Insight into Female Endocrine Infertility and its Relationship to Body Mass Index

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Abstract

Objective: Endocrine subfertility among females is increasing worldwide due to the epidemic of obesity. The objective of this study was to determine the clinical and hormonal presentation of subfertile women of endocrine aetiology and its relationship to Body Mass Index (BMI) and to classify the causes of anovulation according to the World Health Organization (WHO).

Methods: This observational, cross-sectional study was done in infertility clinic at Jinnah Medical College Hospital, from January 2015 to December 2015. Seventy-three subfertile females aged from 15 to 45 years with endocrine cause were included. After detailed history and clinical examination, ultrasound pelvis for follicular tracking and hormone profile on day 2-3 of menstruation cycle was done. Statistical analysis was done using SPSS version 20. Mean values of age and duration of subfertility with their standard deviations were determined.

Results: Total 73 patients with endocrine subfertility were indentified out of which 48 (66.7%) had primary infertility and 24 (33.3%) had secondary subfertility, while the mean duration of infertility was 3.3 years (5.2 ± 4.2). Normal cycle was found in only 14 (19.2%) and 38 (52.1%) had oligomenorrhea. Significant number of patients i.e. 18 (24.7%) were known hypertensive, 22 (15.1%) had thyroid disorders, 3 (4.1%) hyperprolactinemia and Tuberculosis, 1 (1.4%). Patients with pelvic surgery and 1 (1.4%) had abdominal surgery. A normal BMI was found in 21 (31.5%), while 24 (32.9%) patients were overweight and 21 (28.8%) were obese.

Conclusion: Endocrine infertility is strongly associated with (BMI). Menstrual irregularities, clinically androgen excess and galactorrhea are more frequent in obese and overweight women when compared with desirable weight.

Keywords: Anovulation, infertility, female, ovulation, body mass index.

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Introduction

Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse[1]. Approximately 10-15% of couples suffer from infertility all over the world. Female factor is responsible in 35% and male factor in 45% of cases while the rest of the couples either have combination of factors or unexplained infertility[2].

The most common identifiable factors that accounted for female infertility were ovulatory disorders (25%), endometriosis (15%), pelvic adhesions (11%), other tubal abnormalities (11%), and hyperprolactinaemia (7%). Some other reports describe ovulatory disorders as responsible for more than half of the causes of female infertility[3].

Although Pakistan is among the currently most populous countries of the world, and has a growth

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population rate of around 2%, it also has high rate of infertility, the prevalence of infertility in Pakistan is 21.9%[4].

The ovulatory factor refers to the ability of a woman to normally undergo the process of ovulation. Abnormalities in ovulation are broadly divided into three categories according to the gonadotropic status of the individual. These categories are important in deciding the treatment as well as in counselling. The World Health Organization (WHO) group I named hypogonadotropic hypogonadism includes women with reduced activity of the hypothalamus and the pituitary, resulting in under-stimulation of the ovaries. The WHO group II named normogonadotropic-normogonadism consists of women with abnormal ovarian activity in spite of normal gonadotrophins. Polycystic ovarian syndrome is the main contributor of this group whiles other endocrinopathiese. Hyperprolactinaemia and thyroid disorders can also lead to ovulatory dysfunction. WHO group III or hypergonadotropic hypogonadism is made up of women with ovarian failure in whom the lack of ovarian response results in the loss of negative feedback and therefore a rise in gonadotropin levels[5]. Studies done suggest that the intricate and complex hormonal balance governing the hypothalamic-pituitary-gonadal axis is affected by an individual's BMI affecting fertility[6].

