Archives of Razi Institute, Vol. 77, No. 5 (2022) 1699-1707

DOI: 10.22092/ARI.2022.357806.2103

Original Article

Role of Serum Leptin Levels in Women with Primary Subfertility

Zuhair Abdul-Majeed Alkhwaja, S[1 *], Jabir Edan, B[1], Raad Muhi, Z[2]

1. College of Medicine, University of Babylon, Babylon, Iraq
2. College of Medicine, Mustansiriyah University, Baghdad, Iraq

Received 12 February 2022; Accepted 21 April 2022
Corresponding Author: essam.2t.essam@gmail.com

Abstract

Subfertility significantly affects couples and their families and challenges obstetrics and gynecologists with long-term treatment. Leptin has been widely studied in different types of infertility. However, the results of previous studies are contradictory and the role of leptin is still debated in the reproductive process. The present study aimed to investigate the relationship between serum leptin concentration and some reproductive hormones and endometrial thickness in women with primary subfertility. The present case-control study was conducted from December 2020 to July 2021. A total of 100 women with primary subfertility and 100 fertile women participated in this study as a control group. Blood samples were collected and ultrasonography examinations were performed on all patients. The recorded data indicated that the mean leptin level was higher in women with subfertility compared to that of the control group, 26.8±15.2 ng/mL and 6.4±2.3 ng/mL, respectively (P<0.001). Leptin level significantly increased with a higher body mass index (P<0.001). Leptin at a level of 11 ng/ml or higher is a significant predictor of infertility (odds ratio=2.793). Leptin levels showed high sensitivity, specificity, and accuracy of 96%, 98%, and 96.9%, respectively as predictors of subfertility. As a result, a high leptin level was a strong and valid predictor of subfertility.

Keywords: Diagnosis, Epidemiology, Leptin, Pathogenesis, Subfertilit

1. Introduction

Subfertility refers to the inability of a couple to conceive despite unprotected sexual activity without using any method of contraception. Data on infertility are scattered and vary from Asia to Latin America. WHO estimates the prevalence of infertility among couples of reproductive age at 8-12% in these countries (1-3).

Leptin is a peptide hormone produced by adipose tissue which plays an important role in obesity and appetite disorders as a lipostatic factor. Leptin is believed to bind to specific receptors in the hypothalamus and signal that the stomach is full. Violation of this signal leads to increasing total body mass, blood sugar, and insulin resistance (4). Leptin positively affects the reproduction system in women through the association between energy homeostasis and fertility. However, excessive leptin levels may negatively affect fertility in women. This hypothesis has been proven mainly in obese women compared to the general population (4, 5). Leptin is bound by T-cell receptors in addition to neuroreceptors in the hypothalamus. This is supposed to be related to adipocytes and the immune system. Leptin acts by blocking neuropeptide Y and agouti-related peptides in addition to triggering melanocyte-stimulating hormone (α-MSH). Leptin must cross the blood-brain barrier as in interaction with the CNS by leptin receptors in

endothelial cells, which act as transporters (6, 7). Leptin is a pleiotropic molecule that is mainly produced by adipose tissue (8) and acts as an energy regulator (9-11). Leptin is considered a predictor of menstrual function as leptin levels have been shown to vary during the menstrual cycle, however, its mechanism of action is unclear (12). Various assumptions have been made about the possible physiological role of placental leptin in regulating the function of the human reproductive system, ovaries, endometrium, and embryonic development (13, 14). Leptin binds to neuroreceptors in the hypothalamus and reduces levels of neuropeptide Y, which reduces appetite and signaling of adipocytes for the destruction of triglyceride as the attempt to release free fatty acids which are later used for the oxidation process, is affected by insulin and some cytokines (12, 15). Therefore, the role of leptin is clearly defined in female reproduction (15). In addition, leptin is thought to stimulate the secretion of FSH, and LH from the pituitary gland. In animal studies, leptin administration leads to the resumption of fertility (16). Leptin receptors have been discovered on the gonads which support the role of leptin and its effect on the ovaries. The present study aimed to investigate the relationship between serum leptin concentration and some reproductive hormones and endometrial thickness in women with primary subfertility.

2. Materials and Methods

The present case-control study was conducted from December 2020 to July 2021 at Kamal Al-Samarrai Specialized Hospital for fertility, infertility, and IVF, Baghdad, Iraq.

