CHARACTERISTICS OF INFERTILE PATIENTS WITH OVULATORY DYSFUNCTION AND THEIR RELATION TO BODY MASS INDEX

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Background: Ovulatory dysfunction is a group of disorders with variable clinical presentations occasionally having serious long-term adverse effects. It accounts for 30% of female fertility problems. Evidence suggests an association between an individual's weight and disorders of ovulation. The objective of our study was to describe the clinical and hormonal profile of subfertile women with ovulatory dysfunction in relation to their body mass index (BMI). **Methods:** This prospective, descriptive study was carried out in Mother and Child Health Centre, PIMS, Islamabad and Railway hospital, Rawalpindi from April 2001 to March 2007. One hundred & thirty eight infertile patients with ovulatory dysfunction were included. The clinical data including BMI of each patient was recorded in addition to reports of investigations comprised of cervical smear, pelvic ultrasound and hormonal profile. **Results:** Primary infertility was found in 61% while secondary in 39% of the patients. The mean age was 29 years and mean duration of infertility was 6 years. Menstrual pattern was normal in 56.5%. BMI was normal in 30.4% while most patients were overweight and obese. Prolonged cycles, history of systemic endocrine disorders, abnormal vaginal discharge, hirsutism, polycystic ovarian morphology and hormonal abnormalities were more frequent in patients with increased BMI. During the study period, 21.7% of the women conceived. **Conclusion:** Infertile patients with ovulatory dysfunction present more frequently with primary infertility. They usually have higher than required BMI. Oligomenorrhoea amenorrhoea, hirsutism and hormonal abnormalities are more frequent in overweight than infertile patients with ovulatory dysfunction having a normal BMI.

Keywords: Infertility, Ovulatory Dysfunction, Clinical Characteristics, Body mass index, BMI

INTRODUCTION

Although the prevalence of infertility has remained fairly constant over the years, the demand for services has increased. Physical morbidity usually stems from the cause of infertility and not infertility itself. However psychological morbidity from infertility may be severe. Over 22% of gynaecological consultations in Pakistan are involved for the treatment of infertility.[1]

Infertility resulting from ovulatory dysfunction account for about 21% or a fifth of all of infertility and 30% of female infertile patients.[2] Studies carried out in Pakistan quote this figure between 16–48%.[3] It was placed at a much higher figure in India in a community based study.[4]

The ovulatory factor refers to the ability of a woman to normally undergo the process of ovulation. The absolute proof of ovulation is pregnancy. The World Health Organization (WHO) scientific group on 'Agents stimulating ovarian function in the human' has proposed a working classification of ovarian dysfunction. Despite many advances in the understanding of ovulatory pathophysiology since then, this classification has stood the test of time; it remains widely used and provides logical approach to a diagnosis-oriented management. Ovulatory dysfunction is divided into seven main groups namely hypothalamic-pituitary failure, hypothalamic-pituitary dysfunction, ovarian failure, congenital or acquired genital tract disorders, hyperprolactinemia with a space occupying lesion in the hypothalamic-pituitary region, hyperprolactinemia without a space occupying lesion in the hypothalamic-pituitary region and amenorrhoea with a space occupying lesion in the hypothalamic-pituitary region with normal or low prolactin. The investigation of infertile couples should identify any one or more of these events so that therapy of proven value can be initiated. Whereas in our part of the world, physicians working with such couples should design a series of investigations that will meet these needs rapidly, accurately, without invasion and in the least expensive manner, advanced research in this context[5,6] is underway in the developing countries. Studies abroad suggest that the intricate and complex hormonal balance governing the hypothalamic-pituitary-gonadal axis is affected by an individual's BMI affecting fertility[7] as well as early pubertal[8] and premenarcheal[9] hormonal mileau implying long term consequences. Since weight management is a relatively simple and inexpensive intervention it may have profound significance in devising treatment strategies for our patients.

This study aimed to describe the clinical as well as hormonal profile of subfertile women with ovulatory dysfunction and to determine the distribution of these characteristics in relation to body mass index in order to address these factors while making management protocols for our community.

MATERIAL AND METHODS

In this prospective study a total of four hundred and twenty seven infertile patients who attended out-patient

clinic or remained admitted for any surgical procedure were recruited initially by convenient sampling technique. One hundred and twenty seven patients were excluded due to incomplete investigations. Of the remaining 300 patients investigations according to protocol were complete. One hundred and thirty eight subjects were diagnosed to have ovulatory dysfunction and having fulfilled the inclusion criteria they were included in the study.

