WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 5, Issue 1, 24-34. Research Article ISSN 2277– 7105

IMPACT OF AGE AND WEIGHT ON LEVELS OF SOME REPRODUCTIVE HORMONES FOR IRAQI INFERTILE WOMEN

Prof. Dr. Muhammad-Baqir M-R. Fakhrildin[1] and Hind Mahmood Jumaah AL-Mafraji[2*]

[1]Department of Physiology, Collage of Medicin, Jabir Ibn Hayyan Medical University, Al-Najaf Al-Ashraf.

[2]Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq.

Article Received on
25 Oct 2015,

Revised on 15 Nov 2015,
Accepted on 05 Dec 2015

***Correspondence for Author**
Hind Mahmood Jumaah AL-Mafraji
Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq.

ABSTRACT

The present study aims to assess the changes in the levels of some reproductive hormones including follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E_2), testosterone and thyroid stimulating hormone (TSH) classified according to age and weight for infertile women. In this study, 250 women with infertility aged 16 to 53 years were investigated who attended to the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain University. Women were divided into four age groups: ≤ 20 years old, 21-30 years old, 31-40 years old and ≥ 41 years old. Blood samples were collected to determine the levels of serum FSH, LH, PRL, E_2, testosterone and TSH. The crude data were statistically analyzed. Levels of S.FSH were increased gradually as the age increase. Regarding S. testosterone, highest mean level showed for female with age group (≤ 20 years) and lowest level of S. testosterone for females with age group (≥41years). Highest levels of serum prolactin and serum testosteronewere observed for infertile women with BMI group (≤18.5 kg/m^2), while the lowest levels of S. PRL were assessed for women with BMI group (25-29.9 kg/m^2). Regarding serum testosterone level, the lowest levels in infertile females with BMI group (18.5-24.9 and ≥30 kg/m^2). However, the mean level of S.TSH was highest in infertile women with BMI group (18.5-24.9 kg/m^2) and lowest in infertile women with BMI group (≤18.5 kg/m^2). From the results of present study appeared that the increasing age has a impact on the fertility of women through hormonal imbalance. Any weight abnormalities negatively affects levels of serum reproductive hormones.

KEY WORDS: Female, Reproduction, Infertility, Hormone, Age, Weight.

INTRODUCTION

Female reproductive hormones rarely operate alone, functioning in harmony to either synergise, or antagonize outcomes throughout the female reproductive tract.[1,2] Fluctuating hormones regulate both the ovarian and endometrial cycles, with dysfunction causing irregular cycling.[3] There are many reproductive hormones which have a big role in folliculogenesis, oocyte maturation, corpus luteum formation and endometrial preparation for implantation of fertilized ovum and they can affect fertility if any disturbance occurred in their level. These hormones include hypothalamic gonadotropin releasing hormone (GnRH), pituitary hormones including follicular stimulating hormone (FSH) and luteinizing hormone(LH) and the steroidal gonadal hormones (oestrogen, progesterone and testosterone).[4] Furthermore, thyroid hormones interact with reproductive hormones, estrogens and progesterone, to preserve normal function of the ovaries and maturation of the egg (oocyte).[5]

Clinically, infertility seems to be a multidimensional health issue which occurs not only due to health problems, but it may also be a result ovulation problems, tubal blockage, age-related factors, uterine problems, hormone imbalance and the choices imposed by the modern lifestyle, like the higher average age of people who get married and stress.[6] Fertility can be adversely affected by obesity. In women, the early onset of obesity promotes the development of menses irregularities. Obesity in women may also increase the risk of miscarriage and impair the outcomes of assisted reproduction procedures and pregnancy, when the body mass index greater than 30 kg/m^2.[7] Therefore, aim of the present study was to assess the levels of some reproductive hormone including FSH, LH, PRL, E_2, Testosterone and TSH for unselected Iraqi infertile women classified according to age and weight.

MATERIALS AND METHODS

Patients

Two hundred fifty Iraqi infertile women have been involved in the current study during their attendance to the (High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/University of Al-Nahrain). The subjects' ages were 29.992±0.505 with a range from 16 to 53 years. A full history has been obtained from each women including: personal history, menstruation history and infertility status.

Body Mass Index (BMI)

The female body mass index (BMI) was measured according to the following equation by dividing the weight in kilograms by the height in squared meters (kg/m2).[8,9,10] Weight status was classified into four categories as shown in table (1).

Table (1): The categories of the weight status according to the value of BMI (European Society of Human Reproduction and Embryology, 2009).

