Impact of Obesity on Frequency and Pattern of Disease in Polycystic Ovarian Syndrome (PCOS)

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Background: Obesity plays an important role in the genesis and maintenance of polycystic ovarian disease. PCOD is the leading cause of anovulatory infertility in females and affects 1 in 10 women of reproductive age. PCOD is strongly associated with obesity.

Aims and Objectives: To study frequency of weight distribution and differences in disease pattern of PCOD in obese and non obese females.

Study Design: Cross-sectional analytical Study.

Place and Duration of Study: The study was conducted in Qassim University Clinic, College of Medicine, Buraida (Kingdom of Saudi Arabia) over 2 years (June 2007-June 2009).

Materials and Methods: A sample of 500 non pregnant Saudi females of reproductive age presenting with different gynecological complaints was included in the study. Body Mass Index was calculated for all 500 patients after recording height and weight using formula; BMI = Weight (Kg)/Height (m)^2. The sample was divided into two groups depending upon their i.e. BMI = 18.5-24.9 (Normal weight) and BMI > 25 (overweight/obese). Frequency of PCOD was calculated in both groups in the first step and in the 2nd step obese PCOD patients (Study group) were compared with normal weight PCOD patients (control group) regarding clinical manifestations, endocrine profile, metabolic profile, ovarian morphology and difficulties encountered in the management. Data were collected on a structured proforma and analyzed using computer programme SPSS Version 14 for windows and a p-value of < 0.05 was used as statistically significant.

Results: Out of 500 patients 344 (68.8%) had BMI > 25 (overweight and obese) while 156 (31.2%) had BMI between 18.5-24.9 (normal weight). A significantly increased frequency of PCOD was found in obese patients; 152 (44%) as compared to those with normal weight; 14 (9%). All manifestations of PCOD (infertility, menstrual irregularity, skin problems like hirsutism, acne and Acanthosis nigricans) as well as disturbance in endocrine and metabolic profile were present with higher frequency and severity in obese as compared to non obese patients. Greater difficulties were encountered in the management of obese as compared to non obese PCOD patients.

Conclusion: Saudi females have high frequency of obesity which is the most important risk factor for PCOD. All manifestations of PCOD are more frequent and severe in obese patients making PCOD with obesity a big medical as well as a social issue and a real challenge to manage. The study stresses on the need to control weight as the cornerstone of management of obese patients with PCOD.

Key words: Obesity, Polycystic ovarian disease, disease pattern, obese, non obese Saudi females.

Introduction

Obesity plays a crucial role in the genesis of many chronic and complex disorders such as adult onset diabetes mellitus and PCOD which is the commonest endocrinological problem and affects 6%-10% females of reproductive age. PCOD was first described by Stein and Leventhal in 1935 in women with oligo-anovulation, obesity, hirsutism and enlarged polycystic ovaries.

The cause of PCOD is multifactorial and complex. The disease has genetic basis affected by environmental factors. Patients with PCOD have relatives with type II diabetes, hypertension, raised s/cholesterol, obesity, infertility, hirsutism, and menstrual irregularities. An autosomal dominant mode of inheritance has been found in females with PCOD.

PCOD is defined by different criteria. National Institute of Health (NIH, 1991) defines PCOD as the condition having ; (1) hyperandrogenism and or hyperandrogenemia, (2) oligo-anovulation and (3) exclusion of related disorders. While Rotterdam (2003) criteria defines PCOD after excluding other relevant problems by two of three characteristics; (1). oligo-anovulation (2) clinical and or biochemical evidence of excess androgen production (3) polycystic ovaries on ultrasound. The probable criteria for PCOD include insulin resistance, onset around menarche, raised luteinizing (LH) to follicle stimulating (FSH) ratio and polycystic ovaries seen on ultrasound.

Obesity is an important risk factor for PCOD. Literature review shows that 30-70% of PCOD females are obese, though disease is also seen in women of normal weight but with less frequency. The presence of obesity markedly
modifies the clinical and biochemical expression of disease and makes the management of the syndrome very difficult. About 40% of females with PCOD have insulin resistance which is also increased to up to 70% by the presence of obesity.8 Obesity also exacerbates the co-morbidities related with PCOD like hypertension, diabetes, hypercholesterolemia (metabolic syndrome) and heart disease.8,9 Anovulation in PCOD leads to unopposed estrogen secretion which is a risk factor for endometrial hyperplasia and carcinoma. These effects are further increased by the presence of obesity through increased levels of estrone converted from androstenedione in the adipose tissues.

