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EDITORIAL

Dear Colleagues,

We are pleased to present the first issue of 2024. This esteemed scientific publication, continues to gain recognition in the national scientific community, with its increasing scientific value and growing prestige on national platforms. One noteworthy indicator of our journal's success is the rising number of authors seeking publication on our pages, particularly evident in the increased volume of articles, especially those received from abroad and accepted for publication in our latest issue.

Despite the great pain experienced by our nation in 2023, I express the hope that 2024 will usher in a year of love, peace, happiness, and tranquility for our country, and I extend my respect to all my colleagues.

Looking ahead to 2024, we are committed to continuing our efforts and striving to elevate our scientific publication, a national treasure, to the esteemed position it deserves.

Cordially Yours…

Prof. Oya GÖKMEN, MD
Honorary Editor in Chief

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ORIGINAL ARTICLES

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Original Article

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Investigation of the correlation of prognostic parameters in cases of endometrium carcinoma

Nurgül Ulusoy[1], Ahmet Gülkılık[2]

[1]Private Gynecology and Obstetric Clinic, İstanbul, Turkiye
[2]Specialist, Retired, İstanbul, Turkiye

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Corresponding Author: Nurgül Ulusoy, nculusoy17@gmail.com

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ABSTRACT

Aims: Endometrial carcinoma is the most common gynecological cancer in developed countries and the second most common in Turkiye. Due to its significant impact on survival rates, recurrence rates, as well as treatment and post-treatment approaches, identifying and studying prognostic factors is of great importance. This article aims to review the prognostic parameters established for endometrial carcinoma and investigate the studies and findings related to these parameters.

Methods: The study included 50 patients who underwent surgery for endometrial carcinoma at our clinic between January 1999 and May 2001. Investigations and results related to prognostic factors in endometrial carcinoma were examined in these patients.

Results: The average age of the patients was found to be 56.72±8.02 years. %70 of the patients were in Stage 1, 6% were in Stage 2, 22% were in Stage 3, and the remaining 2% were in Stage 4. Peritoneal cytology was positive in 5 out of 41 patients in whom peritoneal cytology was examined (12.2%). Among the 49 patients evaluated for myometrial invasion, 11 had tumor confined to the endometrium without myometrial invasion. In 16 patients, there was 1/3 inner myometrial invasion, 15 patients had 1/3 middle myometrial invasion, and 7 patients had 1/3 outer myometrial invasion. When we compared grade and depth of myometrial invasion in the cases examined, it was observed that out of 17 patients with Grade 1 tumors, 1 had deep myometrial invasion (½ outside), while out of 22 patients with Grade 2 tumors, 8 had deep myometrial invasion, and out of 4 patients with Grade 3 tumors, 3 had deep myometrial invasion.

Conclusion: The results of the examination of prognostic parameters, including age, histological grade, myometrial invasion, peritoneal cytology, histological type, adnexal spread, and tumor size, in the studied patient group were consistent with previous research in this field.

Keywords: Endometrial carcinoma, age, prognosis, cancer, prognostic parameters

INTRODUCTION

Endometrial carcinoma is the most common malignancy of the female genital system in developed countries, constituting approximately 4% of all carcinomas worldwide.[1] In Turkiye, the age-standardized rate of uterine corpus tumors is reported to be 10.5 per 100,000 women.[2] The incidence of endometrial carcinoma has increased over the years due to factors such as the prevalence of obesity, extended lifespan, and the widespread use of hormonal therapies like Tamoxifen in the treatment of breast cancer. The most common histopathological type is endometrioid carcinoma (EC), which accounts for 70-80% of the 288,000 uterine corpus cancers newly diagnosed worldwide in 2008.[1,3]

According to the classification of the World Health Organization (WHO), endometrial tumors encompass seven histological types: serous carcinoma, clear cell carcinoma, mucinous carcinoma, neuroendocrine tumor, mixed carcinoma, undifferentiated carcinoma, and dedifferentiated carcinoma.[1] In endometrial carcinoma, stage, histological type, grade, depth of myometrial invasion, presence of lymphovascular invasion, and the patient's age are the most significant prognostic factors.[4] According to the International Federation of Gynecology and Obstetrics (FIGO) grading system, there are three histological grades of EC determined by the percentage of solid growth of tumor cells and the level of cytological atypia in the nuclei of tumor cells. Grades I and II ECs have a better clinical course, whereas Grade III ECs have a poorer prognosis and are considered part of the "high-grade" carcinoma group, along with serous and clear cell carcinomas.[1] Undifferentiated carcinoma represents endometrial carcinoma with no differentiation, while dedifferentiated carcinoma consists of tumors composed of

components of undifferentiated carcinoma and low-grade (Grade I and II) endometrioid carcinoma. Both of these are high-grade and aggressive tumors. Neuroendocrine tumors of the endometrium are quite rare and are classified into low-grade neuroendocrine tumors and high-grade neuroendocrine carcinoma (small cell and large cell).[1]

Prognostic factors defined for endometrial carcinoma can be listed as follows: age, histological type, histological grade, myometrial invasion, peritoneal cytology, adnexal spread, intraperitoneal disease, lymphovascular space invasion (LVSI), cervical invasion, tumor size, steroid receptors, oncogenes, DNA ploidy, and molecular markers.