2.1. Study Design and Sampling

A total of 200 participants of reproductive age (15-45 years) reffered to Kamal Al-Samarrai Specialized Hospital for fertility, infertility, and IVF, Baghdad, Iraq. Then, 100 women were identified with primary infertility and were included in the case group. Additionally, 100 healthy fertile women were included in the control group regarding their demographic characteristics. Inclusion criteria included women aged 15-45 years with confirmed primary subfertility and the exclusion criteria were a history of diabetes mellitus or thyroid disease. Data were collected using demographic information, anthropometric measurements, and clinical parameters.

Biochemical tests performed on the second day of the menstrual cycle including FSH, LH, prolactin, estradiol, testosterone, and leptin were performed for all the 200 participants. Transvaginal ultrasonography was performed for all participants by a professional radiologist to assess the endometrial thickness and antral follicle count (AFC). A blood sample was taken on day 2 or 3 to measure the levels of estradiol, FSH, LH, AMH, testosterone, and prolactin. All men should have at least one semen sample analyzed in a laboratory or IVF center.

2.2. Leptin ELISA Kit

All procedures and methods were performed according to the manufacturer's instructions for the DRG Leptin ELISA Kit, Instruments GmbH, Germany (17).

2.3. Statistical Analysis

Data were analyzed for any errors or inconsistencies using SPSS software, IBM, and appropriate statistical tests. A *P*-value less than 0.05 is considered to be statistically significant.

3. Results

The mean age of the case and control groups was 29.7±6.5 and 29.1±8.2 years, respectively. Both groups were almost identical in terms of demographic and anthropometric characteristics. FSH, LH, Testosterone, and Prolactin were significantly higher in women with infertility than in controls ($P<0.001$). Leptin level in the case group was 26.8 ± 15.2 ng/mL and 6.4±2.3 ng/mL in the control group ($P<0.001$) (Table 1). AMH and AFC were significantly lower in the case group compared to the control one ($P<0.001$) (Table 2). Women with female factors had lower leptin levels compared to other subgroups (Table 3), however, the difference between these subgroups was statistically insignificant in leptin levels ($P>0.05$) (Table 4). Cases

with normal BMI had lower leptin levels (19.4±5.6 ng/mL) compared to the overweight (26.3±6.7 ng/mL) and obese subfertile women (34.7±8.9 ng/mL) (P<0.001) (Table 5). No significant difference was observed in leptin levels of different age groups (P>0.05) (Table 6).

Table 1. Comparison of hormonal indices, endometrial thickness and antral follicle count in the studied groups

Parameters	Case Group (n=100)	Control Group (n=100)	*P*-value
FSH (mIU/mL)	8.2±2.9	6.3±1.7	<0.001
LH (IU/L)	7.8±2.1	5.9±1.6	<0.001
Testosterone (ng/mL)	0.85±0.17	0.53±0.11	<0.001
Prolactin (ng/mL)	19.4±9.0	13.9±6.1	<0.001
Leptin (ng/mL)	26.8±15.2	6.4±2.3	<0.001
AMH (ng/mL)	1.7±1.2	3.0±1.8	<0.001
AFC (per ovary) median (range)	10 (2–32)	13 (7–50)	0.015
E2	35.7±14.5	37.6±20.7	0.451
Endometrial thickness	4.3±1.7	4.6±2.5	0.436

Table 2. Comparison of leptin levels between the case and control groups according to BMI

BMI category	Case Group (n=100)		Control Group (n=100)		*P*-value between Groups
	N	Leptin (ng/mL) Mean±SD	N	Leptin (ng/mL) Mean±SD	
Normal	28	19.4±5.6	33	6.3±2.4	<0.001*
Overweight	43	26.3±6.7	44	6.4±1.9	<0.001*
Obese	29	34.7±8.9	23	6.7±1.8	<0.001*
P-value within groups		<0.001*		0.769 ns	

Table 3. Comparison of leptin levels according to the cause of subfertility

Groups		Number of Subjects	Leptin level (ng/mL) Mean±SD	*P*-value vs. Control
Subgroup of the case group	Female factors	49	26.6±16.9	<0.001
	Unexplained factors	39	26.7±13.6	<0.001
	Male and female factors	12	28.4±18.4	<0.001
Control group		100	6.4±3.9	-
P-value between subgroups of women with subfertility			0.935^{ns}	

Table 4. Comparison of leptin levels among the case and control groups according to age

