

The Impact of Obesity on Infertile Women with Polycystic Ovaries in Iraq

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ABSTRACT

The study has focused on obesity in women with Polycystic Ovary Syndrome (PCOS), as a potential new indicator of infertility by evaluating twelve biochemical and hormonal variables such as progesterone, estrogen, Follicle Stimulating Hormone (FSH), LH/FSH ratio, Luteinizing hormone (LH), Thyroid Stimulating Hormone (TSH), Prolactin, Cholesterol, Triglyceride (TG), Very Low Density Lipoprotein (VLDL), High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL). In all women, biochemical and hormonal tests have been examined. The effect of Waist to Hip ratio (WHR) and Body Mass Index (BMI) has been evaluated. The correlation between being afflicted with PCOS and WHR has been found to be positively correlated with LH, LH/FSH ratio, TSH, Cholesterol, TG, LDL and VLDL, whereas the negative correlation with estrogen, progesterone, FSH and HDL. Therefore, we conclude that WHR and BMI are new Indexes in obesity, indicating the increase of infertility with PCOS risk.

Keywords: Polycystic Ovary Syndrome, Infertility, Obesity, BMI, WHR.

(PCOS)

INTRODUCTION

Polycystic Ovary Syndrome (PCOS), affecting 5-10% of reproductive age women, is a usual endocrine disorder (Shoaib *et al.*, 2015). Among the general female population, the prevalence is approximately 10%. The gonadal and hormonal balance in PCOS women is disturbed. Altered gonadal cycle in PCOS demonstrates a continuous anovulation and abnormal menses (oligomenorrhea, amenorrhea), leading to infertility. The other clinical characteristics of PCOS are symptoms and indications of hyperandrogenism (HA) including hirsutism, baldness and acne. Acanthosis nigricans and insulin resistance are also usual (Ramanand *et al.*, 2012). Obesity helps in the occurrence of the metabolic syndrome in PCOS subjects. Central obesity is mostly accompanied with PCOS and associated with elevated chance of developing type 2 diabetes and cardiovascular disease. The abdominal obesity as the specific indicators, is the best for discriminating the high coronary hazard, compared to the common obesity sign, BMI. In the clinical setting, waist-to-hip ratio (WHR) has been applied to examine the presence of central obesity (Gateva and Kamenov, 2012). Increased abdominal fat accumulation (Waist Hip Ratio >0.8 in women) contributes to reproductive dysfunction (Kuchenbecker *et al.*, 2011).

Few studies have been performed to find out about the changes in hormonal profiles and serum lipid of PCOS subjects; therefore, the aim of this study is to investigate the effect of obesity through BMI and WHR as new indicators of the increase infertility, in women with PCOS, in Iraq.

MATERIALS AND METHODS

This analytic, descriptive, hospital-based and cross-sectional, study was performed in the Educational Hospital of Azadi / Azadi Center for Infertility and In Vitro Fertilization (IVF) in Dohuk, from June 2017 to April 2018. All patients included, demonstrated a history of Infertility. Cases participated in the study were 107 infertile women, 40 of them diagnosed with PCOS and their ages ranged between 18–43 years. BMI was between (20-58.59) kg/m², the WHR was greater than 0.8 and the clinical data for each case were included in a questionnaire, prepared for this purpose. The following conditions have been ruled out, diabetes, high blood pressure and thyroid disease. A total of 54 normal fertile women (control group) were collected in this study; their ages ranged between (17–40) years with BMI (18–24.9) kg/m² and WHR less than 0.8. Blood samples were drawn after an overnight fast of 12 hours, during the early follicular phase (cycle day 2 or 3) for evaluation of Estrogen (E2), FSH, LH, LH/FSH ratio, TSH and progesterone, prolactin in the luteal phase (cycle day 21) in serum, using the commercial kits (Bio Merieux Kits). The enzyme linked fluorescent assay (ELFA) was performed, using the hormone analyzer (minividas –France). The lipid profile included analysis of measured total cholesterol (TC), TG and HDL, using commercial kits (Biolabo Kits). LDL and VLDL were determined indirectly, using the Friedewald formula. BMI (Kg/m²)= Weight (Kg) / Height(m²) and WHR= W(Waist) / H(Hip) were also calculated as shown (Akwasi, 2011).