The purpose of this study is to retrospectively assess the correlation between surgical staging, histological grade, lymphatic involvement, peritoneal cytology, tumor histology, and tumor size in cases of endometrial carcinoma diagnosed and treated in our clinic.

METHODS

This study is a scientific investigation based on Nurgül Ulusoy master's thesis titled "Investigation of the Correlation of Prognostic Parameters in Cases of Endometrial Carcinoma," registered with the number 103431 at the National Thesis Center in 2001. All procedures conducted in this study were in accordance with ethical guidelines and the principles outlined in the Declaration of Helsinki.

A total of 50 patients diagnosed with Endometrial Carcinoma and treated at Bakırköy Women and Children's Diseases Training and Research Hospital Gynecologic Oncology Service between January 1, 1999, and May 28, 2001, were retrospectively examined. In this study, parameters related to prognostic factors of endometrial carcinoma, such as age, histological grade, myometrial invasion, peritoneal cytology, histological type, adnexal spread, and tumor size, were investigated. Parameters for which information could not be obtained, such as steroid receptors, oncogenes, DNA ploidy, and molecular markers, were excluded from the study.

Parameters known to be indicators of poor prognosis, such as the surgical stage of the disease, histological grade of the tumor, adnexal spread, myometrial invasion, and histological types of the tumor, were investigated in the advanced age group of patients. The most critical prognostic factors, including histological grade, depth of myometrial invasion, and lymph node involvement rates, were also compared. The predictive value of peritoneal cytology positivity for factors like increased histological grade, depth of myometrial invasion, and lymph node metastasis was evaluated in relation to these parameters and compared with patients with negative peritoneal cytology. The tumor histologies observed in both patient groups were examined. The relationship between tumor size, which is a known independent prognostic factor, and lymph node positivity rates and depth of myometrial invasion were also examined.

Endometrial Carcinoma cases were evaluated in terms of prognostic significance, particularly with respect to age, surgical stage, histological grade, myometrial invasion, peritoneal cytology, lymphatic involvement, tumor histology, adnexal spread, and tumor size.

For staging the patients, the surgical staging system recommended by FIGO in 1988 was used instead of clinical staging. In the assessment of myometrial invasion, following the 1988 FIGO staging, it was categorized as ½ inner and ½ outer myometrial invasion. However, since many sources consider myometrial invasion depth as 1/3 inner, 1/3 middle, and 1/3 outer myometrial invasion, both approaches were noted in our study.

Tumor size, which has been reported as an independent prognostic factor, was evaluated in this study by considering the largest dimension of the tumor in cases where three dimensions of the tumor were provided, and by taking the tumor size indicated in other cases into account.

Statistical Analysis

As this research is descriptive in nature, numerical values were expressed as mean and standard deviation, while categorical data were presented as percentages.

RESULTS

The average age of the patients was found to be 56.72±8.02. Similar to the 21st FIGO Annual Report, if we consider patients with Grade 1-Stage 1 and Grade 3-Stage 3, 4, and report their average ages, the average age of Grade 1-Stage 1 patients was 50.93±5.25, while the average age of Grade 3-Stage 3, 4 patients was 63.00±2.82.

According to the FIGO 1988 surgical staging system, 70% of the patients were in Stage 1, 6% in Stage 2, 22% in Stage 3, and the remaining 2% were in Stage 4. There were no patients diagnosed with Stage 2a due to the absence of histopathological diagnosis of "endocervical glandular involvement." In terms of histopathological differentiation grades, it was observed that 17 patients were Grade 1, 22 patients were Grade 2, and 5 patients were Grade 3. There was no information available on grading for 6 patients.

Among the 49 patients evaluated for myometrial invasion, 11 had tumors limited to the endometrium with no myometrial invasion. In 16 patients, there was 1/3 inner myometrial invasion, in 15 patients, there was 1/3 middle myometrial invasion, and in 7 patients, there was 1/3 outer myometrial invasion. Among the 49 patients, 25 had myometrial invasion in the first half of the myometrium, while 13 had invasion in more than half of the myometrium.

Peritoneal cytology was examined in all stages, and 5 out of 41 patients had positive peritoneal cytology (12.2%).

Out of the 50 patients operated on for endometrial carcinoma, 45 underwent pelvic lymph node dissection, and 13 underwent pelvic-paraaortic lymph node dissection. Among patients who had pelvic lymph node dissection, 9 (20%) were positive for lymph node involvement in all stages, while among those who had paraaortic lymph node dissection, 1 (7.7%) was positive in all stages.

The examination revealed that the majority of the 50 patients had "endometrial adenocarcinoma." **Table 1** provides the histological types of tumors.

Table 1. Histological types of tumor

Tumor Histology	Number of patients	(%)
Endometrial Adenocarcinoma	42	84
Papiller Adenocarcinoma	6	12
Adenosquamous Carcinoma	1	2
Clear Cell Carcinoma	1	2

Adenoacanthoma, Mucinous Carcinoma, Mixed Type, and Other Undifferentiated Carcinoma diagnoses were not encountered.

