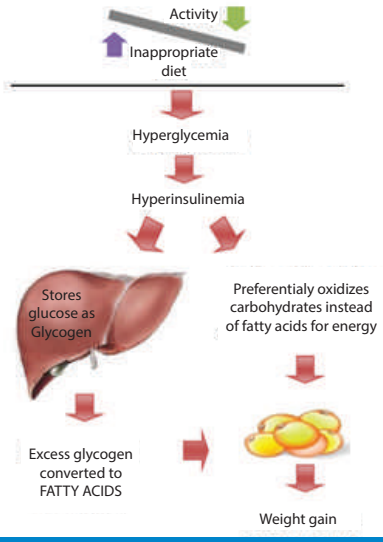

Fig 3

Fig 4

Fig 3 & 4 - Cascade of metabolic events

Thus, increased circulating Leptin and insulin, both an aftermath of increased adipose tissue, directly or indirectly cause derangements in the ovarian follicular activity and thereby the ovulatory function.

Limitations

The study is done in an infertility clinic and not in the general population, which could probably affect the results. Larger prospective studies following up women from menarche are required to conclude that weight gain is the precipitating factor for the development of PCOS, but the feasibility of conducting such studies is questionable.

Though we are not aware of the presence or absence of polycystic ovaries in these patients before the weight gain, previous studies have shown that polycystic ovarian morphology in an ultrasound is seen in 20-33% of normal women[4]. Therefore, just the presence of ultrasound features is not tantamount to the presence of the syndrome. In this study, additional features like irregular cycles have developed after a substantial event, that is, weight gain. Moreover, patients with anovulation due to other causes were excluded and PCOS being the commonest cause of anovulation, it can be considered that these women developed PCOS following weight gain.

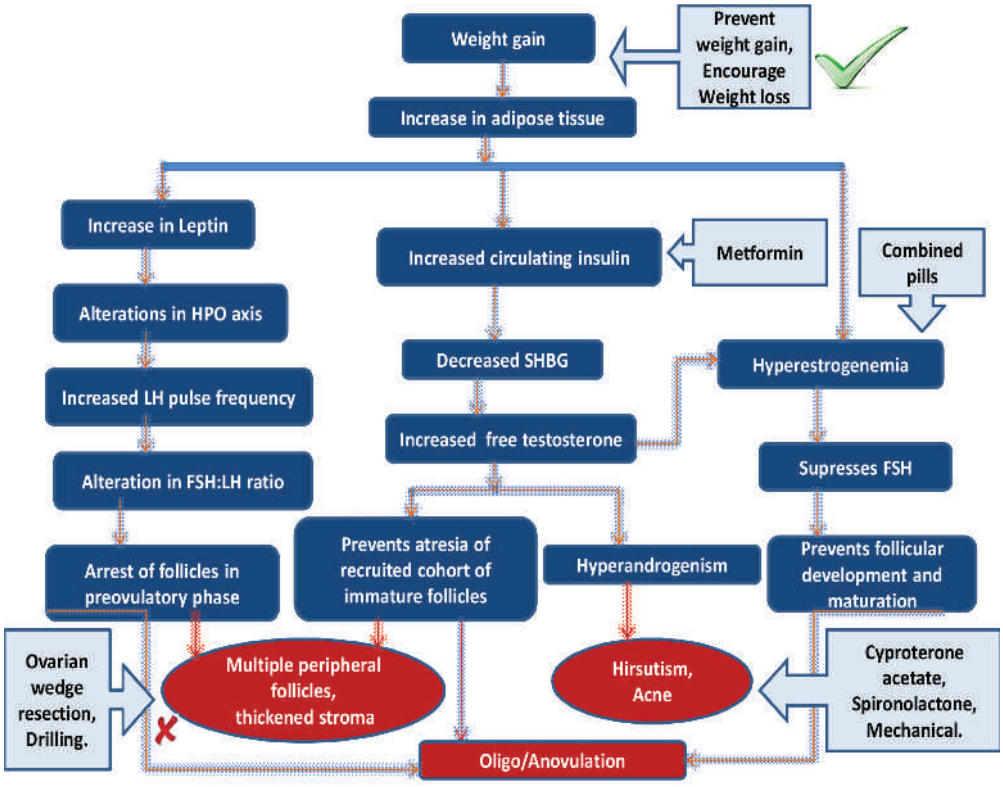

Fig 5 - Flow-chart showing the probable pathogenesis and the interventions in PCOS women

Conclusion

Our study group had women belonging to all categories of BMI. We observed that a highly significant group of women with normal as well as high BMI, developed oligo (or) anovulation and features of hyperandrogenism following a distinct event, which is weight gain. Moreover, many observational studies have noted that weight loss is associated with improved spontaneous ovulation rates in women with PCOS[20]. Therefore, the converse may equally be applicable too.

Thus, with the aid of previous studies and our data, we arrive at a hypothesis that weight gain could probably be the major precipitating factor for the development of Polycystic ovarian syndrome in a genetically susceptible patient, irrespective of their BMI. And therefore all patients shall be counseled for lifestyle modification and thereby weight reduction, which should be the primary target and initial treatment mode. Focusing on the consequences (as shown in Figure 5), would only lead to a transient alleviation of symptoms and not correct the intrinsic pathology and thereby does not prevent pregnancy complications or long-term health consequences.

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The authors declare no conflict of interest.

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