BMI (kg/m^2)	Weight status
≤ 18.5	Underweight
18.5-24.9	Normal
25-29.9	Overweight
≥ 30	Obese

Blood Collection

Blood sampling has performed during the early follicular phase (cycle day 2 or 3); venous blood sample (5 mL) has been collected from unselected infertile women, the blood has then been transferred to a clean dry plain plastic tube and allowed to clot at 37°C for 10 minutes. The tubes have been centrifuged at 2500 rpm for 5 minutes, and then the serum has been collected and kept at -20°C until used.

Hormonal Profile

Hormonal analyses of infertile women has been done in second or third day of menstrual cycle by using hormone analyzer (Minividas–France), through an enzyme linked fluorescent assay (ELFA) technique. Reproductive hormones (FSH, LH, PRL, E_2, Testosterone and TSH) levels of the serum have been determined for the women of all groups according to manufacture recommended procedure by using specific kit for each hormone. The normal range for each hormone as shown in table (2).

Table (2): Normal hormonal range for females.

Hormone	Normal range (follicular phase)	Units
S.FSH	2.9-12	mIU/ml
S.LH	2-8.0	mIU/ml
S.prolactin	5-35.0	ng/ml
S.E_2	18-147	pg/ml
S.testosterone	0.1-0.9	ng/ml
S.TSH	0.25-5.0	mIU/ml

Statistical Analysis

The statistical analysis has been done using statistical analysis system (SPSS, 2010) program to study the differences of data between groups.[11] All results have been expressed as mean ± standard error (M ± SE). Differences between groups have analyzed using an analysis of variance (ANOVA) and (LSD).

RESULTS

In regard to levels of serum hormones were presented in the table (3). In infertile women, levels of S.FSH were increased gradually as the age increase. Highest level of S.FSH was recorded in the age (≥ 41 years) group. While, lowest level of S.FSH was appeared in the age group (≤20 years). But, non significant differences (P>0.05) in the level of S.FSH were assessed between age groups (≤20 vs. 21-30 years and 31- 40 vs. ≥ 41 years). From the same table, non significant differences (P>0.05) were noticed in the levels of S.LH, S.prolactin, S.estradiol and S.TSH among all age groups. Regarding S.testosterone, highest mean level showed for females with age group (≤20 years) and lowest level of S. testosterone for females with age group (≥ 41 years). But, non significant differences (P>0.05) were assessed among age group (≤ 20 years, 21-30 years and 31-40 years) as compared to other two groups. Similarly, non significant difference (P>0.05) in the level of S.testosterone among women at age groups (21-30 years, 31- 40 years and ≥ 41 years).

Table (3): Levels of serum reproductive hormones for infertile females classified according to age groups.

Hormone	Female age group (years)			
	≤ 20	21-30	31-40	≥41
S.FSH (µIU/ml)	5.517^{b} ± 0.079	6.212^{b} ± 0.039	8.278^{a} ± 0.082	10.307^{a} ± 0.279
S.LH(µIU/ml)	3.597^{a} ± 0.073	4.698^{a} ± 0.047	4.729^{a} ± 0.044	3.794^{a} ± 0.107
S.Prolactin (ng/ml)	22.127^{a} ± 0.505	21.962^{a} ± 0.146	18.454^{a} ± 0.159	19.326^{a} ± 0.687
S.Estradiol (Pg/ml)	59.266^{a} ± 2.168	105.068^{a} ± 3.322	64.262^{a} ± 1.363	89.833^{a} ± 3.511
S.Testosterone (ng/ml)	1.041^{a} ± 0.064	0.799^{ab} ± 0.018	0.720^{ab} ± 0.015	0.339^{b} ± 0.015
S.TSH (µIU/ml)	2.476^{a} ± 0.214	2.169^{a} ± 0.081	1.724^{a} ± 0.082	1.347^{a} ± 0.129

*Values are (Mean±S.E).

*****Means with different superscripts within each row are significantly different (P<0.05).

*Means with similar superscripts within each row are non significantly different (P>0.05).

No. females ages (≤ 20 years) are (27; 10.8%).
No. females ages (21-30 years) are (112; 44.8%).
No. females ages (31- 40 years) are (80; 32%).
No. females ages (≥ 41 years) are (31; 12.4%).