Among the cases of endometrial carcinoma, among a total of 50 patients in all stages, adnexal spread was present in 3 of them. Out of these 3 patients with adnexal spread, peritoneal cytology was examined in 2, and it was found to be negative.

After examining the 50 patients, it was reported that in 4 of them, endometrial curettage was performed, and the entire tumor was removed with no residual tumor. Among the remaining patients, 16 had tumors smaller than 2 cm, 18 had tumors larger than 2 cm, and 6 had tumors that covered the entire endometrial cavity. Information regarding the tumor size of 6 patients could not be obtained.

In 16 of the 50 patients with endometrial carcinoma, the region from which the carcinoma originated was reported. In most of these patients (13 of them), the carcinoma was found to originate from the fundus. In 1 patient, the tumor originated from the anterior wall, in 1 patient from the posterior wall, and in 1 patient, it was near the endocervical canal.

As is known, numerous prognostic factors have been identified, and the presence or degree of some of them (such as myometrial invasion, lymphatic involvement, peritoneal cytology) increases with the presence of others (such as grade, tumor size, tumor histology). Therefore, it would be appropriate to present the information we have obtained together and comparatively.

With advancing age, an increase in the stage and grade of the disease is significant. As seen in **Tables 2** and **3**, the stage and grade at the time of diagnosis appear to increase with age.

Table 2. Age-stage relationship

	40-49 age	50-59 age	60-69 age	70 age
Number of patients	9	22	15	4
Stage 1	8 (88.9%)	18 (82.0%)	8 (53.3%)	1 (25%)
Stage 2	1 (11.1%)	1 (4.5%)	0	1 (25%)
Stage 3	0	3 (13.5%)	6 (40%)	2 (50%)
Stage 4	0	0	1 (6.7%)	0

Table 3. Age-grade relationship

	40-49 age	50-59 age	60-69 age	70 age
Number of patients	8	19	14	3
Grade 1	6 (75%)	9 (47.4%)	1 (7.1 %)	1 (33%)
Grade 2	2 (25%)	8 (42.1%)	11 (78.7%)	1 (33%)
Grade 3	0	2 (10.5%)	2 (14.2%)	1 (33%)

It is known that prognosis worsens in advanced age, and survival rates significantly decrease. This decline is in conjunction with extrauterine disease and an increase in the depth of myometrial invasion.

With advancing age, the increased risk of recurrence is reported to be associated with a higher tumor grade and a more frequent occurrence of poor histological types.

One of the most important prognostic factors of endometrial carcinoma, "grade", increasing is also associated with an increase in the depth of myometrial invasion and lymph node involvement.

In the cases we examined, we compared grade and the depth of myometrial invasion. Among the 17 patients with Grade 1 tumors, 1 had deep myometrial invasion (½ outer), while among the 22 patients with Grade 2 tumors, 8 had it, and among the 4 patients with Grade 3 tumors, 3 had deep myometrial invasion. **Tables 4** and **5** provide the depth of myometrial invasion in ½ and 1/3 slices.

Table 4. Grade-myometrial invasion relationship

Grade	Myometrial Invasion				
	n	Absent	1/3 inner	1/3 medium	1/3 outer
Grade 1	17	8 (47%)	7 (41%)	2 (12%)	0
Grade 2	22	1 (4.5%)	7 (31.8%)	9 (41%)	5 (22.7%)
Grade 3	4	0	1 (25%)	1 (25%)	2 (50%)

Table 5. Grade-myometrial invasion relationship

Grade	Myometrial invasion			
	n	Absent	½ inner	½ outer
Grade 1	17	8 (47%)	8 (47%)	1 (6%)
Grade 2	22	1 (4.5%)	13 (59.1%)	8 (36.4%)
Grade 3	4	0	1 (25%)	3 (75%)

Out of the 17 patients with Grade 1 tumors, lymph node dissection was performed in 16 of them, and 1 of these patients had a positive lymph node. Among the 22 patients with Grade 2 tumors, lymph node dissection was performed in 20 of them, resulting in 4 patients with positive lymph nodes. Among the 5 patients with Grade 3 tumors, lymph node dissection was performed in 4 of them, and 2 patients had positive lymph nodes.

When patients with lymph node involvement were separated based on pelvic and paraaortic lymph node positivity, the results in **Table 6** were obtained:

Table 6. Relationship between histological grade and lymph node involvement

Grade	Lymph Node Involvement			
	n	Pelvic	n	Paraaortic
Grade 1	16	1 (6.25%)	6	0
Grade 2	20	4 (20%)	4	1 (25%)
Grade 3	4	2 (50%)	1	0

Obtaining information about the rate of paraaortic lymph node positivity in cases with pelvic lymph node positivity has not been possible due to the limited number of cases where both pelvic and paraaortic lymph node dissection were performed.

Myometrial invasion, which is a measure of tumor virulence, is the most reliable indicator of tumor volume. Increased myometrial invasion is also associated with an increase in extrauterine spread and lymph node metastasis.

Out of the 50 patients with endometrial carcinoma examined, 11 had no myometrial invasion and were limited to the endometrium; none of them had adnexal spread. Among the 25 patients with ½ inner myometrial invasion, only 1 had adnexal spread, while among the 13 patients with a depth of myometrial invasion of more than ½, 2 had adnexal spread.