Epidemiological data suggests obesity accounts for 6% of primary infertility[7]. Obesity contributes to anovulation and menstrual irregularities, with reduced conception rate and a reduction in the response to fertility treatment. It also increases the risk of miscarriage and contributes to maternal and perinatal complications[8]. The relative risk of anovulatory infertility is 2.7 (95% CI, 2.0-3.7) in women with BMI $\geq$32 kg/m ^{2} at age 18, while in an ovulatory but subfertile woman the chance of spontaneous conception decreases by 5% for each unit increase in the BMI[9]. Unfortunately, data also shows that patients with a BMI greater than 30 have up to 68% less chance of having a live birth following their first ART (Artificial Reproductive Technique) cycle compared with women with a BMI less than 30[10]. Although research supports the theory that low BMI is also associated with lower pregnancy rates in infertile women, there is a clear bias in the literature towards the risk of obesity. Women with a low BMI have lower clinical pregnancy rates than normal weight women[11]. Underweight women also have an increased risk of miscarriage[12]. A woman's fertility is related to the number of oocytes remaining in her ovaries, referred to as ovarian reserve, which influences the chance of becoming pregnant, for this purpose the follicular stimulating hormone (FSH) and luteinizing hormone (LH) are measured[13]. In Pakistan, research has been done on Polycystic ovarian syndrome[4], but locally, only few sparse data is available on other types of ovulatory disorders. The study aimed to find out the prevalence of all other types of endocrine infertility and its relationship to BMI in our population.

Patients and Methods

The study was carried out in infertility clinic of Jinnah Medical College Hospital (JMCH) from January 2015 to December 2015. An observational, cross-sectional prospective study was conducted and the participants were followed up till the investigatory work-up was completed. Sampling technique was by non-probability purposive sampling technique. Participants were recruited at the initial presentation to the clinic after verbal consent and were assessed with a detailed clinical history and examination to identify duration and type of infertility. A total of 73 females with ovulatory dysfunctions, who completed the investigation and fulfilled the inclusion criteria, were included. Sample size of 73 was calculated by using Rao-soft sample size calculator, in which proportion of presence of ovulatory subfertility was 25%, and margin of error was 10%, with 95% confidence interval and 25% response distribution.

The clinical review and research committee of Jinnah Medical College (JMC) gave ethical approval prior to starting the research study.

All clinic attendees were assessed for suitability for the study. We included all patients with age

>15 years to 45 years, presenting with menstrual irregularity, clinically having hirsutism, goiter, galactorrhoea, known case of thyroid disorder, diabetes, hyperprolactinaemia and with ultrasound evidence of small follicles in spite of ovulation induction and also with previous history of any pelvic, ovarian and endometriosis surgery. Patients with evidence of ovulation and incomplete investigations were excluded. Endocrinological assessment of participants was done by hormone profile, which included FSH (follicle stimulating hormone), LH (lutenizing hormone), serum prolactin and serum TSH (thyroid stimulating hormone) on 2nd day of the menstrual cycle. Ovulation was assessed by ultrasound follicle tracking with a follow-up method.

The data of each patient was recorded in predesigned proforma, which contained demographic data, type and duration of infertility and number of children. Detailed menstrual, medical and surgical history, clinical profile like BMI, hirsutism, vaginal discharge, goiter, galactorrhoea, abnormal pelvic finding on examination and investigations included were pelvic ultrasound and hormonal profile.

Body mass index was measured as weight in kilogram per square of height in meter (kg/m^2). The patients were categorized as follows: underweight < 20, Normal weight: 20-24.9, overweight: 25-29.9 and obese >30. The initial investigation comprised of pelvic ultrasound and semen analysis. Serum prolactin, thyroid function tests, luteinizing hormone (LH), follicle stimulating hormone (FSH), ordered if indicated by history and examination. Two of the given three criteria were required to diagnose polycystic ovarian syndrome (PCOS) according to the Rotterdam workshop after exclusion of other causes of androgen excess.

Since a woman's fertility is related to the number of oocytes remaining in her ovaries, which are referred to as ovarian reserve, and influences the chance of her becoming pregnant[13], hence, both FSH and LH were measured preferably on day 2-3 of the cycle. FSH was used as a gauge of ovarian reserve. The normal range was 3-20 mIU/ml, 21-29 impending ovarian failure while >30 irreversible ovarian failure. Day 2-3 LH more than 20 mIU/ml was labeled very high while Day 2-3 serum prolactin levels of more than 24 ng/ml was termed hyperprolactinemia. The normal range of thyroid stimulating hormone (TSH) was taken as 0.4-4mIU/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 labeled in case of low FSH, overweight (BMI >23-24.9), obese (BMI >25), PCOS, thyroid disease, hyperpro-lactinemia, decreased ovarian reserve and premature ovarian failure.

Statistical analysis was done using SPSS version 20. Mean values of age and duration subfertility with their standard deviations were determined. The percentage and frequency of all clinical variables of menstrual irregularities and anovulation were calculated, out of the total sample size of seventy-three patients.