The data of each patient was recorded in identical pre-designed proforma after informed consent. Initial assessment was carried out by taking a detailed history and clinical examination with particular attention to duration and type of infertility, age of the patient, menstrual and coital history, relevant past, systemic and surgical history, abnormal pelvic findings, goitre, hirsutism, galactorrhoea and body mass index (BMI). A regular menstrual cycle between 21 to 35 days was called normal. A prolonged cycle of more than 35 days but less than 6 months was termed oligomenorrhoea while a cycle longer than 6 months was called amenorrhea. A cycle shorter than 21 days was called polymenorrhoea.

Body mass index was measured as weight in kilogram per square of height in meter (Kg/m^2). The patients were categorized as follows: Severely thin <16.9, under weight 17–18.4, desirable weight 18.5–24.9, over weight 25–29.9 and obese when BMI was >30 Kg/m^2.

The initial investigations comprised of cervical smear, pelvic ultrasound and midluteal phase progesterone. The patient was asked to maintain a menstrual calendar.

Serum prolactin, thyroid function tests, luteinising hormone (LH), follicle stimulating hormone (FSH), oestrogen and testosterone was ordered if indicated by history or examination.

Two of the given three criteria were required to diagnose PCOS according to the Rotterdam workshop after exclusion of other causes of androgen excess. A level more than 10 ηg/ml of day 21 serum progesterone was considered to be indicative of an ovulatory natural cycle. Levels within the range 5–10 ηg/ml were called low while those below 5 ηg/ml were termed very low indicating an anovulatory cycle. LH/ FSH ratio of more than 2 was considered in favour of the diagnosis of polycystic ovarian syndrome (PCOS). Both LH and FSH were measured preferably on day 3 of the cycle. FSH was used as a gauge of ovarian reserve. The normal range was 3–20 mIU/ml, less than 6 was good/normal, between 6 and 13 fair, 14–20 diminished reserve, 21–29 impending ovarian failure while >30 irreversible ovarian failure.

Day 3 LH levels less than 7 were considered normal, between7 to 20 high and more than 20 mIU/ml very high.

Day 3 oestradiol levels were considered normal in the range of 25–75 pg/ml. Abnormally high levels on day 3 indicated diminished ovarian reserve or existence of a functional cyst. Day 3 total testosterone more than 50 ηg/ml was considered elevated.

Day 3 prolactin of more than 24 ηg/ml on two occasions was termed hyperprolactinemia. This was followed up by x-ray skull and neurological opinion.

The normal range for thyroid stimulating hormone (TSH) was taken as 0.4–4 mIU/ml. A high level with a low or normal T4 level indicated hypothyroidism while hyperthyroidism was indicated if the levels were vice versa.

Ovulatory dysfunction was labelled in case of PCOS, thyroid disease, hyperprolactinemia and premature ovarian failure. The patients were further managed according to the etiologic factor determined during the course of investigations.

Since this was a descriptive study, no inferential tests or *p*-value was required. Descriptive statistics were applied by SPSS Version 11.0. Mean values of age & duration of subfertility with their standard deviations were determined. The percentage of clinical variables was calculated out of the total sample size of 138 subjects.

RESULTS

There were 138 infertile patients who had ovulatory dysfunction. Eighty-four (61%) had primary while 54 (39%) had secondary sub fertility. Primary was slightly more frequent than secondary infertility in lean patients. The mean duration of sub fertility was approximately 6±4.3 years within the range of 1–16 years. The mean age of the patients was 29±4.9 years while the age at which menarche occurred ranged from 10–18 years (mean 13 years). Interestingly more than half of the patients (56.5%, n=78) had a normal menstrual cycle. Oligomenorrhoea was seen in 42 (30.4%), amenorrhoea in 12 (8.7%) and hypomenorrhoea in 3 (2.2%) subjects. Three patients with thyroid disease had polymenorrhoea.

There was no significant past medical or surgical history in 78 (56.5%) patients. However, 6 (4.3%) patients each had history of diabetes mellitus and thyroid disorder, all of them having an increased BMI. Abnormal vaginal discharge was a complaint of 33 (23.9%) while 15 (10.8%) women underwent pelvic surgery in the past. Again vaginal discharge was more commonly seen in women with BMI >25 Kg/m^2.