In terms of lymph node involvement rates, out of the 11 patients with no myometrial invasion, 10 underwent lymph node dissection, and 1 of them had lymph node involvement.

It is known that the presence of positive peritoneal cytology in patients with endometrial carcinoma is predictive for factors such as increased grade, depth of myometrial invasion, and lymph node involvement, and other poor prognostic indicators are often found in conjunction with positive peritoneal cytology. In the 50 patients with endometrial carcinoma, it was reported that peritoneal fluid sampling was positive in 5 patients in all stages. Among the 5 patients with positive peritoneal cytology who had pelvic lymph node examination, 3 of them had positive pelvic lymph nodes. In the same group of patients, paraaortic lymph nodes were examined in 3 cases, and 2 of them were positive.

In patients with positive peritoneal cytology, the presence of lymphatic involvement and other poor prognostic indicators were examined, and the results are provided in **Table 7**.

Table 7. Relationship of poor prognostic factors in peritoneal cytology positive patients

Presence of deep myometrial invasion:			
Absent invasion:	0	Absent invasion:	0
1/3 inner invasion:	1	½ inner invasion:	2
1/3 medium invasion:	2	½ outer invasion:	3
1/3 outer invasion:	2		
Grade 3 tumor rate: (Grade was not checked in 1 patient)			
Grade 1 tumor:	0		
Grade 2 tumor:	3		
Grade 3 tumor:	1		
Pelvic lymph node positivity:	3/5		
Paraartic lymph node positivity:	1/3 (Not examined in 2 patients)		
Adnexal spread:	0		

In patients with negative peritoneal cytology, the presence of lymphatic involvement along with other poor prognostic indicators was examined, and the results are provided in **Table 8**.

Table 8. Relationship of poor prognostic factors in peritoneal cytology-negative patients

Presence of deep myometrial invasion:			
Absent invasion:	9 (26%)	Absent invasion:	9 (26%)
1/3 inner invasion	11 (31%)	½ inner invasion:	17 (48.5%)
1/3 medium invasion:	10 (29%)	½ outer invasion:	9 (25.5%)
1/3 outer invasion:	5 (14%)		
Grade 3 tumor rate: (Grade was not checked in 1 patient)			
Grade 1 tumor:	13 (38%)		
Grade 2 tumor:	18 (53%)		
Grade 3 tumor:	3 (9%)		
Pelvic lymph node positivity:		5/34 (14.7%)	
Paraartic lymph node positivity:		0 (Not examined in 8 patients)	
Adnexal spread:		2/36	(5.5%)

Prognostic Factors	Peritoneal Cytology			
	n	Negative	n	Po
Grade 3 tumor rate	34	3 (9%)	4	1 (25%)
Pelvic lymph node metastasis	34	5 (14.7%)	5	3 (60%)
Paraaortic lymph node metastasis	8	0	3	1 (33%)
Adnexal spread	36	2 (5.5%)	5	0
Deep myometrium invasion rate:				
>2/3 invasion	35	5 (14%)	5	2 (40%)
>1/2 invasion	35	9 (25.5%)	5	3 (60%)

When examining the tumor histologies encountered in patients with negative and positive peritoneal cytology, it was observed that the majority of histological types other than "endometrial adenocarcinoma" were present in the group of patients with positive peritoneal cytology.

Tumor size significantly affects lymph node involvement, myometrial invasion, and, consequently, survival rates in endometrial carcinoma. Among the 16 patients with a tumor diameter of less than 2 cm, none had pelvic lymph node metastasis. Among the 18 patients with a tumor diameter of more than 2 cm, 4 had positive pelvic lymph nodes. Among the 6 patients with the tumor involving the entire endometrial lining, 3 had pelvic lymph node metastasis.

Among the 16 patients with a tumor diameter of less than 2 cm, 3 had tumors limited to the endometrium. In these patients, 11 had invasion within the first ½ of the myometrium, and only 2 had invasion of more than ½. Among the 18 patients with a tumor diameter of more than 2 cm, 3 had tumors limited to the endometrium, 10 had invasion within the first ½ of the myometrium, and 5 had invasion of more than ½ of the myometrium. Among the 6 patients with the tumor involving the entire endometrial cavity, none had limited tumor in the endometrium, while 1 had invasion within the first ½ of myometrial invasion, and 5 had invasion of more than ½.

Among the 11 patients with a tumor diameter of less than 2 cm and myometrial invasion within the first ½, none had lymph node metastasis.

DISCUSSION

It appears that the stage and grade of endometrial carcinoma increase with age. According to the 21st FIGO Annual Report, the average age of patients using surgical staging is reported to be 60.4 for Grade 1-Stage 1 and 64.2 for Grade 3-Stage 4.[5] In our study, when the surgical stage of the disease was examined with advancing age, it was observed that patients in the older age group were in advanced stages.