Statistical Analysis

The statistical analysis was performed, using the statistical analysis system (SPSS) version 20 (IBM). The statistical techniques applied to analyze the data, including standard deviation, mean, maximum and minimum, while T-test was performed to compare total patients and total controls, based on the occupation at and $p \leq 0.001$ and $p \leq 0.05$, respectively (Kirkpatrick and Feeney, 2012).

RESULTS AND DISCUSSION

A total, 107 infertile women were included in the study with a mean age of 30.0 ± 6.06 years and 54 control group with a mean age of 27.04 ± 5.55 years. Other basic parameters of the study participants, including body mass index (BMI) and WHR of the infertile women were significantly increased, compared to the control group, (Table 1). BMI and WHR may have an effect on the reproductive function of the women. Obesity in the upper body has been shown to affect ovulation (Wilkes and Murdoch, 2009; Dawood, 2013).

Table 1: Age and anthropometric parameters of infertile women and control group

Age and anthropometric parameters	infertile group Mean \pm SD	Control group Mean \pm SD	P- value
Age	30.0 ± 6.06	27.04 ± 5.55	0.003**
Weight (Kg)	77.7 ± 13.6	62.93 ± 5.14	0.001***
BMI (Kg/m ²)	30.93 ± 4.99	23.81 ± 1.71	0.001***
WHR	0.912 ± 0.097	0.767 ± 0.042	0.01**

Significant differences at $P \leq 0.01$, *Significant differences at $P \leq 0.001$

The level of hormonal and biochemical parameters of infertile women, compared with the control group are shown in (Table 2). A significant increase in the level of estrogen (E2) at $P = 0.025$ was found. This may be because of the high body weight and increased fatty tissue, which associated with sex hormone imbalance and low level of sex hormone-binding globulin (SHBG). This is due to the capability of the adipose tissue to collect hormones in deposits, and also to interconvert and metabolize them via local enzymatic reactions that can significantly influence the practical conditions of the reproductive axis. This may explain the high concentrations of estrogen in obese women, compared to women with normal weight (Suskić *et al.*, 2016). This may affect the Hypothalamic Pituitary Gonads axis (HPG) and the high estrogen creates a decrease in the secretion of GnRH hormone through negative response, causing menstrual disorder and an ovulation (Dag and Dilbaz, 2015). There was a significant decrease in the level of progesterone ($P = 0.01$) that might be due to an ovulation. This is observed in women with PCOS, which can contribute to the risk of endometrial cancer, leading to infertility (Carlson *et al.*, 2014). A significant decrease was found in the level of FSH ($P = 0.019$), while there was a significant increase in the levels of LH ($P = 0.016$) and LH/FSH ($P = 0.001$), as shown in (Table 2). The exact cause of infertility appears to be the absence of long an ovulation due to hyper androgenism caused by obesity (Hymavathi *et al.*, 2016).

A significant increase in the level of prolactin ($P = 0.02$) was found in the infertile women, compared with the control group. Hyperprolactinemia adversely affects fertility potential by impairing GnRH plasticity, and thereby ovarian function (Hivre *et al.*, 2014). In addition, there was a significant increase in the concentration of TSH ($P = 0.0013$). Obesity most likely correlates with chronic low inflammatory state and high TSH levels, seen in obese women that could be a consequence of high amounts of circulating antibodies to the thyroid (Seth *et al.*, 2013). Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities, infertility and high miscarriages (Hivre *et al.*, 2014). There was a significant increase in the level of cholesterol ($P = 0.001$), TG ($P = 0.001$), VLDL ($P = 0.008$) and LDL ($P = 0.007$). A significant decline in HDL level was seen ($P = 0.0016$) in infertile women. This suggests that there may be a relationship between abnormal lipoprotein metabolism and female infertility. Dyslipidemia is most likely seen in obese subjects, with high level of triglyceride in plasma and free fatty acids, and low level of HDL and slightly increased LDL have also been observed. Fatty acids and cholesterol are determining factors of reproductive activity, at the level of the uterus and ovary. An irregular lipoprotein

metabolism has been corresponding to defective acolyte and infertility (Al-Attar and Al-Fakhry, 2006 ; Fontana and Torre, 2016).

