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Evaluation of *in vitro* Fertilization Planned Patients in terms of Internist Perspective

ORIGINAL INVESTIGATION

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ABSTRACT

Objective: Infertility is defined as the inability to become pregnant after a year of unprotected intercourse and is a growing problem worldwide, with an incidence of 15% among couples. In our study, women with a diagnosis of infertility and who were scheduled for *in vitro* fertilization (IVF) were assessed for medical problems that may be the cause of their infertility. Thus, this study aimed to determine whether the report by the Board of Health, which is mandatory in some institutions, is beneficial in terms of internal medicine in patients scheduled for IVF.

Materials and Methods: The study group included 120 women scheduled for IVF and consulted the Department of Internal Medicine as well as 35 control women in a similar age group. Their medical history, drug use, and smoking status were recorded. Blood pressure, body height, and body weight were measured. Biochemical measurements including complete blood count and fasting blood glucose, creatinine, liver enzyme, fasting insulin, and thyroid stimulating hormone (TSH) levels were performed.

Results: Smoking was found to increase infertility risk by 2.63-fold. There was a significant difference in body mass index between the patient and control groups (p=0.045).

Conclusion: Assisted reproductive techniques, particularly IVF, are widely used in many public and private health institutions for couples who are admitted to reproductive health units with infertility. In our study, body weight and body mass index were found to affect infertility. We believe that early recognition and improvement of modifiable factors may improve pregnancy outcomes.

Keywords: Infertility, reproductive techniques, assisted, internal medicine

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INTRODUCTION

An intact hypothalamic-pituitary-gonadal axis is needed to maintain a normal and healthy reproductive life. Impairment in the function of this axis results in reproductive dysfunction (1). Obesity is usually associated with anovulation and hence plays a role in female infertility. Abdominal obesity and insulin resistance are specific underlying factors for metabolic syndrome and impair the quality of oocytes (2). Increased body mass index (BMI) results in anovulatory cycles, as well as abortion, stillbirth, and increased congenital abnormality risk, during pregnancy (3). Obesity may also result in decreased anti-Müllerian hormone (AMH) secretion and thus decreased ovarian reserve (4, 5).

Several previous studies have reported a significant association between AMH and infertility in obese and normal weight individuals (4, 6-9). Additionally, in women scheduled for assisted reproductive techniques, obesity increases gonadotropin deficiency and decreases fertilization rate. However, obesity also predisposes individuals to many complex metabolic disorders, including insulin resistance, diabetes, hypertension, metabolic syndrome, and hyperlipidemia. Moreover, several endocrine disorders, particularly Cushing's syndrome, are associated with obesity.

In recent years, thyroid dysfunction and autoantibody positivity were also suggested to be other metabolic factors associated with female infertility. The American Thyroid Association and Association of Turkish Endocrinology and Metabolism recommended that TSH levels should be ≤2.5 mIU/L before pregnancy (10, 11). This cutoff was also established as the target level before the performance of assisted reproductive techniques (12). Infertility, impaired ovulation, pregnancy loss, and late-term pregnancy complications may occur in cases of overt hypothyroidism (13). However, organ-specific autoantibodies (presence of circulating anti-thyroid antibodies) may decrease spontaneous pregnancy rates and the success of assisted reproductive techniques and increase the rate of pregnancy-related complications (14, 15).

In light of all these data, we believe that a multi-directional evaluation is needed for female fertility, and we conducted this study on women with infertility scheduled for in vitro fertilization (IVF) and were referred to the Department of Internal Medicine by the Board of Health. These women were evaluated in terms of anthropometric, clinical, and hormonal parameters that can affect female infertility to determine the major physical examination and laboratory findings that should be included in the report to the Board of Health.