The grade of the disease increases with age.[5] Increased risk of recurrence in older women is associated with the frequency of Grade 3 tumors. When patients in the older age group were examined for the histological grade of the tumor, Grade 3 tumors were not found in patients aged 40-49, whereas the rate of Grade 3 tumors was 10.5% in the 50-59 age group. In patients aged 60 and above, this rate increased to 18%.[6-8]

Survival rates decrease with increasing age in women with endometrial carcinoma, and this decrease is associated

with an increase in extrauterine disease and deep myometrial invasion.[8] In our study, among 50 cases of endometrial carcinoma, adnexal spread was detected in 3 cases. When these 3 patients were evaluated according to age groups, it was observed that there was no adnexal spread in patients aged 40-49 while in the 50-59 age group, the rate of adnexal spread was 4.5%. In patients aged 60 and above, this rate increased to 10.5%. As a result, it was observed that adnexal spread rates increased with advancing age.

Myometrial invasion is one of the factors that reduce survival rates in older age groups.[8] When we looked at the relationship between age and myometrial invasion depth, it was observed that there was no deep myometrial invasion (outside 1/3) in young patients aged 40-49. In patients between the ages of 50-59, the rate of deep myometrial invasion was 5%, while in those aged 60 and above, this rate was 31.5%. Similar to disease stage, grade, and adnexal spread, the depth of myometrial invasion was also found to increase with advancing age.

Increased risk of recurrence with advancing age is associated with Grade 3 tumors and poor histological types.[9] In our study, when patients were examined for the histological grade of the tumor, it was found that there was no Grade 3 tumor in patients aged 40-49, while the rate of Grade 3 tumors in the 50-59 age group was 10.5%. In patients aged 60 and above, this rate increased to 18%.

The histological grade of the tumor is one of the most important prognostic factors in endometrial carcinoma. It is reported that with increasing grade, the depth of myometrial invasion also increases, and deep myometrial invasion is found in 50% of Grade 3 cases.[10-12] In our study, it was observed that patients with higher histological grades had higher rates of myometrial invasion.

Studies have shown that lymph node involvement increases with increasing grade.[10-12] In our study, it was observed that 6.25% (1 patient out of 16) of Grade 1-Evolution 1 patients had pelvic lymph node involvement, and this rate increased to 20% in Grade 2 patients. Among the 4 patients with Grade 3 tumors, 50% had pelvic lymph node involvement.

Increased myometrial invasion is associated with an increase in the rate of extrauterine disease in endometrial carcinoma.[13,17,18] In our study, while there was no adnexal spread in patients without myometrial invasion, adnexal spread was observed in 4% of patients with 1/2 inner myometrial invasion and 15.4% of patients with 1/2 outer myometrial invasion.

Studies confirm the relationship between myometrial invasion depth and lymph node involvement. In patients without myometrial invasion, the rate of pelvic lymph node metastasis is 1%, whereas in patients with deep myometrial invasion, this rate increases to 25%. The rate of para-aortic lymph node metastasis in patients with deep myometrial invasion is reported as 17%.[13] In our study, it was observed that lymph node involvement rates were higher in patients with deep myometrial invasion compared to those without invasion.

Positive peritoneal cytology is predictive of prognostic factors such as advanced histological grade, deep myometrial invasion, and lymph node metastasis.[14,19] In patients with positive peritoneal cytology, pelvic lymph node metastasis was found in 25% and para-aortic lymph node metastasis in 19%.[20] In our study, lymph node involvement was observed in 60% of the positive peritoneal cytology patients who underwent pelvic lymph node dissection and in 33% of those who underwent para-aortic dissection.

Among patients with negative peritoneal cytology, 34 underwent pelvic lymph node dissection, and 8 underwent para-aortic lymph node dissection. The rate of pelvic lymph node involvement in these patients was 14.7%, and there was no para-aortic lymph node involvement. It was observed that lymph node involvement rates were higher in positive peritoneal cytology patients.[14]

Patients with positive peritoneal cytology often have other poor prognosis indicators, and the rate of Grade 3 tumors in these patients is reported to be 37%. In our study, when patients with positive peritoneal cytology were examined for grade, it was found that 25% of them had Grade 3 tumors. In contrast, the rate of Grade 3 tumors in patients with negative peritoneal cytology was 9%.

Deep myometrial invasion is a poor prognostic indicator and is often found in patients with positive peritoneal cytology. It is reported that in patients with positive peritoneal cytology, this rate is 37%.[14] In our study, the rates of deep myometrial invasion were compared between two patient groups with positive and negative peritoneal cytology. Among the 5 patients with positive peritoneal cytology, it was observed that 40% had 1/3 outer myometrial invasion (1/2 outer myometrial invasion was present in 3 patients, 60%). In the group with negative peritoneal cytology, the rate of deep myometrial invasion was 14% (1/3 outer) and 25.5% (1/2 outer).

When the histological types of tumors were examined, it was observed that among the 36 patients with negative peritoneal cytology, 92% had tumors of the endometrial adenocarcinoma type, and the remaining 8% had papillary adenocarcinoma.

Studies have shown that tumor size is an independent prognostic factor and particularly affects survival rates in relation to lymph node metastasis, myometrial invasion, and their associated factors.[15,16] In tumors smaller than 2 cm, the rate of pelvic lymph node metastasis is 4%, while in tumors larger than 2 cm, it is 15%, and in cases where the tumor covers the entire endometrial cavity, it is 35%.[6]

In our study, tumor size and pelvic lymph node involvement rates were investigated, and it was observed that lymph node involvement rates increased with increasing tumor size.