Age (year)	Case Group (n=100)		Control Group (n=100)		*P*-value between Groups
	N	Leptin (ng/mL) Mean±SD	N	Leptin (ng/mL) Mean	
≤20	6	26.7±9.3	7	6.0±2.9	<0.001*
21 - 30	56	25.6±9.8	54	6.5±2.0	<0.001*
31 - 40	33	29.0±14.9	3	6.4±2.1	<0.001*
41 - 50	5	25.9±11.2	8	6.1±2.1	<0.001*
P-value within groups		0.746 ns		0.912 ns	

Table 5. Correlation of leptin with age and anthropometric measurements in women with infertility

	Case Group		Control Gro	
Variables	**R**	***P*-value**	**R**	***P*-value**
Age	0.052	0.605	0.133	0.188
Duration of infertility	0.042	0.678	0.187	0.722
Thigh circumference (cm)	0.070	0.489	0.010	0.924
Arm circumference (cm)	0.007	0.944	0.060	0.552
Weight (kg)	0.356	0.001	0.119	0.240
Height (cm)	0.068	0.503	0.046	0.649
BMI	0.707	<0.001	0.071	0.481

R: Correlation coefficient

Table 6. Correlation of leptin with other hormonal indices and endometrial thickness in women with infertility

Parameters	**Case Group**		**Control Group**	
	R	***P*-value**	**R**	***P*-value**
FSH	0.120	0.234	0.137	0.176
LH	0.102	0.144	0.136	0.141
Testosterone	0.011	0.917	0.086	0.394
AMH	0.001	0.994	0.120	0.233
E2	0.063	0.532	0.160	0.111
Prolactin	0.092	0.361	0.087	0.390
AFC	0.038	0.709	0.044	0.664
Endometrial thickness	0.013	0.899	0.058	0.568

R: Correlation coefficient

Bivariate correlation analysis revealed no significant correlation between leptin level, age, and anthropometric measurements except body weight and BMI (Table 7). None of these variables showed a significant correlation with leptin levels in the control group (P>0.05) (Table 8). Bivariate correlation analysis indicated nosignificant correlation between leptin, other hormonal indices, and endometrial thickness in both studied groups (P>0.05). Binary regression testing revealed that 6 parameters appeared to be significant predictors of subfertility, however, a higher odds ratio (OR) has been reported with leptin (OR=2.793). ROC curve (Figure 1) showed that leptin level at a cutoff point of 11 ng/mL has a high sensitivity, specificity, and accuracy of 96%, 98%, and 96.9%, respectively with a positive predictive value of 98% and negative predictive value of 96.1% (Table 8).

Table 7. Results of binary regression analysis for the predictors of subfertility

Variables in the Equation	**Odds ratio (OR)**	**95% C.I. for OR**		***P*-value**
		Lower	**Upper**	
FSH	1.381	0.9	2.118	0.139
LH	1.421	1.24	1.63	0.018
Testosterone	2.468	1.379	4.418	0.002
Prolactin	1.182	1.049	1.333	0.006
Leptin	2.793	1.189	6.561	0.001
AMH	1.36	1.108	2.642	0.024
AFC	1.067	0.926	1.229	0.369
E2	1.026	0.955	1.101	0.487
BMI	1.391	1.06	2.602	0.011

Table 8. Validity parameters of leptin level in prediction of infertility

Validity parameters	Value
AUC	0.956
Cutoff point of Leptin (ng/mL)	11.0
Sensitivity	96.0%
Specificity	98.0%
Accuracy	96.9%
Positive predictive value	98.0%
Negative predictive value	96.1%

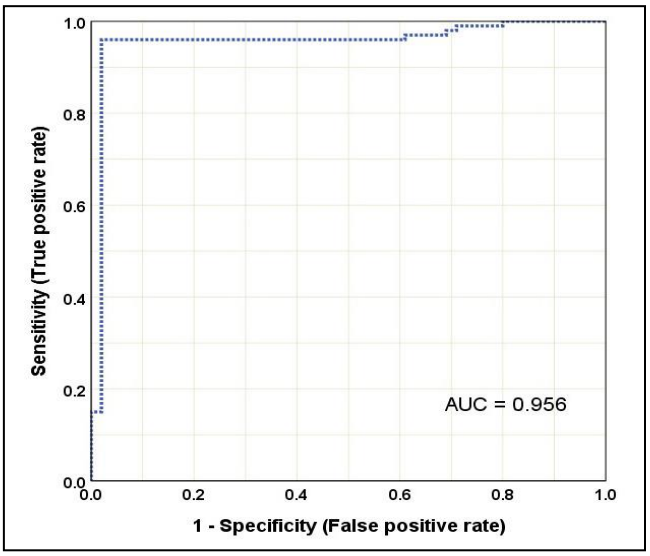

Figure 1. Diagram of ROC curve for the validity of leptin level in prediction of infertility