A normal BMI was recorded in only 30.4% (n=42). As expected most of the patients were overweight (43.5%, n=60) and obese (21.7%, n=30). However, 6 (4.3%) patients were underweight. Menstrual irregularity was more often recorded in the

obese women relative to those who were overweight or had a desirable BMI (Table-1).

On general physical examination, no abnormality was detected in 50% (n=69) of the study population. Hirsutism was seen in 42 (30%) and goitre in 24 (17%) ladies. There was demonstrable galactorrhoea in 3 women. Out of the 42 patients with desirable weight, 78.6% (n=33) did not have any abnormality on general physical examination while out of the 90 patients having an increased BMI, 40% (n=36) had hirsutism and17% (n=15) had goitre. The patients with galactorrhoea were overweight too. Nearly all (95.7%, n=132) the patients did not have any abnormality on abdominopelvic examination. The cervical smear report was normal in 82.6% (n=114) and inflammatory in 11% (n=15) however, 9 patients (6.5%) had inadequate smears for reporting. The patients with inflammation on smear were overweight or obese as well.

The pelvic ultrasonograhic findings were consistent with polycystic ovarian morphology in 39 (28.3%), fibroid uterus in 9 (6.5%) and adnexal mass in 3 (2.2%) patients. The findings were normal in 87 (63%). Abnormal findings were more frequent in patients with an increased BMI.

Serum progesterone level was very low <5 ηg/ml in 93 (67.4%) and between 5 to 10 ηg/ml in 30 (21.7%) patients (Table-2). Fifteen (11%) patients had FSH levels more than 15 mIU/ml pointing to diminished ovarian reserves. Six women had impending ovarian failure. Thirty (71.0%) of the 42 ladies with normal BMI had good ovarian reserves as indicated by their FSH levels in contrast to 39 (43%) of the 90 women with high BMI. Though hyperprolactinemia was seen in 21 (15.2%), only 3 patients had complaint of galactorrhoea. Normal weighing patients were more likely to have normal laboratory levels of prolactin than heavier ones. The X-ray skull was normal in all the patients with hyperprolactinemia who needed further evaluation.

On evaluating the thyroid functions 12 (8.7%) were found to have hypothyroidism while 3 (2.2%) had hyperthyroidism. Only 3 of these subjects had BMI in the normal range. Out of the 30 (21.7%) women who conceived during the study period, 24 (17.4%) needed treatment while 6 (4.3%) did so spontaneously.

DISCUSSION

The incidence of sub fertility in Pakistan is 21.9% according to a survey by WHO (1983). Ovulatory dysfunction was found in 138 out of the initially 300 infertile patients recruited in our study. This is in lieu with the findings in one of the largest studies carried out in Pakistan by Rana and Saeed.[10]

Population based studies quote the prevalence of ovulatory disorders at 21%. The reason for the higher frequencies encountered in tertiary level hospital based data is the large number of patients referred to these institutes after being evaluated initially and at times even mismanaged at smaller centers or by local hawks. The mean age of the patients was 29 years with it being the same in lean as well as overweight patients. Approximately 90% of the patients had presented by 35 years of age. Since chances of conception decrease dramatically after this age, our study may reflect the awareness of the general population regarding the significance of age in infertility. Secondly, the causes of infertility in older women are different from those in younger women. Women over 35 years of age are nearly twice as likely to present with unexplained infertility.[11]

The mean duration of infertility at the time of booking of about 6 years was the same in both lean and overweight women although lean women had slightly increased frequency of primary than secondary infertility. This does not match the findings in other researches where patients with primary infertility took longer to present for the first time than secondary infertility.[12]

Table-1: Menstrual cycle-BMI cross-tabulation

	Body mass index				
Menstrual history	**Desirable 18.5–24.9**	**Obese >29.9**	**Overweight 25–29.9**	**Underweight 17–18.4**	**Total**
Amenorrhoea [n (%)]	3 (2.2)	6(4.4)	3(2.2)		**12 (8.7)**
Hypomenorrhoea [n (%)]	3 (2.2)				**3 (2.2)**
Normal [n (%)]	24 (17.4)	6 (4.4)	42 (30.4)	6 (4.4)	**78 (56.5)**
Oligomenorrhoea [n (%)]	9 (6.5)	18 (13)	15 (11)		**42 (30.4)**
Polymenorrhoea [n (%)]	3 (2.2)				**3 (2.2)**
Total n (%)	**42 (30.4)**	**30 (21.7)**	**60 (43.5)**	**6 (4.4)**	**138(100)**