The size of the tumor is an important factor in influencing survival along with myometrial invasion.[18] In our study, it was observed that as the tumor size increased, the rate of localized tumors in the endometrium decreased, and the rate of deep myometrial invasion increased.

Studies have reported that in tumors smaller than 2 cm and with myometrial invasion depth less than 1/2, there is no lymph node metastasis.[6] In our study, none of the 11 patients with tumors smaller than 2 cm and myometrial invasion less than 1/2 had lymph node metastasis, which is consistent with the literature data.

CONCLUSION

In the elderly age group, there is an increase in adnexal spread, the rate of deep myometrial invasion, and aggressive histological types. As the grade increases, the depth of myometrial invasion and lymph node involvement also increase. The increasing depth of myometrial invasion is associated with higher rates of adnexal spread and lymph node involvement.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study is the scientific study of Nurgül Ulusoy master's thesis named "Investigation of the correlation of prognostic parameters in cases of endometrium carcinoma", registered at the National Thesis Center with the number 103431, dated 2001.

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study had no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Nurgül Ulusoy

I graduated from Istanbul University, Istanbul Medicine Faculty in 1997. I'm specialist in gynecology and obstetrics. I completed my specialization at Bakırköy Women and Children's Diseases Training and Research Hospital in 2002. I worked at Gynecology and Obstetrics Department of Bakırköy Women and Children's Diseases Training and Research Hospital between 2002-2006 as chief assistant. Then I worked as a Gynecology and Obstetrics specialist at Private Avicenna Esenler Ensar Hospital between 2006-2016 and at Private Incirli Ethica Hospital between 2016-2017. I served at VM Medicalpark Florya Hospital as a Physician Lecturer at İstanbul Aydın University Gynecology and Obstetrics Department between March 2017-2020. As of 2023, I have been continuing my proffesional studies at my own private clinic (Bakirkoy, İstanbul) since January 2021.

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Evaluation of patients under the age of 18 who applied to an adult psychiatric policy clinic

Özlem Özcanlı Çay[1], Merve Şahin Can[2]

[1]Department of Pediatrics, Balıkesir City Hospital, Balıkesir, Turkiye
[2]Department of Mental Health and Diseases, Faculty of Medicine, Balıkesir University, Balıkesir, Turkiye

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Corresponding Author: Özlem Özcanlı Çay, ozlemozcanli@yahoo.com

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ABSTRACT

Aim: The aim of this study is to evaluate the sociodemographic data and diagnoses of patients under the age of 18 who applied to an adult psychiatry clinic.

Methods: 311 applicants under the age of 18 who applied to the adult psychiatry outpatient clinic of our hospital between January 2020 and December 2022 were included in the study. has been included. Sociodemographic data and diseases were evaluated retrospectively.

Results: Of the 309 applicants in total, 194 (62.8%) were girls and 115 (37.2%) were boys. Considering the ages, 12.3% of the applications were 15 years old and under, and 86.7% were over 15 years old. The psychiatric diagnosis rate was 84.5 % when both genders were evaluated. This rate was 86.5% for girls and 82.6% for boys. Looking at the most common diagnoses in total; Diagnosis of anxiety disorders (21.7%), depressive disorder (21.7%), and activity and attention disorders (15.2%) were in the top 3 ranks.

Conclusion: This study is important as it is the first study on adolescent patients admitted to an adult psychiatric service in our city. It is thought that these findings may guide interventions in the field of child and adolescent psychiatry.

Keywords: Pediatric, adult psychiatry, sociodemographic data, adolescent psychiatry

INTRODUCTION

The first onset of mental disorders usually occurs in childhood or late adolescence, but treatment is typically sought several years later.[1] Child and adolescent mental disorders began to attract attention in the healthcare system and became more evident after the 1960s.[2] Compared to the increase in the prevalence of mental disorders in children and adolescents, the low number of professionals such as physicians and psychologists and inpatient services serving in this field makes it difficult to access services in this field. In our country, child and adolescent mental health services are mostly provided as outpatient follow-up and treatment. However, there are also situations that require inpatient treatment. Considering the situations requiring inpatient treatment; In recent years, it has been observed that there has been a decrease in the average length of stay of children and adolescents in the inpatient ward, while the rate of admission to the inpatient ward has increased threefold.[3] The most common reasons for hospitalization are psychiatric emergencies, defined as suicide attempts, psychotic exacerbations, substance-related conditions, and behavioral problems. Considering the groups in terms of drug use frequency, the most frequently used drugs were antipsychotics, antidepressants, anxiolytic drugs and mood stabilizers, respectively.[4] In small cities, adult psychiatry services try to replace child and adolescent psychiatry services.[4] While there is a shortage of inpatient services for child psychiatrists, the number of institutions and physicians providing outpatient treatment has recently increased. However, families still occasionally bring their children, especially those aged 15 and over, to an adult psychiatrist for various reasons. Determining the prevalence of mental problems in children in society provides data on areas that can be improved in terms of protective measures. Our study aims to determine the diagnosis, gender and age distribution of people under the age of 18 who apply to adult mental health. Our hypothesis is that the ages and diagnoses of child and adolescent patients applying to adult psychiatry outpatient clinics will vary when compared to child and adolescent psychiatry outpatient clinics.