Table (4) shows levels of serum hormones classified according to BMI groups. The mean levels of serum FSH, LH and estradiol were non significantly different (P>0.05) among different BMI groups. Serum prolactin level showed higher significantly with BMI group (≤18.5 kg/m^2) and lower significantly with BMI group (25-29.9 kg/m^2). However, no significant difference (P>0.05) in the level of S. prolactin between BMI groups (25-29.9 and ≥30 kg/m^2). Regarding serum testosterone level, the S.testosterone showed significantly higher (P<0.05) in females with BMI group (≤18.5 kg/m^2) and significantly reduced (P<0.05) in females with BMI group (18.5-24.9 and ≥30 kg/m^2). But, its mean level observed non significant difference (P>0.05) in females with BMI group (25-29.9 kg/m^2). While the mean of S.TSH was significantly higher (P<0.05) in BMI group (18.5-24.9 kg/m^2) and significantly lower (P<0.05) in BMI group (≤18.5 kg/m^2). Meanwhile, no significant difference (P>0.05) in the level of S.TSH for BMI group (≥30 kg/m^2) as compared to other BMI groups (18.5-24.9 and 25-29.9 kg/m^2).

Table (4): Levels of serum reproductive hormones for infertile females classified according to BMI groups.

Hormone	Body mass index (Kg/m^2)			
	≤18.5	18.5-24.9	25-29.9	≥ 30
S.FSH (µIU/ml)	5.800^a ±0.000	6.565^a ± 0.187	7.421^a ± 0.044	7.499^a ± 0.057
S.LH (µIU/ml)	5.450^a ±0.000	4.798^a ± 0.103	3.969^a ± 0.028	4.734^a ± 0.044
S.Prolactin (ng/ml)	40.830^a ±0.000	26.814^b ± 0.488	17.376^c ± 0.130	20.788^c ± 0.145
S.Estradiol (Pg/ml)	49.000^a ±0.000	114.136^a ± 5.620	77.937^a ± 1.650	61.561^a ± 0.471
S.Testosterone (ng/ml)	1.200^a ±0.000	0.625^b ± 0.033	0.761^{ab} ± 0.023	0.748^b ± 0.010
S.TSH (µIU/ml)	0.040^c ±0.000	2.616^a ± 0.091	1.619^b ± 0.055	1.928^{ab} ± 0.096

*Values are (Mean±S.E).

*****Means with different superscripts within each row are significantly different (P<0.05).

*Means with similar superscripts within each row are non significantly different (P>0.05).

No. females with BMI (≤18.5 kg/m^2) are (1; 0.4%).

No. females with BMI (18.5-24.9 kg/m^2) are (38; 15.2%).

No. females with BMI (25-29.9 kg/m^2) are (89; 35.6%).

No. females with BMI (≥30 kg/m^2) are (122; 48.8%).

DISCUSSION

Regardin the age for infertile women enrolled in this study, the mean of age showed high significant increment (P<0.05) in female with secondary type of infertility when compared to other primary type of infertility. This result agrees with Aziz[12] who reported that the mean age at presentation was 28 years in primary infertility and 32 years in secondary infertility. Another study done by Pegu *et al*.[13] shows similar results. It may be due to delayed marriage and child bearing.

Concerning FSH levels, in the current study, levels of S.FSH were increased gradually as the age increase. Highest level of S.FSH was recorded in the age (≥ 41 years) group. While, least level of S.FSH was appeared in the age group (≤ 20 years). The results noticed by this study were in agreement with Fiza *et al*.[14] who stated that the serum FSH levels showed a positive correlation with increasing age. While some studies are contrary to the present finding that they have shown no correlation between serum FSH and age until the age of 40 years.[15,16] Furthermore, altered pituitary cell number, leading to dysfunction, is one of the main causes of endocrine disease. Disorders display such far-reaching ramifications as dwarfism or gigantism, metabolic dysregulation as well as reproductive disorders leading to infertility in males and females.[17,18]

Regarding the level of LH, the result showed non significant differences (P>0.05) were noticed in the levels of S.LH and S.estradiol among all age groups. The result agree with study.[14] They showed that serum E_2 and LH was very low and the reduction did not indicate a significant correlation with age. Hence, the estimation of serum LH may not be considered as a marker of ovarian aging. LH plays a key role in initiation of the ovulatory process of preovulatory follicles by activating multiple cellular signaling pathways.[19] The hormonal balance between estrogen, progesterone, FSH and LH is important to induce and promote

fertility. The most common cause of female infertility is ovulatory disorder characterized by anovulation or infrequent ovulation and/or irregular.[20]

In the current study, non significant differences (P>0.05) were noticed in the levels of S.prolactin and S.TSH among all age groups. Measurement of PRL has been considered an important component of infertility work up in women.[21] Hyperprolactinemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation.[22]