Table-2: Hormonal profile

	S. Progest.	**LH**	**FSH**	**LH/FSH**	**Oestradiol**	**Prolactin**	**TFT**
Normal [n (%)]	15 (10.9)	30 (21.7)	69 (50)	60 (43.5)	48 (34.8)	84 (60.9)	39 (28.3)
Abnormal [n (%)]	123 (89.1)	93 (67.4)	54 (39.1)	63 (45.7)	3 (2.2)	21 (15.2)	15 (10.9)

S. progest=serum progesterone, LH=luteinizing hormone, FSH= follicle stimulating hormone, TFT=thyroid function tests.

The 12 patients with history of endocrine disorders of diabetes and thyroid disease as well as those with abnormal vaginal discharge were all overweight. Thus, metabolic and hormonal abnormalities which in addition to causing ovulatory dysfunction, significantly increase risk for coronary artery disease, type 2 diabetes mellitus, endometrial carcinoma and obstructive sleep apnoea should have early recognition as they can pose significant health risk if untreated.[13]

Abnormal menstrual cycle pattern is an important predictor of reduced fertility as it may indicate disturbances of the hypothalamic-pituitary-ovarian axis, ovulation, conception, implantation or sustained pregnancy.[14] Regular menstrual cycle was seen in almost 57% (n=78) of our study population while prolonged cycle length was recorded in only 40% (n=54). However, in other studies[15] the presence of oligomenorrhoea was 63% while amenorrhea was 20%. It has long been recognized[16] that extremes of weight-BMI of more than 27 or less than 17 Kg/m^2 are associated with anovulation and consequent infertility. This was further confirmed by our study where 65.2% of the patients had body mass index greater than the desirable level. Approximately half of all women with ovarian dysfunction such as polycystic ovary syndrome (PCOS) are overweight or obese, and other studies[17] have reported endocrine and metabolic differences between lean and obese women as seen in our study too. Obese women in our study group more frequently complained of prolonged cycles further endorsing other research works where body mass index ≥ 25 Kg/m^2 and amenorrhoea appear to be associated with severe endocrine and metabolic abnormalities.[18]

Thyroid diseases have significant effect on oestrogen and androgen metabolism, menstrual function and fertility. Clinically goitre was diagnosed in 24 patients while thyroid function tests were deranged in only 15 patients thus proving the low sensitivity of this clinical parameter.

Out of the 42 patients who had hirsutism, 36 had a higher than normal BMI. This finding is confirmed in other studies as well where hirsute women had a higher BMI.[19] The observation that obese women with polycystic ovary morphology (PCOM) had a greater risk of developing of PCOS and ovulatory dysfunction than non-obese women with PCOM was confirmed in our study as well where abnormal pelvic ultrasonographic finding of PCOM was more frequently encountered in women with increased BMI.

The development of diminished ovarian reserve generally reflects the process of follicular depletion and decline in oocyte quality. In our investigation most of the patients with normal BMI had good reserves on the other hand less than half of those with high BMI had adequate ovarian reserves. The association of decreased fecundity with increased basal FSH levels is confirmed by other studies as well.[20]

Hyperprolactinemia interferes with the normal pulsatility of GnRH leading to menstrual disorders and ovulatory dysfunction. In infertile female patients, it is quoted at 13.2% in Pakistan.[21] Hyperprolactinemia was found in 21 while galactorrhoea in only 3 of our patients. These findings are lower than the findings of other researches carried out in Pakistan.[21] However the finding that normal BMI is associated with normal laboratory values of prolactin is in lieu with other studies.

In our circumstances the conception rate of 21.7% (n=30) is quite encouraging. Newer drugs, sophisticated techniques and expertise have encouraged large number of infertile couples to seek medical advice and help. The treatment is still a tedious process involving time and money. The significance of public awareness regarding the role of time and age factor in the treatment of infertility cannot be overemphasized. Patients should seek advice at the right time and from the right place instead of wasting time, money and energy uselessly.

CONCLUSION

Infertile patients with ovulatory dysfunction present more frequently with primary infertility. They usually have higher than desirable BMI. Oligomenorrhoea/ amenorrhea, hirsutism and hormonal abnormalities are more frequent in overweight/obese patients than infertile patients with ovulatory dysfunction having a normal BMI.