The distribution of weight is also peculiar in PCOD. This is well documented that it is the central or apple shaped obesity with raised waist hip ratio than the pear shaped obesity that characterizes PCOD. Reduction in waist hip ratio in both lean and obese patients results in improvement in hormonal profile as well as reduction in insulin resistance in PCOD9.

Different mechanisms including enzymes, polypeptides and genes have been described to explain the link between obesity and PCOD. Females with PCOD have functional abnormality in cytochrome P450c17 which is the rate limiting enzyme10 in androgen production. This defect may lead to hyperandrogenemia seen in PCOD.

Certain polypeptides like leptin and ghrelin have been implicated as a link between PCOD and obesity. Leptin11 is the protein product of obesity gene (ob gene) secreted by adipocytes. Leptin acts as a messenger from adipose tissues to the hypothalamus to tell the brain about how much fat cells are there in adipose tissues. In response to this, hypothalamus changes the secretion of gonadotrophin releasing hormone (GRH) which modifies the secretion of LH by the anterior pituitary which further regulates ovulation and reproduction.

In addition to leptin, ghrelin12 which is a natural ligand of the growth hormone secretagogue receptor has also been shown to play an important role as a link between PCOD and obesity. Ghrelin has been demonstrated to increase appetite, reduce fat utilization and cause obesity after administration to rodents and human beings.

Research has shown that a gene implicated in the development of obesity is also related with susceptibility to PCOD. Recently a gene named FTO gene is identified as a link between obesity and PCOD.13

Obese patients with PCOD are not only physically but also psychologically depressed. The disfigurement due to obesity along with hirsuitism, acne and acanthosis nigricans is very traumatic. These problems along with prolonged infertility resistant to treatment make them further depressed. Weight reduction is a big challenge in PCOD patients. PCOD, is therefore, a big medical as well as social issue affecting especially the young ladies along with long term complications like type 11 diabetes, heart disease, hypertension and endometrial cancer.

It is possible, however, for women to develop PCOS without being overweight or obese. Therefore, although obesity is strongly associated with PCOS, it is not always necessary for its development. The present research is focused to find out the difference in the frequency as well as disease pattern of PCOD in obese and normal weight females.

Materials and Methods
A sample of 500 randomly selected patients attending Qassim University clinic (KSA) with various gynecological problems was selected during study period (June 2007-June 2009). In the first step, we calculated Body Mass Index (BMI) of all 500 patients and divided them into two groups; normal weight (BMI = 18.5 – 24.9), and overweight/obese (BMI > 25 / > 30 respectively). In the 2nd step, we calculated the frequency of polycystic ovarian disease (PCOD) in both groups. Finally we defined two subgroups of patients; PCOD patients with normal BMI (control group) and PCOD patients who were overweight and obese (study group) followed by comparison of these two subgroups in respect of clinical, endocrine, metabolic and ultrasonographic ovarian profile along with special difficulties regarding management of PCOD in both groups.

Inclusion Criteria: The study included all females of reproductive age both married and unmarried presenting with:

1) Infertility (oligo-anovulation).
2) Menstrual irregularity (oligomenorrhea, secondary amenorrhea).
3) Clinical evidence of hyperandrogenism i.e. hirsuitism, acne, Acanthosis nigricanes and alopecia.

Exclusion Criteria: Patients with hyperandrogenism and anovulation other than PCOD like Cushing syndrome, untreated hypo or hyperthyroidism, ovarian tumors and adrenal hyperplasia/tumors were excluded from the study.

Outcome Measures;
1. Frequency of overweight and obesity in Saudi females of reproductive age.
2. Frequency of PCOD in normal and overweight/obese patients.
3. Pattern of PCOD in terms of clinical features, endocrine and metabolic profile and ovarian morphology as seen on ultrasound in study and control groups.
4. Difficulties encountered in the management of obese and normal weight patients with PCOD.

We defined obesity using World Health Organization (WHO)14 and National Institute of Health (NIH)15 criteria; underweight as body mass index (BMI) < 18.5, normal weight as BMI between 18.5-24.9, overweight as BMI between 25-29.9 and obesity as a BMI of 30 or greater. Obesity is further divided into class I (BMI 30-34.9), class II (BMI 35-39.9) and class III (BMI > 40).
Height and weight of all the 500 patients were recorded by the on duty staff nurse using standard techniques. BMI or Quetelet index was calculated using formula; BMI = Weight (Kg) / Height(m)^2. We used Rotterdam criteria to define and diagnose PCOD in our study i.e. after excluding other causes of hyperandrogenism, presence of 2 out of the following 3 features; (1) oligo or anovulation, (2) clinical and or biochemical features of hyperandrogenism and (3) Presence of polycystic ovaries on ultrasound.