Results

There were seventy-three patient with endocrine subfertility, two third that is 48 (66.7%) had primary infertility while one third 24 (33.3%) had secondary subfertility. The mean duration of subfertility was 3.3 years. Mostly patients 63 (86.3%) were <35 years, while only 8 (11%) were between 36-40 years. Normal cycle was found in only 14 (19.2%), mostly patient 38 (52.1%) came with complaint of oligomenorrhea. Regarding number of previous children mostly 56 (77.8%) were having no children, while 12 (16.7%) had 1-2 children and only 4 (5.6%) had 3 or more children. Surprisingly in our data no patient presented with known case of diabetes, although significant numbers of 18 (24.7%) were known hypertensive, thyroid disorders were 22 (15.1%), hyperprolactinemia was present in 16 (21.9%) and known case of tuberculosis were 1 (1.4%). Only 1 (1.4%) had history of pelvic surgery while 1 (1.4%) had history of abdominal surgery.

A normal BMI was found only in 21 (31.5%), as expected most of the patient were overweight

Table 1. The relationship of body mass index with menstrual cycle.

		Body Mass Index				
	Menstrual history	Underweight (<18)	Normal weight (18-22.9)	Over weight (23-24.9)	Obese (>25)	Total
Amenorrhea	Count	1	2	4	1	8
	% of Total	1.4%	2.7%	5.5%	1.4%	11.0%
Hypomenorrhea	Count	1	1	3	4	9
	% of Total	1.4%	1.4%	4.1%	5.5%	12.3%
Normal	Count	2	6	4	2	14
	% of Total	2.7%	8.2%	5.5%	2.7%	19.2%
Oligomenorrhea	Count	1	11	13	13	38
	% of Total	1.4%	15.1%	17.8%	17.8%	52.1%
Polymenorrhea	Count	0	2	0	0	2
	% of Total	0.0%	2.7%	0.0%	0.0%	2.7%
Total	Count	5	23	24	21	73
	% of Total	6.8%	31.5%	32.9%	28.8%	100.0%

Table 2. The distribution of infertile women with ovulatory disorders- According to WHO[5] classification. (n=73)

Primary causes calculated and their classification		Frequency	Percentage
who. group1			
(Hypogonadotrophic hypogonadism) n=1	Low FSH levels (<2IU/L)	1	1.4
who. group 2			
(Normogonadotropic normogonadism) n=61	Low BMI (<18)	3	4.1
	Overweight (23-24.9)	10	13.7
	Obesity (>25)	13	17.8
	Polycystic ovary syndrome	8	11.0
	Low TSH (hyperthyroidism)	3	4.1
	High TSH (hypothyroidism)	8	11.0
	Raised Prolactin (>24ng/ml)	16	21.9
who. group 3			
(Hypergonadotropic hypogonadism) n=11	Impending premature insufficiency (FSH 21-29 mIU/ml)	4	5.5
	Irreversible ovarian failure (FSH >30mIU/ml)	7	9.6

24 (32.9%) and obese 21 (28.8%). The relationship between BMI and menstrual cycle is described in Table 1.

On clinical examination hirsutism, was found in 11 (15.1%). Mostly patient who had hirsutism were obese 6 (8.2%) followed by overweight 3 (4.1%). Only 2 (2.7%) had normal weight. Noticeably goiter was found in large population 31 (42.5%). Out of them, hypothyroidism was present in 8 (11%) in which normal BMI was in 2 (2.7%), overweight 2 (2.7%), obese 8 (5.5%) and no patient was underweight as per expectation. Regarding hyperthyroid 3 (4.1%), mostly had normal BMI 2 (2.7%), overweight were 1 (1.4%) with no obese and underweight found in our study. Regarding galactorrhea 14 (19.2%), of which 6 (8.2%) were normal weight, 3 (4.1%) overweight, 3 (4.1%) obese and only 2 (2.7%) were underweight.

The distribution of participant with ovulatory dysfunction according to WHO classification is shown in Table 2. The distribution of participants with ovulatory dysfunction according to WHO classification is shown in Table 2, where Group 1 (hypogonadotrophic-hypogonadism) were found in 1 (1.4%) while mostly 61 (83.5%) were in Group 2 and Group 3 (hypergonadotrophic-hypogonadism) is 11 (15.1%).