Table 2: The level of hormonal and biochemical parameters of infertile women compared with the control group

Hormonal and biochemical parameters	Infertile group Mean \pm SD No. =107	Control group Mean \pm SD No. =54	P-value
Estrogen (E2) (pg/ml)	72.1 \pm 30.9	56.53 \pm 26.4	0.025*
Progesterone (ng/ml)	1.94 \pm 0.83	3.96 \pm 2.4	0.01**
FSH (mIU/ml)	5.15 \pm 5.12	6.84 \pm 1.69	0.019*
LH (mIU/ml)	6.19 \pm 3.0	3.84 \pm 1.5	0.016*
Prolactin (ng/ml)	32.7 \pm 21.5	15.68 \pm 7.1	0.02*
TSH (μ IU/ml)	2.09 \pm 1.04	1.554 \pm 0.67	0.0013**
LH / FSH	1.35 \pm 1.24	0.561 \pm 0.32	0.001***
Total Cholesterol (mg/dL)	186.3 \pm 34.1	151.93 \pm 33.5	0.001***
Triglyceride (TG) (mg/dL)	162.5 \pm 83.7	110.1 \pm 55.4	0.001***
VLDL (mg/dL)	32.5 \pm 16.6	21.87 \pm 10.9	0.008**
HDL (mg/dL)	41.44 \pm 8.7	68.1 \pm 26.89	0.0016**
LDL (mg/dL)	113.3 \pm 34.4	85.51 \pm 26.8	0.007**

*Significant differences at $P \leq 0.05$, **Significant differences at $P \leq 0.01$, *** Significant differences at $P \leq 0.001$, N=No significant differences

The comparison of the level of hormonal and biochemical parameters of women with PCOS and a control group, indicating a significant increase in the concentration of estrogen, TSH, LH and an increase in LH / FSH ($P = 0.009$), ($P = 0.001$), ($P = 0.005$) and ($P = 0.01$), respectively, shown in (Table 3). In women with PCOS, a significant decrease in the concentration of progesterone (P4) and FSH, has been observed, $P = 0.006$ and $P = 0.001$, respectively. Insulin resistance and Hyperinsulinaemia have important roles in the physiology of PCOS, where ovaries respond to insulin hormone through interaction with their own receptors. Excess insulin can stimulate steroidogenesis, and increase the secretion of LH to increase the production of androgen from theca cells, leading to an excess of androgen (hyperandrogenemia) (Kumar *et al.*, 2016). Ovarian response to LH is the main source of high androgen in female subjects with PCOS (Valderhaug *et al.*, 2015). Hyperandrogenemia, because of hyperinsulinemia results in granulosa cell apoptosis, and this may have an influence on ovaries' activities. It is shown that estrogen production in granulosa cells is induced by insulin. Because of the increased steroid genesis due to insulin and its interaction with LH, the destructive environment causes termination of the follicle growth. Therefore, follicular arrest and premature utilization develop and lead to obesity-induced oligo-an ovulation and menstrual cycle diseases (Dag and Dilbaz, 2015). High levels of LH lead to high levels of estrogen, causing a decrease in FSH level by negative feedback. LH / FSH a diagnostic marker for women with PCOS, obesity may damage reproductive activities by influencing both the endometrium and ovaries. The HPG axis declines because of alterations in hormones and some substrate (Lal *et al.*, 2016). Obesity and overweight in women with PCOS may be an important factor, affecting levels of thyroid hormones. The occurrence of hypothyroidism in reproductive age group is up to 4 % and it is accompanied with a wide array of reproductive diseases, varying from menstrual abnormalities to abortions and infertility. Thyroid responsiveness by the ovaries could be explained by the presence of the thyroid hormone receptors on human oocytes. TSH also decreases production of sex hormone binding globulin influences estrogen metabolism. In PCOS patients with hypothyroidism, serum testosterone levels have been increased. This suggests that

hypothyroidism elevates free testosterone and decreases sex hormone binding globulin. This free testosterone is accountable for most of the characteristics of PCOS, such as acne, hirsutism, polycystic ovaries, infertility etc. (Enzevaci *et al.*, 2014; Chen *et al.*, 2017).