4. Discussion

Subfertility is one of the major health problems worldwide which is mostly borne by women. However, the results of previous studies are contradictory and the role of leptin is still debated in the reproductive process (9, 18-20). In the present study, the studied groups were almost identical in terms of demographic characteristics as a homogenous population sample is an important factor in controlling confounders and possible bias in case-control studies which strengthens the results of the study (21). The mean leptin level in women with infertility and fertile women was 26.8±15.2 and 6.4±2.3 ng/mL, respectively (P<0.001). These findings are consistent with those of Al-Jawadi (18) who found that the mean leptin level was significantly higher in women with infertility (39.2 ± 1.2 ng/mL) compared to the fertile group (35.4±0.9 ng/mL). Moreover, the results of the present study are in line with those reported by Kumari, Jaiswar (22), who found higher leptin levels in infertile women than those with infertility, however, they reported lower mean leptin compared to the present study which may be due to selecting women only with unexplained infertility. Baig, Azhar (16) studied the association of serum leptin with other hormones in women with unexplained infertility compared to fertile women and found no significant difference in serum leptin levels between fertile women and those with unexplained infertile. Also, Tafvizi and Masomi (23) documented statistically insignificant lower leptin levels in infertile women (24.89±2.93 ng/mL) compared to women with fertility (31.2±2.85 ng/mL). Other studies have shown an

inverse correlation between leptin and AMH as well as a stronger correlation in fertile women compared to those with infertility. Therefore, findings are contradictory regarding the correlation between AMH and leptin as well as the role of AMH in infertility (24). However, lower levels of AMH in women with infertility can be attributed to the reduced number of remaining primordial follicles (24). The present study found no significant differences in the levels of leptin among the causes of infertility which is consistent with the results of previous studies comparing levels of leptin in different causes of infertility (16, 25, 26). Previous studies have investigated the association between leptin and infertility; however, the results are contradictory. Chou and Mantzoros (25) stated that leptin concentration has no important role in the hypothalamic-pituitary-gonadal axisdisorders or hyperandrogenemia as well asin infertility and the regulation of ovarian function; however, it is directly correlated with BMI which causes infertility. Wertel, Gogacz (27) studied the levels of leptin in three groups of women according to their cause of infertility and concluded that leptin was not involved in the pathophysiology of infertility. Furthermore, leptin may have an inhibition effect on the ovarian sterodogenesis and development of ovarian follicles (15, 28).

The present study concluded that leptin levels significantly increased with higher BMI in women with infertility, while no such correlation was observed in the control group. The correlation between leptin and body mass index is attributed to the fact that leptin is secreted by white adipose tissue and its level reflects the volume of fat in the body (15, 28). No significant difference was found in leptin levels when the age groups were compared in the case and control groups. However, leptin levels were significantly higher in women with subfertility in all age groups compared to the corresponding control group. Although aging is an important risk factor for infertility as older women are more likely to develop ovulation disorders, in the present study 95% of women with infertility were aged 40 or younger; therefore, the correlation with age appeared to be not significant. Additionally, leptin levels proved to be declined with aging; therefore; higher levels of leptin in the group with infertility can obscure the effect of age on the levels of leptin in this group (29). A previous study reported no significant relationship between leptin and age in Chinese women after adjusting for BMI (30).