Regarding S.testosterone, highest mean level showed for females with age group (≤ 20 years) and lowest level of S. testosterone for female with age group (≥ 41 years). There are several conditions that have been shown to associate with low testosterone levels in women. These include ovarian dysfunction (e.g. oophorectomy, chemotherapy, and radiation), adrenal dysfunction (e.g. adrenal insufficiency and adrenalectomy), hypothalamic-pituitary dysfunction and drug-related effects (e.g. corticosteroids, antiandrogens, oral contraceptives, oral estrogen replacement therapy).[23] Although available data are scarce, they suggest that androgen deficiency in women is characterized by symptoms such as diminished sense of well-being or dysphoric mood, fatigue, sexual dysfunction, decreased muscle strength and bone mass.[24] Abnormally high levels of testosterone in women can lead to a variety of symptoms. In most cases, hair growth, especially on their faces and chests.[25] More rarely, over time some women may experience virilization, which is increased muscle mass, the redistribution of body fat, enlargement of the clitoris, deepening of the voice, baldness, acne, and increased sweating. Increased testosterone levels in women are most often caused by polycystic ovaries. Less commonly, when testosterone levels are very elevated, ovarian cancer is a concern. Adrenal gland problems may contribute as well.[26]

Regarding the BMI, the current study revealed that the levels of S. FSH were non significantly increased as the BMI for women increased. Similar results were noticed for levels of S. LH, S. E_2 and S. TSH. Obesity is one of the clinical characteristics of the PCOS along with oligomenorrhea, hirsutism, and infertility. These adverse effects of obesity are particularly evident in the polycystic ovary syndrome. High body mass index (obese) affect reproduction by causing menstrual disturbances and anovulation. The obesity affects the reproductive cycle by impaired estrogen metabolism as reported by Norman and Clark.[27] This investigation evaluates the hormonal profile of infertile women. However, not all obese women have PCOS and not all PCOS women are obese.[28] Furthermore, this study suggests

that higher prevelence for women with PCOS in our country as in most countries, have a higher body weight than other counterparts.[29,30]

Like present results, obesity is a common finding of women with PCOS but it is not part of the diagnostic criteria.[31] Those PCOS women usually have greater abdominal fat distribution (truncal abdominal fat distribution) and gluteofemoral deposition.[32,33] Women with PCOS usually have so-called central obesity (Visceral adiposity) or upper-body obesity, and therefore tend to have an increased waist-hip ratio and waist to thigh ratio.[34,35]

CONCLUSION

From the results of present study appeared that the increasing age has a impact on the fertility of women through hormonal imbalance. Any weight abnormalities negatively affects levels of serum reproductive hormones.

REFERENCES

1. Wira CR, Sullivan DA. Estradiol and Progesterone Regulation of Immunoglobulin A and G and Secretory Component in Cervicovaginal Secretions of the Rat. Biol Reprod, 1985; 32: 90-95.
2. Bentley PJ. 2001. Sex Hormones in Vertebrates. In Encyclopaedia of Life Sciences. London, UK: Nature Publishing Group.
3. Goldfien A. Ovaries. In: Greenspan FS, Gardner DG, ed. A Lange Medical Book: Basic and Clinical Endocrinology. 6th ed. New York: Lange Medical Books/McGraw-Hill Medical Publishing Division, 2001; 453-508.
4. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Rep Biol Endocrinol, 2005; 3: 28.
5. Poppe K, Glinoer D, Tournaye H et al. Thyroid function and assisted reproduction. In: The Thyroid and Reproduction, METS Riga 2008. Georg Thieme Verlag Stuttgart, 2009; 33-38.
6. Roupa Z, Polikandrioti M, Sotiropoulou P, Faros E, Koulouri A, Wozniak G, Gourni M. Causes of infertility in women at reproductive age. Health Science Journal, 2009; 3(2): 80-87.
7. Mohan K, Sultana M. Follicle Stimulating Hormone, Luteinizing Hormone and Prolactin Levels in Infertile Women in North Chennai, Tamilnadu. J Biosci Res, 2010; 1(4): 279-284.

8. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA, 2005; 293(15): 1861-1867.
9. De Saint Pol T. Evolution of Obesity by Social Status in France, 1981–2003. Economics and Human Biology, 2009a; 7: 398-404.
10. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and Trends in Obesity among U.S. Adults, 1999–2008. Journal of the American Medical Association, 2010; 303(3): 235-241.
11. Cleophas TJ, Zwinderman AH. SPSS for Starters. Springer Science Business Media. New York, Heidelberg, London, 2010.
12. Aziz N. Laparoscopic evaluation of female factors in infertility. J Coll Physicians Surg Pak, 2010; 20(10): 649-652.
13. Pegu B, Gaur BPS, Sharma N, Singh AS. Laparoscopic Evaluation of Female Infertility. Int J Med Health Sci, 2014; 3(3): 172-176.
14. Fiza B, Mathur R, Sinha M, Saraswat P. Endocrine Markers And Decline In Reproductive Potential Of Women. Int J Pharm Bio Sci, 2014; 5(1): 1074-1080.
15. Schipper I, de Jong FH, Fauser BC. Lack of correlation between maximum early follicular phase serum follicle stimulating hormone concentrations and menstrual cycle characteristics in women under the age of 35 years. Hum Reprod, 1998; 13(6): 1442-1448.
16. van Rooij IA, Broekmans FJ, Scheffer GJ, Looman CW, Habbema JD, de Jong FH, Fauser BJ, Themmen AP, te Velde ER. Serum antimüllerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study. Fertil Steril, 2005; 83(4): 979-987.
17. Melmed S. Mechanisms for pituitary tumorigenesis; the plastic pituitary. Journal of Clinical Investigation, 2003; 112: 1603-1618.
18. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. The Prevalence of Pituitary Adenomas. Cancer, 2004; 101: 613-619.
19. Russell DL, Robker RL. Molecular mechanisms of ovulation: coordination through the cumulus complex. Hum Reprod, 2007; 13: 289-312.
20. Elghblawl E. Polycystic ovary syndrome and female reproduction. Br J Nurs, 2007; 16(18): 1118 -1121.
21. Cramer DW, Sluss PM, Powers RD, McShane P, Ginsburgs ES, Hornstein MD, Vitonis AF, Barbieri RL. Serum prolactin and TSH in an in vitro population: is there a link between fertilization and thyroid function? J Assist Reprod Genet, 2003; 20: 210-215.

22. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Hum Reprod, 2003; 9: 149-161.
23. Bachmann G, Bancroft J, Braunstein G, Burger H, Davis S, Dennerstein L, Goldstein I, Guay A, Leiblum S, Lobo R, Notelovitz M, Rosen R, Sarrel P, Sherwin B, Simon J, Simpson E, Shifren J, Spark R, Traish A. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril, 2002; 77(4): 660-665.
24. Bhasin S. Female androgen deficiency syndrome-an unproven hypothesis. J Clin Endocrinol Metab, 2005; 90(8): 4970-4972.
25. Shemran KA. Total, Free Testosterone and Insulin Hormone Levels in Patients with Hirsutism. Medical Journal of Babylon, 2012; 9(2): 307-312.
26. Karakurt F, Sahin I, Guler S, Demirbas B, Culha C, Serter R, Aral Y, Bavbek N. Comparison of the clinical efficacy of flutamide and spironolactone plus ethinyloestradiol/cyproterone acetate in the treatment of hirsutism: a randomised controlled study. Adv Ther, 2008; 25(4): 321-328.
27. Norman RJ, Clark AM. Obesity and reproductive disorders. Reprod Fertil, Dev., 1998; 10: 55-63.
28. Vrbikova J, Hainer V. Obesity and polycystic ovary syndrome. Obesity Facts, 2009; 2: 26-35.
29. Azziz R, Ehrmann D, Legro R, Whitcomb RW, Hanley R, Fereshetian AG, Keefe M, Ghazzi MN. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial: J Clin Endocrinol Metab, 2001; 86(4): 1626-1632.
30. Carmina E, Legro R, Stamets K, Lowell J, Lobo R. Difference in body weight between American and Italian women with polycystic ovary syndrome: influence of the diet. Hum Reprod, 2003; 18: 2289-2293.
31. Setji TL, Brown AJ. Polycystic ovary syndrome: Diagnosis and treatment. Am J Med, 2007; 120: 128-132.
32. Kirchengast S, Huber J. Body composition characteristics and body fat distribution in lean women with polycystic ovary syndrome. Hum Reprod, 2001; 16: 1255-1260.
33. Ma RC, Liu KH, Lam PM, Cheung LP, Tam WH, Ko GT, Chan MH, Ho CS, Lam CW, Chu WC, Tong PC, So WY, Chan JC, Chow CC. Sonographic measurement of mesenteric fat predicts presence of fatty liver among subjects with polycystic ovary syndrome. J Clin Endol Meta, 2011; 96(3): 799-807.

34. Cascella T, Palomba S, De Sio I, Manguso F, Giallauria F, De Simone B, Tafuri D, Lombardi G, Colao A, Orio F. Visceral fat is associated with cardiovascular risk in women with polycystic ovary syndrome. Hum Reprod, 2008; 1: 153-159.
35. Huang A, Brennan K, Azziz R. Prevalence of hyperandrogenemia in the polycystic ovary syndrome diagnosed by the National Institutes of Health 1990 criteria. Fertil Steril, 2010; 93(6): 1938-1941.