Progesterone levels are significantly lower in infertile women with PCOS when compared with the control group. It may be due to obesity, which influences the HPG axis by increasing free estrogen levels because of elevated conversion of androgens to estrogens in adipose tissue. Elevated estrogen diminishes GnRH by the negative response. Therefore, the affected HPG axis creates an ovulatory or abnormal cycles and hence lowers the levels of progesterone hormone (Valderhaug *et al.*, 2015). There was also a significant increase in the levels of cholesterol, TG, LDL and VLDL (P=0.001), (P=0.001), (P = 0.007) and (P=0.008), respectively. A significant decline in HDL level was seen (P=0.001), in the infertile women with PCOS, in comparison with the control group. The reason for dyslipidaemia in PCOS may be attributed to hyperinsulinaemia and hyperandrogenemia. This causes adiposities to experience elevated catecholamine-induced lipolysis and deliver free fatty acids into the blood. Elevated free fatty acids in the liver induce secretion of VLDL, which ultimately leads to hypertriglyceridemia. Through the reverse cholesterol transport pathway, hypertriglyceridaemia leads to low HDL cholesterol and increased LDL cholesterol levels. It is also possible that Hyperandrogenism may also affect lipid metabolism by the induction of hepatic lipase activity, which engages in the catabolism of HDL particles (Shoaib *et al.*, 2015; Swetha *et al.*, 2015).

The results shown in (Table 3) did not demonstrate a significant difference in the level of prolactin in women with PCOS, compared with the control group.

Table 3: Comparison of the hormonal and biochemical parameters levels between the two groups of infertile women with PCOS and Control group

Hormonal and biochemical parameters	PCOS group Mean \pm SD No. =40	Control group Mean \pm SD No. =54	P-value
Estrogen (E2) (pg/ml)	80.1 \pm 32.4	56.53 \pm 26.4	0.009**
Progesterone (ng/ml)	1.297 \pm 0.828	3.96 \pm 2.4	0.006**
FSH (mIU/ml)	4.86 \pm 2.97	6.84 \pm 1.69	0.001***
LH (mIU/ml)	5.7 \pm 3.34	3.84 \pm 1.5	0.005**
Prolactin (ng/ml)	27.3 \pm 1.7	15.68 \pm 7.1	N
TSH (μ IU/ml)	2.47 \pm 1.23	1.554 \pm 0.66	0.001***
LH/FSH	1.7 \pm 1.20	0.561 \pm 0.32	0.01**
Total Cholesterol (mg/dL)	183.4 \pm 39.4	151.93 \pm 33.5	0.001***
Triglyceride (TG) (mg/dL)	166.3 \pm 86.7	110.1 \pm 55.4	0.001***
VLDL (mg/dL)	33.4 \pm 17.2	21.87 \pm 10.9	0.008**
HDL (mg/dL)	40.86 \pm 8.85	68.1 \pm 26.89	0.0016**
LDL (mg/dL)	111.6 \pm 35.5	85.51 \pm 26.8	0.007**

*Significant differences at P \leq 0.05, **Significant differences at P \leq 0.01,

*** Significant differences at P \leq 0.001, N=No significant differences.

The results shown in (Table 4), by comparing the level of hormonal and biochemical parameters of women with and without PCOS, indicating a significant increase in the levels of estrogen and TSH P= 0.047 and P= 0.006, respectively, in infertile women with PCOS. It may be due to leptin that has

direct influences on all ovarian cells and looks to have a physiologic controlling impact on folliculogenesis (Chou and Mantzoros, 2014). A leptin concentrations are consistently found to be strongly related to weight, some reports suggested the hyperleptinemia observed in PCOS, as only a consequence of this condition. On the other hand, data correlating leptin levels to estradiol, insulin, and testosterone in women with PCOS advocate a more complex role of leptin in its pathophysiology (Rojas *et al.*, 2014).