MATERIALS and METHODS

A total of 120 women examined by the Department of Obstetrics and Gynecology at Eskişehir Osmangazi University between July 2014 and January 2015 who were scheduled for IVF and had been referred to the Department of Internal Medicine by the Board of Health were included in the study. The control group included 35 women with at least one healthy birth from a similar age group. We excluded male infertility and women with polycystic ovarian syndrome. Informed consent was obtained from all patients, and the study was approved by the appropriate Institutional Review Board (number: 80558721/238). Medical history, family history, medications, smoking status, and years of marriage were recorded. Body weight and height, BMI, arterial blood pressure, fasting blood glucose level, fasting insulin level, creatinine level, alanine aminotransferase level, aspartate transaminase level, TSH level, complete blood count, and complete urinalysis were measured. Homeostatic model assessment of Insulin Resistance (IR) (HOMA-IR) was used to assess insulin resistance and was calculated using the following formula: fasting blood glucose level × fasting insulin level/405. Patients with a HOMA of ≥2.7 were considered to have insulin resistance. Patients were classified according to their BMI as normal (BMI=20-24.9 kg/m^2), overweight (BMI=25-30 kg/m^2), and obese (BMI≥30 kg/m^2). TSH levels were divided into three categories: ≥2.5 mIU/L, 2.5-4 mIU/L and TSH >4

Statistical Analysis

Continuous data are expressed as mean±standard deviation and categorical data as percentages (%). The Shapiro-Wilk's test was performed to assess the normality of the data. Independent sample t-test analysis was performed for the comparison of two groups with a normal distribution. The Mann-Whitney U test was performed for the comparison of two groups without a normal distribution. The Pearson chi-square and Pearson exact chi-square tests were performed to analyze the cross-tables. Data were evaluated using the Statistical Packages for the Social Sciences (SPSS) version 21.0 (IBM Corp.; Armonk, NY, USA). Statistical significance was set at p<0.05.

RESULTS

The mean ages were 29.25±4.133 and 31.77±4.911 years in the patient and control groups, respectively. The mean age, weight, height, HOMA, and BMI of the patients and controls are presented in Table 1. There were 24 patients with a BMI of ≥30 and 39 patients with a BMI of ≤30 and ≥25 (Table 2). Infertility risk was found to increase with increasing BMI (=6.199; p=0.045). No significant difference was found in HOMA insulin resistance between the patient and control groups =1.930; p=0.165). There were 37 smokers in the patient group, and smoking was found to increase infertility risk by 2.63-fold (%95 Confidience interval(CI) 0.94-7.35). Similarly, TSH levels were not significantly different between the patient and control groups (Table 3) (p=0.365). In the patient group, there were no significant differences in HOMA-IR and BMI between patients with an AMH level of <1.1ng/mL and ≥1.1ng/mL (p=0.425, p=0.280, respectively) (Table 4).

Table 1. Mean age, body height and weight, HOMA-IR, BMI and TSH inpatients and controls

	Patient group n=120 (Mean±SD)	Control group n=35 (Mean±SD)	p
Age	29.25±4.133	31.77±4.911	0.003
HOMA-IR	2.33±1.91	1.74±0.74	0.076
BMI	25.87±4.86	23.64±3.19	0.012
TSH	2.20±1.30	1.99±0.98	0.378

HOMA-IR: homeostatic model assessment of insulin resistance; BMI: Increased Body Mass Index; TSH: thyroid stimulating hormone

Table 2. Distribution of patients and controls by BMI

BMI	Patient group (n=120)	Control group (n=35)	p
20-24.9	57	20	5.890
25-29.9	39	14	0.053
30+	24	1	

BMI: Increased Body Mass Index

Table 3. Distribution of patients and controls by TSH levels

TSH	Patient group (n=120)	Control group (n=35)	p
2.5≤	75	25	2.015
2.5< ≥4.0	33	9	0.365
≥4.0	12	1	