Discussion

Obesity has grown to epidemic proportion, currently nearly half of the reproductive age women are overweight and obese[1]. There seems to be a strong association between increased BMI and lower pregnancy rate, live birth rate and miscarriages[14].

Endocrine infertility was found in 73, out of 244 (29.9%) patient who visited infertility clinic, which is comparable to the previous studies, which demonstrated prevalence of ovulatory dysfunction in about 20-30%[15,16]. The mean age of participants was 26.65 ± 5.93 which is also comparable with the study done in Srilanka[17]. Primary infertility was found in 66%, while secondary infertility was 33% this does not match the finding in other large research done in India which showed prevalence of primary infertility of 50.9%, while secondary infertility was 47.5%[18].

Anovulatory women typically presents with oligomenorrhea or amenorrhea, although about 10% of women with regular cycles could be anovulatory[19]. In this study, oligomenorrhea, was reported in 38 (52.1%) and normal cycle 14 (19.2%) which is consistent with other studies[20]. Although local study done at Abbotabad showed oligomenorrhea in only 30% of patients and more than half were having normal cycle[21], these findings were not compatible with our study results. Overweight and obese women are associated with a higher incidence of menstrual disturbances, ovulation disorders and subfertility of women[19]. This was further confirmed by our study where 45 (61.7%) infertile women were having BMI greater than the desirable range. Weight loss should be advised before fertility treatment in overweight and obese women. Even a modest weight loss of 5% may restore spontaneous ovulation and improve pregnancy rate[22,23].

Approximately half of our patients with PCOS were overweight and obese. The definition of PCOS recognizes obesity as an association and not a diagnostic criteria and the Royal College of Obstetrics and Gynaecology study group also confirmed that only 40-50% of women with the syndrome are overweight[24]. Furthermore in PCOS, 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 apnea should have early recognition as they can pose significant health risk if untreated[25].

Clinically hirsutism was found in 11 (15.1%), while PCOS was diagnosed in 8 (11%) that is consistent with the finding that most common cause of hirsutism is PCOS[26,27].

Clinically, thyroid was palpable in 31 (42.5%) while out of these only 11 (15.1%) were confirmed to be so by thyroid function test, which is contrary to the study done in Lahore where clinical diagnosis of thyroid disorder was accurate in 91.17% of cases[28].

Raised prolactin levels were found in 16 (21.9%), while clinically galactorrhea was present in 14 (19.2%) of cases. Mostly patients with hyperprolactinemia present with hypomenorrhea, oligomenorrhea and secondary amenorrhea furthermore in two patients hyperprolactinemia was also associated with thyroid disorders. This is in lieu with finding that when galactorrhea is accompanied by amenorrhea, it is usually caused by hyperprolactinemia[29]. However, when a patient has normal ovulatory menses and galactorrhea, prolactin levels are usually normal[30].

Premature ovarian failure or insufficiency (POI), is a disorder, characterized by amenorrhea, low estrogen and increase gonadotrophin levels in women aged <40 years. POI is the result of premature exhaustion of the follicular pool, or can be attributed to follicular dysfunction[3]. In our study, POI were 11 (15.1%) which is contrary to research done in Sri Lanka where it was only 1.8%[14]. Furthermore in our investigations three patients with POI also showed deranged thyroid function test which endorsed the auto-immune multi-glandular cause of it. Most of the patients with POI were overweight and obese. The association of decreased fecundity with increased basal FSH levels is confirmed by other studies as well[31].

Conclusion

Infertile patient with endocrine subfertility usually are overweight and obese. Weight reduction is cheap, effective and beneficial treatment option for our population. Efforts are needed to raise awareness about this.

Conflict of interest

Authors have no conflict of interests and no grant/funding from any organization were obtained for this study.