Detailed history and physical examination were carried out on all patients including current age, age of menarche, age of onset of menstrual irregularity, infertility and occurrence of similar cases in the family. Clinical features of hyperandrogenism (hirsuitism, acne, Acanthosis nigricans, and alopecia) were recorded.

Hirsuitism which is excessive hair growth in male pattern of distribution in a female was graded using index of Ferriman and Gallwey(IFG). Which scores presence of hairs on 11 body areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back, arm, forearm, buttocks). A score of 4-8 is considered as mild, 8-44 as moderate and a score > 44 the most severe.

Acanthosis nigricans which is a marker of insulin resistance and is characterized by the presence of dark thickened area of skin behind the neck, axilla and inside skin folds was staged according to the scoring system given below. Among the sites where severity is taken into consideration, the neck showed the highest agreement.

Staging of Acanthosis nigricans (neck severity)

Absent (0)-not detectable on close inspection

Present;
(1) Clearly seen on close inspection, not visible to the casual observer, extent not measurable.
(2) Limited to the base of skull, usually does not extend to the lateral margins of the neck, extent not measurable.
(3) Extends beyond the lateral margins of the neck, extent is measurable.

Dermatological consultation was taken where necessary.

Endocrine Profile: we measured the serum levels of the following hormones in study and control groups using Elisa test.
1) Luteinizing hormone (LH).
2) Follicle stimulating hormone (FSH).
3) Testosterone (free).
4) Prolactin.

Metabolic profile: we measured the following parameters.
1) Serum cholesterol (triglycerides, LDL).
2) Fasting blood glucose (FBG) and fasting insulin ratio (FI). A ratio of FBG to FI of < 4.5 considered as an evidence of insulin resistance. Ratio of FBG to FI is better index of insulin resistance than only fasting levels of insulin in PCOD.

Ovarian morphology; Ovaries were evaluated by pelvic ultrasound (Transabdominal and transvaginal if needed) defined as enlarged if > 9 cm in diameter), polycystic if they had 10 or more follicles measuring 2 – 10 mm in diameter per ovary and increased density of the stroma.

Statistical Analysis: Data were collected on structured proforma and compared between the two groups using SPSS Version 14 for windows with a p-value < 0.05 taken as statistically significant. The quantitative variables were analyzed by calculating means and standard deviations and comparison made using student t-test while the qualitative parameters were analyzed by frequency and percentages and compared using chi square test.

Results
High frequency (BMI of > 25 in 68.8% cases) of overweight and obesity was recorded in Saudi females of reproductive age as shown in Table 1.

A significantly increased frequency of PCOD was recorded in overweight and obese females (44%) as compared to normal weight group (9%) as demonstrated in Table 2.

Table 3 shows that there is no difference (25 ± 3 versus 24 ± 4 years) in the mean age of the patients at the time of presentation between the control and study group respectively. The age of menarche was delayed in obese girls as compared to non obese (15 ± 4 versus 12 ± 1 respectively). The menstrual irregularity started earlier (19 ± 3 years) in obese women as compared to non obese (24 ± 2).

Significant difference is recorded in frequency of all clinical manifestations of PCOD between obese and normal weight patients. (Menstrual irregularity; 77% versus 54%, infertility; 66% versus 32%, hirsuitism; 22% versus 2%, acne; 15% versus 3% and Acanthosis nigricans; 5.6% versus 1.2% respectively) as shown in Table 4.

Table 5 shows that the endocrine profile is much more disturbed in obese as compared to normal weight females with PCOD (LH; 45.5 ± 3 versus 24.3 ± 4 U/L, LH: FSH ratio; > 3:1 in 66% versus 15% cases, Prolactin; 68 ± 6 versus 46. ± 40 ng/ml and free testosterone; 12.7 ± 4 versus 4.5 ± 3 ng/ml respectively). The levels

Table 1: Frequency of obesity in Saudi Females of reproductive age.