METHODS

Ethical approval, received from the Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee (Decision Date: 10.05.2023, Decision No: 2023/73). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study was planned as retrospective, cross-sectional and descriptive. All patients under the age of 18 who applied to the mental health and diseases polyclinic of our university health practice and research center in our city between January 2020 and December 2022 were included in the study. The data of three hundred and nine patients were used in the study by evaluating the patient file in which the information obtained during the first application to the polyclinic was processed and the psychiatric examination information. Age, gender difference and diagnosis groups of the evaluated cases were determined. Psychiatric diagnoses of the admitted patients were made by the physicians who examined the patients, according to DSM V.

Statistical Analysis

The statistical analysis were completed by using SPSS 23.0 program. The suitability of the data for normal distribution was evaluated with the Kolmogorov-Smirnov test. The results were expressed as mean ± standard deviation. Chi-square test was used for categorical variables such as gender. Independent samples t-test was used for comparisons on numerical variables between groups. Linear regression analyses were used to detect variability between parameters. A p value of less than 0.05 was considered statistically significant.

RESULTS

Between January 2020 and December 2022, it was determined that a total of 309 (100.0%) patients aged 18 and under applied to the adult psychiatry outpatient clinic. Of the applicants, 194 (62.8%) were girls and 115 (37.2%) were boys. Considering the ages, 12.3% of the applications were 15 years old and under, and 86.7% were over 15 years old. Percentage distributions by age are shown in **Table 1**.

Table 1. Distribution of applications by age

Age	N	Percentage (%)
15 years and under	38	12.3
16 years old	47	15.2
17 years	79	25.6
18 years old	145	46.9
Total	309	100.0

Considering the diagnosis distributions; A total of 261 (84.5) of the applicants were diagnosed with at least one psychiatric diagnosis. This rate was 86.5% for girls and 82.6% for boys. Looking at the most common diagnoses in total; anxiety disorders were in the top 3 ranks with 67 people (21.7%), depressive disorders with 67 people (21.7%), and activity and attention disorders with 47 people (15.2%). Adjustment disorder, obsessive compulsive disorder (OCD), bipolar disorders, and other diagnoses (psychotic disorder, mental retardation, pervasive developmental disorder, eating disorders, trichotillomania , behavioral disorders, conversion disorder, and sexual identity-related counseling) were diagnosed. Total diagnosis distributions are shown in **Table 2**.

Table 2. Distribution of diagnoses among applicants

Diagnosis	N	Percentage (%)
Anxiety disorders	67	21.7
Depressive disorder	67	21.7
Bipolar mood disorder	15	4.9
Obsessive compulsive disorder	26	8.4
Adjustment disorder	32	10.4
Activity and attention disorder	47	15.2
Other	7	2.2
Not receiving any psychiatric diagnosis	48	15.5
Total	309	100.0

The first two most common diagnoses in both genders were anxiety disorders and depressive disorders. When looking at the distribution of disease incidence rates by gender; Except for the diagnosis of adjustment disorders, it was found to be significantly higher in girls than boys, and the rates are listed in **Table 3**.

Table 3: Diagnosis distribution rates by gender and age

	Anxiety B.	Depressive B.	Akt and Dik E.	OCD	Bipolar DB	Harmony B.
Gender						
Woman	48 (71.6%)	47 (70.1%)	28 (59.6%)	17 (65.4%)	12 (80%)	14 (43.8%)
Male	19 (28.4%)	20 (29.9%)	19 (40.4%)	9 (34.6%)	3 (20%)	18 (56.3%)
Age						
15 and under	3 (4.5%)	7 (10.4%)	2 (4.3%)	6 (23.1%)	2 (13.3%)	12 (37.5%)
16	10 (14.9%)	9 (13.4%)	5 (10.6%)	6 (23.1%)	7 (46.7%)	2 (6.3%)
17	18 (26.9%)	14 (20.9%)	14 (29.8%)	5 (19.2%)	3 (20%)	8 (25.0%)
18	36 (53.7%)	37 (55.2%)	26 (55.3%)	9 (34.6%)	3 (20%)	10 (31.3)
	67 (100%)	67 (100%)	47 (100%)	26 (100%)	15 (100%)	32 (100%)

Considering the age distributions; although the most common diagnosis for those under the age of 15 was adjustment disorders, the most common diagnoses were anxiety and depressive disorders in the 16-18 age range. Distributions of other diagnoses by age are listed in **Table 3**.

DISCUSSION

In our study, the gender and diagnosis distribution of applications to the adult psychiatry outpatient clinic under the age of 18 were examined. In our findings; The majority of applications are girls; it was determined that the majority of them were around 16-18 years of age, and the most common diagnoses were depressive disorder and anxiety disorder in both genders .