Adiposity enhanced leptin, insulin resistance, sign of abnormal autoimmunity, all of which are existing in both disease conditions of Hypothyroidism and PCOS, appear to play a complicated role in linking these two diseases. High BMI is an integral part of PCOS and is observed in a broad majority (54-68%) of these conditions. The connection between obesity and thyroid functions is again an appealing one, with vague pathophysiological processes; hence, there is, enough proof to confirm that TSH increases in individual with high BMI. Obesity is correlated with milieu changes environment with an elevation of insulin resistance and pro-inflammatory markers. Elevated leptin in obesity has been suggested to function directly on the hypothalamus, leading to increased TRH discharge. High TSH levels, in any of these two pathways, induce adiposities to increase their proliferation (Singla *et al.*, 2015 ; Yu and Wang, 2016).

Table 4: Comparison of the hormonal and biochemical parameters levels between the two groups of infertile women with and without PCOS

Hormonal and biochemical parameters	PCOS group Mean \pm SD No. =40	Non PCOS group Mean \pm SD No. =67	P-value
Estrogen (E2) (pg/ml)	80.1 \pm 32.4	67.7 \pm 29.4	0.047*
Progesterone (ng/ml)	1.297 \pm 0.828	2.30 \pm 0.43	N
FSH (mIU/ml)	4.86 \pm 2.97	5.31 \pm 0.6	N
LH (mIU/ml)	5.7 \pm 3.34	6.47 \pm 4.37	N
Prolactin (ng/ml)	27.3 \pm 1.7	18.28 \pm 8.5	N
TSH (μ IU/ml)	2.47 \pm 1.23	1.88 \pm 0.86	0.006**
LH/FSH	1.7 \pm 1.20	1.36 \pm 1.19	N
Total Cholesterol (mg/dL)	183.4 \pm 39.4	187.8 \pm 31	N
Triglyceride (TG) (mg/dL)	166.3 \pm 86.7	160.4 \pm 82.6	N
VLDL (mg/dL)	33.4 \pm 17.2	32.1 \pm 16.4	N
HDL (mg/dL)	40.86 \pm 8.85	41.77 \pm 8.67	N
LDL (mg/dL)	111.6 \pm 35.5	114.2 \pm 34	N

*Significant differences at $P \leq 0.05$, **Significant differences at $P \leq 0.01$, *** Significant differences at $P \leq 0.001$, N=No significant differences.

The correlation between hormonal and biochemical parameters of the effect of BMI on infertile women with PCOS

The results in (Table 5) proved a correlation between PCOS and BMI, which confirm that obesity is a sign that increases risk factors of PCOS. The correlation between PCOS and BMI is positively correlated with LH, LH/FSH ratio, prolactin, TSH, cholesterol, TG, LDL and VLDL, whereas the negative correlation has been found in estrogen, progesterone, FSH and HDL.

Table 5: The correlation between hormonal and biochemical parameters of the effect of BMI on infertile women with PCOS

Hormonal and biochemical parameters	r-value	P-value
Estrogen (E2) (pg/ml)	-0.014	N
Progesterone (ng/ml)	-0.224	N
FSH (mIU/ml)	-0.058	N
LH (mIU/ml)	0.148	N
LH/FSH	0.082	N
Prolactin (ng/ml)	0.021	N
TSH (μ IU/ml)	0.063	N
Total Cholesterol (mg/dL)	0.371	0.022*
Triglyceride (TG) (mg/dL)	0.398	0.01**
VLDL (mg/dL)	0.379	0.01**
HDL (mg/dL)	-0.399	0.01**
LDL (mg/dL)	0.27	N

*Significant differences at $P \leq 0.05$, **Significant differences at $P \leq 0.01$, ***Significant differences at $P \leq 0.001$, N=No significant differences

The correlation between hormonal and biochemical parameters of the effect of WHR on PCOS

The results in (Table 6) proved that there is a correlation factor of PCOS with WHR, which confirm that abdominal obesity is a sign that increases risk factors of PCOS. The relation between waist to hip ratio and being affected with PCOS show positive correlation with LH, LH/FSH ratio, TSH, cholesterol, TG, VLDL and LDL. Where as, the negative correlation has been found in estrogen, progesterone, FSH and HDL, while prolactin hormone did not show a statistically significant correlation.