REFERENCES

1. Ismail M, Zaidi K. Infertility: causes and treatment at Sheikh Zayed Hospital, Lahore. Mother Child 1998; 36(4):149–53.
2. McClure N, Thompson W. Investigation of the infertile couple. In: Shaw RW, Soutter WP, Stanton SL, editors. Gynaecology. Newyork: Churchill Livingstone, 1997;247–60.
3. Mehmood G, Sadia S. lnfertility data of Maternal & Child Health Center, PIMS. J Surg 2001;21,22:10–3.
4. Sayeed U. Reproductive, demographic and behavioral causes of infertility in India [abstract]. In: Malik MB, Alizadegan S, editors. The 2nd Royan International Research Award: Reproductive health and infertility, Sept 2001. Tehran: Royan Institute, 2001: 18. [http://www.royaninstitute.org]
5. Kassi E, Diamanti-Kandarakis E. The effects of insulin sensitizers on the cardiovascular risk factors in women with polycystic ovary syndrome. J Endocrinol Invest 2008;31(12):1124–31.
6. Aroda VR, Ciaraldi TP, Burke P, Mudaliar S, Clopton P, Phillips S, *et al*. Metabolic and hormonal changes induced by pioglitazone in polycystic ovary syndrome: a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metab 2009;94(2):469–76.

7. Chang RJ. The reproductive phenotype in polycystic ovary syndrome. Nat Clin Pract Endocrinol Metab 2007;3(10):688–95.
8. Chang RJ. Obesity and the emergence of sleep-wake gonadotrophin secretion in girls during early pubertal development. J Clin Endocrinol Metab 2009;94(4):1094–6.
9. Bordini B, Littlejohn E, Rosenfield RL Blunted sleep related luteinizing hormone rise in healthy premenarcheal pubertal girls with elevated body mass index. . J Clin Endocrinol Metab 2009;94(4):1168–75.
10. Rana S, Saeed S. Prevalence of infertility factors in Pakistan. Pakistan J Obstet Gynaecol 1993;6(1):17–34.
11. Maheshwari A, Hamilton M, Bhattacharya S. Effect of female age on the diagnostic categories of infertility. Hum Reprod 2008;23(3):538–42.
12. Usmani AT, Shaheen F, Waheed N. Laparoscopic evaluation of female infertility. Pakistan Armed Forces Med J 1995;45(2);63–5.
13. Futterweit W. Polycystic ovary syndrome: a common reproductive and metabolic disorder necessitating early recognition and treatment. Prim Care 2007;34(4):761–89.
14. Waller K, Swan SH, Windham GC, Fenster L, Elkin EP, Lesley BL. Use of urine biomarkers to evaluate menstrual function in healthy premenopausal women. Am J Epidemiol 1998;147:1071–80.
15. Shi Y, Guo M, Yan G, Sun W, Zhang X, Geng L, Xu L, Chen Z. Analysis of clinical characteristics in large scale Chinese women with polycystic ovary syndrome. Neuro Endocrinol Lett 2007;28(6):807–10.
16. Barbieri RL. The initial fertility consultation: recommendations concerning cigarette smoking, body mass index and alcohol and caffeine consumption. Am J Obstet Gynecol 2001;185(5):1168–73.
17. Silfen ME, Denburg MR, Manibo AM, Lobo RA, Jeffe R, Ferin M, Levine LS, Oberfield SE. Early endocrine, metabolic and sonographic characteristics of polycystic ovary syndrome (PCOS): comparison between nonobese and obese adolescents. J Clin Endocrinol Metab 2003;88(10):4682–8.
18. Cupisti S, Kajaia N, Dittrich R, Duezenli H, Beckmann MW, Mueller A. Body Mass Index and ovarian function are associated with endocrine and metabolic abnormalities in women with hyperandrogenic syndrome. Eur J Endocrinol 2008;158(5):711–9.
19. Liou TH, Yang JH, Hsieh CH, Lee CY, Hsu CS, Hsu MI. Chemical and biochemical presentations of polycystic ovary syndrome among obese and nonobese women. Fertil Steril 2008 Nov 1. (Epub ahead of print).
20. Steeq JW, Sterues P, Eijkemans MJ, Habbema JD, Hompes PJ, Broekmans FJ, *et al.* Predictive value and clinical impact of basal follicle stimulating hormone in subfertile, ovulatory women. J Clin Endocrinol Metab 2007;92(6):2163–8.
21. Tayyab M, Cheema YS, Khan H, Ditta A, Khan RL, Khan AS. Serum levels of prolactin and female infertility. Pakistan J Pathol 1999;10(2):12–4.

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