The present study found no significant correlation between serum leptin, age, duration of infertility, and anthropometric variables in both studied groups. However, a significant positive correlation was reported between body weight and BMI in women with infertility and not in the control group. Similar to the findings of the present study, Al-Jawadi (18) found no significant relationship between leptin levels and obesity indices except BMI. In contrast, the findings are inconsistent with those reported by Senghor, Shivashekar (31) who found a moderate positive correlation between leptin and obesity indices including hip and waist circumference, however, other indices such as thigh and arm circumferences were included in the present study which may not reflect the real status of obesity. Moreover, a significant correlation was found between BMI and serum leptin among Indian women with infertility, while no such correlation existed among fertile women (22). No significant relationship was observed between leptin levels and any of the hormonal indices in both groups ($P>0.05$). The correlation between leptin and other reproductive hormones has been widely studied; however, the results of different studies are not all consistent and further research is needed (16). In the present study, the case group had a relatively lower E2 level compared to fertile women. Al-Jawadi (18) found significantly lower E2 levels in the group with infertility than in the control group. Also, the results of the present study are in line with those of Isong, Okhormhe (32). In contrast, Farooq, Ullah (33) found a strong significant negative correlation between leptin levels and FSH, LH, and testosterone in fertile obese women and healthy males and females. Chou and Mantzoros (25) reported that leptin levels were

not correlated with levels of LH, FSH, testosterone, and E2. However, increasing fat mass in women with infertility seems to play a significant role in this correlation and acts as a confounder for such a correlation (15). Leptin has been suggested to increase angiogenesis and stimulate endothelial cells, however, the endometrium becomes unacceptable for embryo implantation due to a lack of leptin receptors in some cases with infertility at ovulation (34). Chakrabarti, Chatterjee (35) found a negative (inverse) correlation between the level of serum leptin and endometrial thickness, which is inconsistent with the finding of the present study. In the present study, binary regression revealed 6 significant predictors of subfertility. Leptin was a stronger predictor after adjustment for other variables and women with leptin levels of 11 ng/mL or higher were about 2.8 times more likely to be infertile. Plenkin (36) found that failure of treatment could be attributed to higher levels of leptin after adjusting for various possible risk factors and hormonal levels and concluded that women with serum leptin levels above 15 ng/mL were significantly at high risk to fail to respond to treatment independent of other factors (22). Previous studies have attributed other parameters that appear to be significantly related to infertility to the correlation between these parameters from various aspects of the relationship between these parameters and infertility. Lin, Li (37) found that serum testosterone levels between 0.20-0.27 were associated with a higher risk of subfertility (OR = 3.12) when AMH levels were less than 1.2; however, the risk significantly increased in women with AMH levels higher than 5 (OR = 6.54). In contrast, Tafvizi and Masomi (23) found no statistically significant difference in serum leptin levels between fertile women and those with infertility as well as leptin levels and other risk factors of infertility including hormone profiles and AFC. Hernáez, Rogne (38) found in multiple regression analysis that women with BMI higher than 30 kg/m^2 have 18% higher chance of subfertility. Also, they found higher risk in those with BMI lower than 20 kg/m^2 and concluded that a J-shaped relationship was observed between BMI and subfertility, while BMI between 23-25 kg/m^2 is associated with lower risk of subfertility. From another point of view, Musa and Osman (39) found that Qatari women over 35 years who have gained weightsince marriage and have irregular menstrual cycles are significant predictors of primary infertility with odds ratios of 3.7, 2.4 and 4.2, respectively. In Iran, Maharlouei, Morshed Behbahani (20) used logistic regression to analyze predictors of infertility and found that primary infertility was independently related to age (OR=1.37), high BMI (OR=1.95), smoking (OR=1.38), and higher education level (OR=2.23). However, in the present study, the effect of demographic variables was controlled in the phase of study design by adapting to control their confounding effect (21). Al Maskari and Alnaqdy (40) examined the relationship between leptin and obesity among a group of Omani women. Moreover, leptin was evaluated as a predictor of infertility using the ROC curve and a high validity parameter indicated that leptin could be an important predictor of infertility when its level exceeded 11 ng/mL with a sensitivity, specificity, and accuracy of 96%, 98%, and 96.9%, respectively as well as a positive predictive value of 98% and negative predictive value of 96.1%. Plenkin (36) reported a relatively higher cutoff point of 15 ng/mL for leptin above which women are at high risk of infertility; therefore, authors considered leptin as a good predictor of infertility. However, to the best of our knowledge, no previous studies was performed on validity parameters of leptin in predicting infertility.

A significant variation was observed in all fertility hormones except estradiol between fertile women and those with subfertility. Leptin levels were much higher in women with subfertility than fertile women. A significant correlation was observed between high leptin levels and increased BMI. A high leptin level was a strong and valid predictor of subfertility.