Table 6: The correlation between hormonal and biochemical parameters of the effect of WHR on infertile women with PCOS

Hormonal and biochemical parameters	r-value	P-value
Estrogen (E2) (pg/ml)	-0.079	N
Progesterone (ng/ml)	-0.261	N
FSH (mIU/ml)	-0.017	N
LH (mIU/ml)	0.107	N
LH/FSH	0.035	N
Prolactin (ng/ml)	0.0	N
TSH (μ IU/ml)	0.221	N
Total Cholesterol (mg/dL)	0.213	N
Triglyceride (TG) (mg/dL)	0.364	0.01**
VLDL (mg/dL)	0.256	N
HDL (mg/dL)	-0.18	N
LDL (mg/dL)	0.072	N

*Significant differences at $P \leq 0.05$, **Significant differences at $P \leq 0.01$, ***Significant differences at $P \leq 0.001$, N=No significant differences

CONCLUSION

This study brings to our consideration that deviation from normal BMI and WHR in Iraqi infertile women implies to be substantially higher. Obesity is correlated with hormonal abnormalities and dyslipidaemia, which perhaps is accountable for PCOS and defective ovarian follicular development, and quantitative and qualitative development of the oocyte; hence it should be basically targeted in the management of disease in these women before starting any treatment to adjust their hormonal imbalance. The subjects should be informed to adopt a lifestyle and healthy body weight according to interventions before they begin any surgical or medical management for infertility. A holistic approach to control weight and reproductive health requires to be taken to enhance the chances of appreciation in overweight women; this will also ensure a positive influence on their general health.

REFERENCES

- Akwasi, N.O.P. (2011). The correlation between anthropometry and infertility in women. MSc Thesis, Kwame Nkrumah University of Science and Technology, Kumasi, pp. 1-117.
- Al-Attar, H.; Al-Fakhry, S.H. (2006). Estimation of cholesterol level during pregnancy. *Raf. J. Sci.*, **17**(1), 1-4.
- Carlson, M.J.; Thie, K.W.; Yang, S.; Leslie, K.K. (2014). Catch it before it kills: Progesterone, obesity, and the prevention of endometrial cancer. *Discov. Med. J.*, **14**(76), 215–222.
- Chen, L.; Tan, Y.; Cao, P. (2017). Relationship of thyroid stimulating hormone with sex hormones in patients with polycystic ovary syndrome: a single-center, retrospective observational study. *Int. J. Clin. Exp. Pathol.*, **10**(5), 5989-5993.
- Chou, S.H.; Mantzoros, C. (2014). Role of leptin in human reproductive disorders. *J. Endocrinol.*, **223**(1), T49–T62.
- Dag, Z.O.; Dilbaz, B. (2015). Impact of obesity on infertility in women. *J. Turk Ger. Gynecol. Assoc.*, **16**(11), 1-7.
- Dawood, R.M. (2013). Biochemical bone indices and serum uric acid changes in postmenopausal women. *Raf. J. Sci.*, **24**(4), 42-50.
- Enzevaei, A.; Salehpour, S.; Tohidi, M.; Saharkhiz, N. (2014). Sub clinical hypothyroidism and insulin resistance in polycystic ovary is there arelationship?. *Iran J. Reprod. Med.*, **12**(7), 481- 486.
- Fontana, R.; Torre, S. D. (2016). The deep correlation between energy metabolism and reproduction: A view on the effects of nutrition for women fertility. *Nutrients J.*, **8**, 87.
- Gateva, A.; Kamenov, Z. (2012). Cardiovascular risk factors in with polycystic ovary syndrome and/or obesity. *Obstetrics and Gynecol. Intern.*, 2012: 1-12.
- Hivre, M.D.; Bhale, D.V.; Mahat, R.K.; Bujurge, A.A. (2014). Study of serum TSH and prolactin levels in patients of female infertility. *International J. Recent Trends in Sci. and Technol.*, **9**(1), 144-145.
- Hymavathi, K.; Tadisetti, S.; Pusalra, D.; Pambadi, P. (2016). Correlation of serum thyroid hormones and prolactin levels to female infertility. *Int. J. Reprod. Contracept Obstet. Gynecol.*, **5**(11), 4018-4024.
- Kirkpatrick, L.; Feeney, B.C. (2012). "A Simple Guide to IBM SPSS Statistics for Version 18.0 and 19.0". 11th ed., Wadsworth Cengage Learning, Belmont, ISBN-10:1111352550, pp.115.
- Kuchenbecker, W.K.H.; Groen, H.; Asselt, S.J.V.; Bolster, J.H.T.; Zwerver, J.; Slart, R.H.J.; Jagt, E.J.; Kobold, A.C.M.; Wolffenbuttel, B.H.R.; Land, J.A.; Annemieke Hoek, A. (2011). In women with polycystic ovary syndrome and obesity, loss of intra-abdominal fat is associated with resumption of ovulation. *Human Reproduction.*, **26**(9), 2505–2512.