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<thead>
<tr>
<th>Variable</th>
<th>Normal weight BMI=18.5-24.9</th>
<th>overweight/Obese BMI&gt;25</th>
<th>p-value</th>
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<tr>
<td>Weight(BMI) N0 (%)</td>
<td>156/500 (31.2)</td>
<td>344/500 (68.8)</td>
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of FSH and DHEAS remained within normal range in both groups.

Table 6 shows that mean S/cholesterol and fasting blood sugar level were high in the study group as compared to control group (Cholesterol; 216 ± 4 versus 216 ± 4 mg/dl, F/blood sugar; 125 ± 5 versus 102 ± 3 mg/dl). Also the ratio of fasting blood glucose to fasting blood insulin ratio remained < 4.5 in 62% cases in study as compared to 21% cases in the control group which is statistically significant (p-value <0.001).

Figure 1 shows that significant difference was noted in ovarian morphology (polycystic 65 versus 30%) between the study and control group respectively.

Figure 2 shows that greater difficulties were encountered in the management of PCOD in obese as compared to normal weight patients i.e. weight reduction difficult in 35 versus none, intolerance to metformin noted in 22 versus 02 cases, resistance to ovulation induction by clomiphene recorded in 25 versus 05 cases, intolerance to OCPs noted in 26 versus 04 cases, hirsuitism resistant to treatment in 23 versus 02 cases and psychological disturbance due to above mentioned problems and infertility noted in 40 versus 03 cases in the study and control group respectively.

Discussion

High prevalence of overweight and obesity was found in Saudi females (68.8%) in our study. This result resembles with some of the studies conducted in the Kingdom earlier on this issue.\textsuperscript{19} \textsuperscript{20} Al Shammery and coworkers\textsuperscript{19} reported obesity in 41.9% and morbid obesity in 5.18% of Saudi females, while Khashoggi\textsuperscript{20} and coworkers reported 64.3% of Saudi females attending Health Centers to be obese.

There is much evidence to suggest that obesity plays an important role in the development and maintenance of PCOS pathology. There is a close correlation between obesity and symptom severity in women with PCOS, and even modest reductions in weight generally brings significant improvements in menstrual regularity, fertility and hyperandrogenic features. Obesity has been associated with increased PCOD since the syndrome was first described in 1935.\textsuperscript{2} In our study significant difference was found in frequency of PCOD in obese (44%) as compared to non obese (9%) females. The results of study by Jana Vrbikova\textsuperscript{1} show that 30-70% of obese females are affected by PCOD while Adams J\textsuperscript{21} in one study recorded 30-50% of obese females to be affected by PCOD.

The presence of obesity significantly modifies both clinical and laboratory expression of the syndrome. The major characteristic of PCO is chronic anovulation, which in our study was reflected by oligomenorrhea and/or secondary amenorrhea with higher frequency seen in obese (35%, 31%) as compared to normal weight (30%, 10%) females respectively. This chronic anovulation also explains the high incidence of infertility 66% versus 23% detected in obese and non obese patients respectively in our study.

It has been reported that 50% to 70% of patients with PCO have hirsutism.\textsuperscript{22} In our study 46% versus 15% cases

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<th>Table 2: Frequency of PCOD in obese and non obese group.</th>
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<td>Frequency of PCOD No (%)</td>
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<th>Table 3: Mean age, age of menarche and age of onset of menstrual problems.</th>
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<th>Table 4: Frequency of Clinical manifestations of PCOD.</th>
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had hirsutism in obese and non-obese females respectively and the phenomenon was mild in normal weight group (IFG 4 – 8) but severe (IFG > 8) in 80% of obese females. This result shows that the prevalence of hirsutism in none obese PCOD females was only slightly higher than in the general population.

Endocrine profile was markedly disturbed in obese as compared to normal weight females (LH: FSH ratio > 3:1 in 35% versus 15% respectively). There is enough evidence in literature to support the concept of weight reduction as the basic tool to normalize the endocrine profile.

The association of hyperprolactinemia with PCO was noted a long time ago. Some investigators, however, consider it to be a random occurrence because of the relative frequency of the two disorders. Others, however, believe that both conditions may be related to an increase in LH/FSH ratio and to a decrease in dopaminergic tonus. Hyperprolactinemia is estimated to occur in approximately 25 percent of women with PCOD. We detected this association in only 28 versus 6% percent of the patients in study and control groups respectively.