Authors' Contribution

Study concept and design: B. J. E.
Acquisition of data: S. Z. A. A.
Analysis and interpretation of data: Z. R. M.
Drafting of the manuscript: S. Z. A. A.
Critical revision of the manuscript for important intellectual content: B. J. E.
Statistical analysis: Z. R. M.
Administrative, technical, and material support: S. Z. A. A.

Ethics

The present study was approved by the Ethics Committee of the College of Medicine, University of Babylon, Babylon, Iraq. All participants in the study provided oral and written informed consent.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Akhondi MM, Ranjbar F, Shirzad M, Ardakani ZB, Kamali K, Mohammad K. Practical difficulties in estimating the prevalence of primary infertility in Iran. Int J Fertil Steril. 2019;13(2):113.
2. Farquhar CM, Bhattacharya S, Repping S, Mastenbroek S, Kamath MS, Marjoribanks J, et al. Female subfertility. Nat Rev Dis Primers. 2019;5(1):1-21.
3. Hussain R, Nasir F, Hashim N, Naqvi S. Subfertility: aetiological factors. Professional Med J. 2017;24(07):1012-5.
4. Lainez NM, Coss D. Obesity, neuroinflammation, and reproductive function. Endocrinology. 2019;160(11):2719-36.
5. Ramos-Lobo AM, Donato Jr J. The role of leptin in health and disease. Temperature. 2017;4(3):258-91.
6. Kalaiselvi V, Saikumar P, Prabhu K. The anti mullerian hormone-a novel marker for assessing the ovarian reserve in women with regular menstrual cycles. J Clin Diagnostic Res. 2012;6(10):1636.
7. Pérez-Pérez A, Sánchez-Jiménez F, Maymó J, Dueñas JL, Varone C, Sánchez-Margalet V. Role of leptin in female reproduction. Clin Chem LabMed. 2015;53(1):15-28.
8. Anwar AA, Abdullah N, Padjalangi AN, Hamid F, Mappeware NA, Lukas E. Serum leptin concentration is correlated to insulin resistance in polycystic ovary syndrome (PCOS) patients. Mol Cell Biomed Sci. 2021;5(2):93-7.
9. Kargasheh FB, Ansaripour S, Borumandnia N, Moradi N, Zandieh Z, Maleki M, et al. Association of leptin G2548A and leptin receptor Q223R polymorphisms and their serum levels with infertility and recurrent pregnancy loss in Iranian women with polycystic ovary syndrome. PLoS One. 2021;16(8):0255920.
10. Park H-K, Ahima RS. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism. 2015;64(1):24-34.
11. Silvestris E, de Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. Reprod Biol Endocrinol. 2018;16(1):1-13.
12. Salem AM. Variation of Leptin During Menstrual Cycle and Its Relation to the Hypothalamic–Pituitary–Gonadal (HPG) Axis: A Systematic Review. Int J Womens Health. 2021;13:445.
13. Kawwass JF, Summer R, Kallen CB. Direct effects of leptin and adiponectin on peripheral reproductive tissues: a critical review. Mol Hum Reprod. 2015;21(8):617-32.
14. Sylvia KE, Lorenz TK, Heiman JR, Demas GE. Physiological predictors of leptin vary during menses and ovulation in healthy women. Reprod Biol. 2018;18(1):132-6.
15. Childs GV, Odle AK, MacNicol MC, MacNicol AM. The importance of leptin to reproduction. Endocrinology. 2021;162(2):204.
16. Baig M, Azhar A, Rehman R, Syed H, Tariq S, Gazzaz ZJ. Relationship of serum leptin and reproductive hormones in unexplained infertile and fertile females. Cureus. 2019;11(12).
17. Chow VT, Phoon M. Measurement of serum leptin concentrations in university undergraduates by competitive ELISA reveals correlations with body mass index and sex. Adv Physiol Educ. 2003;27(2):70-7.
18. Al-Jawadi ZA. Effect of Leptin on the Infertile Women. Ann Rom Soc Cell Biol. 2020:111-6.
19. Gambineri A, Laudisio D, Marocco C, Radellini S, Colao A, Savastano S. Female infertility: which role for obesity? Int J Obes Suppl. 2019;9(1):65-72.
20. Maharlouei N, Morshed Behbahani B, Doryanizadeh L, Kazemi M. Prevalence and pattern of

infertility in Iran: A systematic review and meta-analysis study. Women's Health Bull. 2021:63-71.