TSH: thyroid stimulating hormone

Table 4. The HOMA- IR and BMI in the patient group by AMH levels

	Patientgroup (n=120)		
	AMH≤1.1ng/mL Mean±SD Median (Q1-Q3)	AMH>1.1ng/mL Mean±SD Median (Q1-Q3)	p*
HOMA-IR	0.67±0.35 1.94 (1.46-2.63)	2.98±1.89 1.80 (1.44-2.42)	0.425
BMI	2.73±2.60 24.99 (22.19-28.05)	1.98±0.88 26.00 (22.76-29.78)	0.280

HOMA-IR: homeostatic model assessment of insulin Resistance; BMI: Increased Body Mass Index; AMH: anti-Mullerian hormone
SD: standart deviation
*Mann Whitney U Test

DISCUSSION

In our study, the couples admitted to the infertility outpatient clinic and who were scheduled for IVF were evaluated in terms of internal medicinal problems that can affect female fertility. Infertility has become a major health problem in the last century due to increased marriage and birth age, as well as environmental factors, lifestyle, and stress-related diseases. In particular, sedentary lifestyle, high-calorie diets, and stress have emerged in a generation experiencing menstrual problems due to being overweight. There is a complex relationship among obesity, metabolic syndrome, insulin resistance, and the reproductive axis. Being overweight or obese, which results in a high BMI, may negatively affect male and female fertility. The adverse effects of insulin resistance associated with obesity on female fertility have been supported by many previous studies in the literature. Abdominal obesity is associated with increased circulation and increased ovarian androgen production. Therefore, hyperandrogenemia results in granulosa cell apoptosis and gonadotropin secretion in women (16). In addition, hyperinsulinism and insulin resistance have been shown to impair the quality of oocytes and embryos and are associated with a decreased pregnancy rate (17-19). In particular, hyperinsulinism causes pregnancy losses due to mitochondrial dysfunction and structural and genetic damage in oocytes (20). Therefore, we evaluated the patients in our study group in terms of insulin resistance and found no significant difference between the patient and control groups. Hyperinsulinemic-euglycemic glucose clamp is the gold standard for measuring IR (21). However, because it is not practical to use, we used HOMA-IR to indirectly assess insulin resistance with a single measurement. It has been reported that high-dose gonadotropin is needed; the response to ovarian stimulation is inadequate; the embryo quality is low; and the pregnancy rate is low not only in infertile couples but also in couples who are scheduled for assisted reproductive techniques (1, 8). In their study, Zhang et al. divided conventional IVF patients into three groups according to their BMI and found statistically higher total oocyte counts in metaphase II in obese patients than in patients with normal weight (22) (p=0.005, p=0.02, respectively). In our study, outcomes were significantly worse in patients with a high BMI than in healthy fertile individuals, suggesting that obesity plays a role in infertility (p=0.045). Because of associated metabolic disorders, obesity is important in the etiology of infertility. Therefore, we believe that infertile women with a BMI of ≥25 should be evaluated by an internal medicine specialist for the risk of obesity-associated metabolic disorders. Similar to previous studies investigating the relationship between obesity and infertility and those mainly focusing on AMH and inhibin B levels, we also measured AMH levels in infertile patients (23). BMI and HOMA insulin resistance did not differ significantly between patients with AMH levels above and below 1.1 ng/mL (p=0.425, p=0.280). In the literature, there are many studies investigating the relationship among AMH, obesity, and HOMA-IR. Although we found no significant difference in terms of this issue in the present study, numerous studies have suggested a statistically significant association among AMH, hormonal normality and BMI, insulin resistance, and ovarian reserve (24-26).

The adverse effects of obesity on infertility are clear. Obesity itself may cause infertility and pregnancy complications in overweight individuals. However, obesity is at the center of a disease series known as metabolic syndrome, which includes several metabolic diseases, such as insulin resistance, dyslipidemia, and hypertension. We suggest that it may be beneficial to evaluate patients according to their BMI initially and then evaluate the high-risk group of patients in terms of insulin resistance and other metabolic syndrome parameters.