Obesity increases the risk of co-morbidities associated with PCOS, such as impaired glucose tolerance, insulin resistance, type 2 diabetes mellitus, hyperlipidemia and arterial hypertension. Our results show increased mean value of fasting glucose (125±5 versus 102±3 mg/dl) and s/cholesterol (216±4 versus 145±5 mg/dl) in the study and control group respectively. We recorded insulin resistance in 62% versus 21% cases in the study and control groups respectively. One study by Eagleson et al showed insulin resistance in 30% of lean and 75% of obese patients with PCOD.

We detected polycystic ovaries in 65% versus 30% of cases in the study and control group respectively. These data suggest that the presence of enlarged and polycystic ovaries is frequently detected by ultrasound, but that their absence does not exclude the diagnosis of PCO. Ultrasonography is particularly useful in borderline cases with suggestive clinical histories which do not present, for example, changes in the LH/FSH ratio.

For gynecologists, obese PCOD patients are a big challenge to manage. We encountered significant difficulties in the management of obese PCOD patients in relation to weight reduction, intolerance to oral contraceptive pills and metformin, hirsutism resistant to treatment and psychological depression observed in 20-40% of cases as compared to study group where these figures

| Table 5: Endocrine profile in obese and non-obese PCOD females. |
|------------------------|----------------|----------------|--------------|
| S. No | Variables | Control group | Study group | p-value |
| 1. | LH(U/L) Mean ± SD | 24.3±4 | 45.5 ± 3 | 0.01 |
| 2. | FSH(U/L) Mean ± SD | 11.1 ± 7 | 12.2 ± 5 | 0.09 |
| 3. | LH:FSH ratio  >2:1(85) >3:1 (15) | > 2 : 1 (34) > 3 : 1 (66) | 0.001 |
| 4. | Prolactin (ng/ml) Mean ± SD | 46 ± 4 | 68 ± 6 | 0.02 |
| 5. | Free testosterone (ng/ml) Mean ± SD | 4.5 ± 3 | 12.7 ± 4 | 0.01 |
| 6. | DHEAS (ugm/dl) Mean ± SD | 176.4 ± 5 | 184.6 ± 4 | 0.093 |

Normal values in females
LH=1.5-10 U/L (follicular phase) Prolanctin=upto 20 ng/ml
FSH=2.9-12 U/L (follicular phase)
LH: FSH ratio < 2:1 Free Testosterone=0.2-2.3 pgm/ml

| Table 6: Metabolic profile of obese and non-obese PCOD patients. |
|------------------------|----------------|----------------|--------------|
| S. No | Variables | Group. A | Group. B | p-value |
| 1 | S/cholesterol mg/dl Mean ± SD | 145 ± 5 | 216 ± 4 | 0.01 |
| 2 | Fasting glucose mg/dl Mean ± SD | 102 ± 3 | 125 ± 5 | 0.03 |
| 3 | Fasting Blood glucose and Fasting insulin ratio < 4:5 No (%) | 3 (21) 95 (62) | 0.001 |

Normal values:
S/Cholesterol < 200 mg/dl
Fasting blood glucose, < 105 mg/dl,
Fasting insulin level < 10 mu/l (normal), 10-14 mu/l (mild IR), > 14 MU/L (moderate to severe IR)
FBG: F1 < 4:5 shows insulin resistance.
IR = Insulin resistance, FI = Fasting insulin
Control Group

Ovarian Morphology on USG

- Normal – 15%
- Enlarged – 10%
- Polycystic – 30%
- Enlarged and Polycystic – 25%

Study Group

Ovarian Morphology on USG

- Normal – 10%
- Enlarged – 15%
- Polycystic – 65%
- Enlarged and Polycystic – 10%

Figure 1: Ovarian morphology as seen on pelvic ultrasound.

Figure 2: Difficulties encountered in Management of PCOD in both groups.

were very low (2-5%).

Conclusion

Obesity is strongly associated with PCOD and the prevalence of disease will increase with rising epidemic of obesity in the Kingdom of Saudi Arabia and worldwide. Obesity is associated with increased frequency of PCOD and all parameters of disease (clinical, endocrine, metabolic and sonographic) are more frequent and severe as well as difficult to manage in obese as compared to normal weight patients. Our study strongly supports the need to control the global epidemic of obesity and weight control as the basic tool to manage obese PCOD patients. Further research is needed to find the exact link between obesity and PCOD and to find out the single root cause which should be tackled to manage this complex syndrome.

Limitations of Study: We could not study the long term complications of PCOD like hypertension, type II diabetes, and endometrial carcinoma due to difficulty in following the patients over prolonged period of time.

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