Reference

1. Gurunath S, Pandian Z, Anderson RA, Bhatacharya S. Defining infertility--a systematic review of prevalence studies. Hum Reprod Update 2011;17:575-88.
2. Butt F, Akram N. Semen analysis parameters: Experiences and insight into male infertility at a tertiary care hospital in Punjab. J Pak Med Assoc 2013;63:558-62.
3. Unuane D, Tournaye H, Velkeniers B, Poppe K. Endocrine disorders and female infertility. Best Pract Res Clin Endocrinol Metab 2011;25:861-73.
4. Arain F, Arif N, Halepota H. Frequency and outcome of treatment in polycystic ovaries related infertility. Pak J Med Sci 2015;31:694-9.
5. World Health Organization. The epidemiology of infertility: Report of a WHO scientific group. Geneva: World Health Organization; 1975.
6. Chang RJ. The reproductive phenotype in polycystic ovary syndrome. Nat Clin Pract Endocrinol Metab 2007;3:688-95.
7. Roonay KL, Domar AD. The impact of lifestyle behaviors on infertility treatment outcome. Cur Opin Obstet Gynecol 2014;26:181-5.
8. Khaskheli MN, Baloch S, Baloch AS. Infertility and weight reduction: influence and outcome. J Coll Physicians Surg Pak 2013;23:798-801.
9. Pandey S, Pandey S, Maheshwari A, Bhattacharys S. The impact of female obesity on the outcome of fertility treatment. J Hum Reprod Sci 2010;3:62-7.
10. Moragianni VA, Jones SM, Ryley DA. The effect of body mass index on the outcomes of first assissted reproductive technology cycles. Fertil Steril 2012;98:102-8.
11. Li Y, Yang D, Zhang Q. Impact of overweight and underweight on IVF treatment in Chinese women. Gynecol Endocrinol 2010;26:416-22.
12. Davis DM, Caswell WA, Reed J, Hill JA, Tucker MJ. Are the adverse effects of weight on reproductive potential an embryo or endometrial factor? Fertil Steril 2013;100:S85-6.
13. Zaadstra BM, Seidell JC, Van Noord PA, teVelde ER, Habbema JD, Vrieswijk B, et al. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ 1993;306:484-7.
14. Weiss RV, Clapauch R. Female infertility of endocrine origin. Arq Bras Endocrinol Metab 2014;58:144-52.
15. Adamson GD, Baker VL. Subfertility: causes, treatment and outcome. Best Pract Res Clin Obstet Gynaecol 2003;17:169-85.
16. Hamilton-Fairley D, Taylor A. ABC of subfertility; Anovulation. BMJ 2003;327:546-9.
17. Palihawadana TS, Wijesinghe PS, Seneviratne HR. Aetiology of infertility among females seeking at a tertiary care hospital Sri Lanka. Ceylon Med J 2012;57:79-83.

18. Mittal A, Yadav S, Yadav SS, Bhardwaj A, Kaur R, Singh P, et al. An epidemiological study of infertility among urban population of Ambala, Haryana. Int J Interdisciplinary Multidisciplinay studies (IJIMS) 2015;2:124-30.

19. Li RH, Ng EH. Management of anovulatory infertility. Best Pract Res Clin Obstet Gynaecol 2012;26:757-68.

20. Shi Y, Guo M, Yan G, Sun W, Zhang X, Geng L, et al. Analysis of clinical characteristics in large scale Chinese women with polycystic ovary syndrome. Neuro Endocrinol Lett 2007;28:807-10.

21. Sadia S, Waqar F, Akhtar T, Sultana S. Characteristics of infertile patients with ovulatory dysfunction and their relationship to Body mass index. J Ayub Med Coll Abbottabad 2009;21:12-6.

22. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to Polycystic ovary syndrome. Hum Reprod 2008;23:462-77.

23. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovarian Syndrome Society. Fertil Steril 2009;92:1966-82.

24. Balen AH. PCO, obesity and reproductive function: RCOG Special Study Group on Obesity. London: RCOG Press; 2007.

25. Futterweit W. Polycystic ovary syndrome: a common reproductive and metabolic disorder necessitating early recognition and treatment. Prim Care 2007;34:761-89.

26. Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Extensive Clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab 2006;91:2-6.

27. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, et al. Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab 2004;89:453-62.

28. Sadiq A, Mahmood S, Bashir EA, Khan SS. Correlation of thyroid function tests and Goiter. J Rawalpindi Med Coll 2012;16:153-55. Available from: http://www.journalrmc.com/volumes/1394805078.pdf. Accessed on August, 2016.

29. Huang E, Molitch ME. Evaluation and management of galactorrhea. Am Fam Phy 2012;85:1074-80.

30. Molitch ME. Disorders of prolactin secretion. Endocrinol Metab Clin North Am 2001;30:585-610.

31. 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;92:2163-8.