However, infertile couples also often experience social problems. Because the family structure in Turkish culture necessitates having a child, infertility induces social stress and deficiencies in body image and results in problems in family and work life. In a study by Alvarez et al. on dependency and infertility, environmental factors, lifestyles, and habits that were considered to affect fertility in the last 10 years were evaluated. In particular, these studies suggested that stress management and prevention of toxic exposure, including smoking, are key factors affecting fertility (27). The toxic metabolites of cigarettes, including cotinine, cadmium, and hydrogen peroxide, alter the composition of follicle fluid and cause oocyte toxicity and apoptosis, resulting in ovarian failure (28). In parallel with the literature, smoking was found to increase infertility risk by 2.63-fold in patients compared with controls in the present study. In a study by Freour et al. (29), smoking was also found to increase infertility risk by 2-fold and decrease ovarian reserve by decreasing AMH levels. In the patient group, AMH levels were found to be significantly higher in non-smokers than in smokers (p=0.035). Thus, smoking cessation should be recommended by all medical experts, and information about the negative effects of smoking on both male and female fertility should be provided to all infertile couples.

In addition to obesity and insulin resistance, another important modifiable medical problem is thyroid disease. Thyroid disease includes (sub) hypo-(sub) hyperthyroidism as well as autoimmune thyroiditis. Available data suggest that overt hypothyroidism is associated with infertility and ovulation, fertilization and implantation problems, and pregnancy complications (30). However, the relationship among hyperthyroidism, subclinical hypo-/hyperthyroidism, and autoimmune thyroiditis with infertility has also been argued. Thyroid hormones directly affect the reproductive organs and are also the main mediator of sex hormone binding globulin (31). Moreover, thyroid autoantibodies have been suggested to be associated with polycystic ovarian syndrome, endometriosis, and tubal problems (32, 33). Thus, thyroid hormones should be evaluated in couples planning a pregnancy, and the recommended upper limit for TSH is 2.5 (34).

In the present study, TSH levels measured before IVF (TSH<or ≥2.5) were not different between the patient and control groups (p=0.365). We believe that the present results should be evaluated in a larger scale study measuring thyroid autoantibodies in addition to TSH levels. However, within the context of the main focus of the present study, we suggest that TSH alone may be sufficient initially in evaluating thyroid function for the report to the Board of Health and that thyroid autoantibody measurements should be performed in infertile patients with an individual or family history of autoimmune disease.

In contrast to the above suggestions, a recent guideline of the American Society for Reproductive Medicine reports that evidence is lacking on the association of infertility with subclinical hypothy-

roidism cases with a TSH level of ≥2.5. However, levothyroxine treatment has been suggested to improve pregnancy rate and decrease abortion rate in subclinical hypothyroidism cases with TSH level of ≥4 (35). Although thyroid autoantibodies are not recommended for routine measurement, they should be measured in patients with repeated measurements of TSH level of ≥2.5 or in patients with suspected thyroid disease and predefined risk factors. These predefined risk factors include being over the age of 30; the presence of a family history of autoimmune thyroid disease or hypothyroidism, goiter, clinical findings suggestive of thyroid dysfunction, other autoimmune disorders, history of radiotherapy to the neck region, and history of infertility; living in geographical areas where iodine deficiency is endemic (35). We believe that both at the time of pregnancy planning or evaluation for infertility, cutoff values for TSH can be questioned in the future.

CONCLUSION

In the present preliminary study evaluating potential infertility-related internal medicine factors, the importance of weight control has gained increasing attention. Moreover, infertility should be considered a social problem, keeping in mind the importance of psychosocial care. Although larger studies are needed to confirm these findings, we believe that the report of the Board of Health is a major step in the evaluation of metabolic statuses of patients and that obtaining individual and family histories for each patient, as well as the results of biochemical measurements, will positively affect the outcome of IVF.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskişehir Osmangazi University Institutional Review Board (number: 80558721/238).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Conceived and designed the experiments or case: PY., YA., HH. Performed the experiments or case: PY. Analyzed the data: MB., PY. Wrote the paper: PY. All authors have read and approved the final manuscript.

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