- Kumar, A.N.; Naidu, J.N.; Satyanarayana, U.; Ramalingam, K.; Anitha, M. (2016). Metabolic and endocrine characteristics of Indian women with polycystic ovary syndrome. *Int. J. Fertil. Steril.*, **10**(1), 22–28.
- Lal, R.Z.; Biyani, S.; Lodha, R. (2016). Correlation of thyroid hormones with FSH, LH and prolactin in infertility in their productive age group women. *Int. Arch. Integrated Med.*, **3**(5), 146-150.
- Ramanand, S.H.; Ghongane, B.B.; Ramanand, J.B.; Patwardhan, M.H.; Patwardhan, V.M.; Ghanghas, R.; Halasawadek, N.R. (2012). Hormonal profile of polycystic ovary syndrome (PCOS) in Indian women. *Research J. Pharmaceutical, Biol. and Chem. Sci.*, **3**(4), 1159-1173.
- Rojas, J.; Chávez, M.; Olivar, L.; Rojas, M.; Morillo, J.; Mejías, J.; Calvo, M.; Bermúdez, V. (2014). Polycystic ovary syndrome, insulin resistance and obesity: Navigating the pathophysiologic labyrinth. *Int. J. Reproductive Med.*, 2014: 1-19. DOI: 10.1155/2014/719050.
- Seth, B.; Arora, S.; Singh, R. (2013). Association of obesity with hormonal imbalance in infertility: A cross-sectional study in north Indian women. *Indian J. Clin. Biochem.*, **28**(4), 342–347.
- Shoaib, O.M.; Mustafa, S.M.; Nourein, I.H. (2015). Serum lipid profile of polycystic ovary syndrome in Sudanese women. *Int. J. Med. Sci. and Public Health.*, **4**(11), 1605-1611. DOI:10.5455/ijmsph.2015.19042015331.
- Singla, R.; Gupta, Y.; Khemani, M.; Aggarwal, S. (2015). Thyroid disorders and polycystic ovary syndrome: An emerging relationship. *Indian J. Endocrinol. and Metabol.*, **19**(1), 25-30.
- Suskic, A.; Suskic, S.H.; Opric, D.; Maksimovic, S. (2016). Obesity as a significant risk factor for endometrial cancer. *Int. J. Reprod. Contracept. Obstet. Gynecol.*, **5**(9), 2949-2951.
- Swetha, R.; Ravi, B.V.; Nalini, K.S. (2015). Serum lipoprotein (a) and lipid profile in polycystic ovarian syndrome. *J. Clin. Sci. Res.*, **4**, 2-6. DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.14.007>.
- Valderhaug, T.G.; Hertel, J.K.; Nordstrand, N.; Dale, P.O.; Hofso, D.; Hjelmæsæth, J. (2015). The association between hyperandrogenemia and the metabolic syndrome in morbidly obese women. *Diabetol. Metabolic Syndrome.*, **7**, 46-56.
- Wilkes, S.; Murdoch, A. (2009). Obesity and female fertility: a primary care perspective. *J. Fam. Plann. Reprod. Health Care.*, **35**(3), 181–185.
- Yu, Q.; Wang, J.B. (2016). Sub clinical hypothyroidism in PCOS: Impact on Presentation, Insulin Resistance, and Cardiovascular Risk. *Bio. Med. Research Int.*, **2016**, 1-7.