21. Ananth CV, Schisterman EF. Confounding, causality, and confusion: the role of intermediate variables in interpreting observational studies in obstetrics. Am J Obstet Gynecol. 2017;217(2):167-75.
22. Kumari P, Jaiswar S, Shankhwar P, Deo S, Ahmad K, Iqbal B, et al. Leptin as a predictive marker in unexplained infertility in north indian population. J Clin Diagnostic Res. 2017;11(3):QC28.
23. Tafvizi F, Masomi M. Comparison of serum leptin level in women with unexplained infertility and fertile women in Iran. J Obstet Gynaecol India. 2016;66(1):466-70.
24. Alao M. Association between Serum Leptin and AntiMullerian Hormones in Women with Infertility in Ogbomoso Southwest Nigeria. Niger J Clin Pract. 2020.
25. Chou SH, Mantzoros C. Role of leptin in human reproductive disorders. J Endocrinol. 2014;223(1):49-62.
26. Kamyabi Z, Gholamalizade T. A comparative study of serum and follicular fluid leptin concentrations among explained infertile, unexplained infertile and fertile women.Int J Fertil Steril. 2015;9(2):150.
27. Wertel I, Gogacz M, Polak G, Jakowicki J, Kotarski J. Leptin is not involved in the pathophysiology of endometriosis-related infertility. Eur J Obstet Gynecol. 2005;119(2):206-9.
28. Nikanfar S, Oghbaei H, Rezaei YR, Zarezadeh R, Jafari-Gharabaghlou D, Nejabati HR, et al. Role of adipokines in the ovarian function: oogenesis and steroidogenesis. J Steroid Biochem Mol Biol. 2021;209:105852.
29. Isidori AM, Strollo F, Morè M, Caprio M, Aversa A, Moretti C, et al. Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights. J Clin Endocrinol Metab. 2000;85(5):1954-62.
30. Zhong N, Wu X-P, Xu Z-R, Wang A-H, Luo X-H, Cao X-Z, et al. Relationship of serum leptin with age, body weight, body mass index, and bone mineral density in healthy mainland Chinese women. Clin Chim Acta. 2005;351(1-2):161-8.
31. Senghor A, Shivashekar M, Vinodhini V. Serum Leptin And Adiposity Indicators In Infertile Females Of Reproductive Age Group. Asian J Pharm Clin Res. 2018:341-3.
32. Isong I, Okhormhe Z, Eze-Bassey I, Okpokam D, Usoro C. Levels of prolactin, progesterone, estradiol, luteinizing hormone and follicle stimulating hormone in infertile women in Calabar, Nigeria. Int J Reprod Contracept Obstet Gynecol. 2016;5(3):804.
33. Farooq R, Ullah SL, Ishaq H. Relation of serum leptin with sex hormones of obese infertile men and women. J Appl Pharm Sci. 2013;3(1):60.
34. Alfer J, Popovici RM, Fattahi A, Krieg J, Dittrich R, Beckmann MW, et al. Endometrial delay is found to be part of a normal individual dynamic transformation process. Arch Gynecol Obstet. 2021;304(6):1599-609.
35. Chakrabarti J, Chatterjee R, Goswami S, Chakravarty B, Kabir SN. Overt leptin response to controlled ovarian hyperstimulation negatively correlates with pregnancy outcome in in vitro fertilization--embryo transfer cycle. J Hum Reprod Sci. 2012;5(2):194.
36. Plenkin FSaD, S. J. Raised Leptin Level Can Predict Infertility in Women Failed to Conceive After 5 Years of Treatment. J Med Surg Pract. 2021;7(3):266-74.
37. Lin L-T, Li C-J, Tsui K-H. Serum testosterone levels are positively associated with serum anti-mullerian hormone levels in infertile women. Sci Rep. 2021;11(1):1-8.
38. Hernáez Á, Rogne T, Skåra KH, Håberg SE, Page CM, Fraser A, et al. Body mass index and subfertility: multivariable regression and Mendelian randomization analyses in the Norwegian Mother, Father and Child Cohort Study. Human Rep. 2021;36(12):3141-51.
39. Musa S, Osman S. Risk profile of Qatari women treated for infertility in a tertiary hospital: a case-control study. Fertil Res Pract. 2020;6(1):1-17.
40. Al Maskari MY, Alnaqdy AA. Correlation between serum leptin levels, body mass index and obesity in Omanis. Sultan Qaboos Univ Med J. 2006;6(2):27.