In the literature review, we could not find any study evaluating data on adolescents followed up as outpatients in adult psychiatry in Turkiye in recent years; The proportion of girls is also high in studies evaluating children hospitalized in adult psychiatry wards. Usta et al.[5] 71.1% of 194 child and adolescent patients receiving inpatient treatment in the adult psychiatric ward were girls; Coskun et al.[6] stated that 63.09% of the children and adolescents receiving inpatient treatment at Istanbul University Faculty of Medicine Psychiatry Clinic were girls. In two studies, 63.1% and 68.1% of the patients treated and discharged from the child psychiatry inpatient

ward were reported to be girls, respectively. In addition to these data, there are also publications in the literature indicating that boys are more frequently admitted to child psychiatry as outpatients.[7-9] In these studies, the authors associated the fact that boys are brought to mental health outpatient clinics more frequently than girls in the general population, with the fact that the physiological maturation process of boys starts and ends later than girls.[8] In a study where data from child psychiatrists were evaluated, the rate of referral was higher in girls than in boys, especially for new-onset problems. It has been reported to be higher than.[10] In another study in 2019, in which child psychiatry data were evaluated, it was stated that girls were more likely to apply during adolescence.[11] Since our study is a retrospective file scanning study, it is difficult to say which factors are responsible for this difference in gender ratio. However, in the data we evaluated, it was thought that the absence of an age group under the age of 15 may contribute to the gender difference between boys and girls.

Average ages from this perspective, it was observed that the majority of the applications in our study were between the ages of 16-18. This may be due to families preferring a child psychiatrist at younger ages or physicians referring younger age groups to child and adolescent mental health physicians more frequently in applications to our department. Similarly, in a study published in 2020 that evaluated adolescent patients hospitalized in an adult psychiatric ward, the average age was stated as 16.50±0.70. Again, in the study of Park et al.[12] where they evaluated children and adolescents who applied to the adult emergency department, it was stated that 73.5% of the patients were between the ages of 16-18 and the youngest age of admission was 12.

Literature in terms of diagnoses When examined by Taş et al.[13] the diagnostic rankings of inpatients in the adult ward were major depression, schizophrenia and bipolar disorder; Coskun et al.[6] They classified them as mood disorders, psychotic disorders and dissociative disorders. In another study examining outpatient follow-ups at the Child and Adolescent Psychiatry outpatient clinic, considering all age groups, the most frequently detected diagnoses were attention deficit and hyperactivity disorder (ADHD), generalized anxiety disorder (GAD), and mental disorder, respectively, unlike inpatients. Retardation (MR) and depression have been observed. When the diagnoses were divided by age groups in the same study, DEHB was followed by depressive disorder and anxiety disorders in the 12-18 age range.[14] In our study, activity and attention disorder was determined to be the second most common diagnosis in boys and the third most common diagnosis in girls. This situation seems to be related to the fact that, due to the clinical course of DEHB, it is frequently diagnosed during the school starting period and its follow-up is usually continued by child psychiatrists. Anxiety disorders , which we see as common diagnoses, often begin in young adulthood and adolescence, while depressive disorders can develop secondary to psychosocial stressors (such as family conflict, exam anxiety) in this age group.[15] In a study evaluating children between the ages of 0-18, the diagnosis rate in this group was stated as 74.7%. In the same study, when the patients were divided into three groups by age, this rate was reported to be 86.4% in the 12-18 age range, similar to our study.[14] Park et al.[12] in their study with child and adolescent patients (n=332), mood disorders (38.2%) and psychotic disorders (25.7%) were determined as the leading diagnoses. Again in this study, 84.6% of the patients applying to adult psychiatry received at least one clinical diagnosis. In our study, the diagnostic order was anxiety disorder, depressive disorder, activity and attention disorder. The reason why the frequency of diagnoses varies between studies and anxiety disorder is more common especially in outpatient applications can be attributed to the fact that most of the studies in question were conducted in the child psychiatry service and the applications to us were often made up of the age group close to the exam period. In addition, the possibility that patients with more severe conditions (such as psychotic attack, conduct disorder, mental retardation) may have applied directly to an institution with an inpatient service for children is another reason that comes to our mind. Again, since ADHD and other conduct disorders are common diagnostic groups in child and adolescent psychiatry clinical practice, applications related to these disorders are primarily directed to child and adolescent psychiatrists, as referrals from schools are located in our city.

Limitation

The retrospective and cross-sectional design of our study, the use of patients' medical records in the evaluation of data is one of the main limitations of our study. The limitations of our study include not defining comorbid medical diseases, using a diagnosis specific to the primary problem area as the main diagnosis in patients with more than one diagnosis , and not being able to evaluate in detail parameters such as education level, economic level, family history, alcohol/ substance use in sociodemographic data. However, the superiority of our study is that no other study was found that evaluated outpatient child and adolescent patients admitted to an adult psychiatrist in Turkiye. In this context, further studies are needed to evaluate the missing areas.

CONCLUSION

It is thought that our study may guide interventions regarding child and adolescent psychiatric patients in our province and allow the results to be compared with other provinces. Increasing number of studies related to this subject; by contributing to the identification of clinical differences, it will provide important data for developing child and adolescent mental health.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee (Date: 10.05.2023 Decision No: 2023/73).

Informed Consent

Since the study was designed retrospectively, no written informed consent forms were obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study had no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Özlem Özcanlı Çay

I was born in 1983 in Nevşehir. I finished my high school education in Gönen high school. I graduated from İstanbul University, İstanbul Medicine Faculty in 2007. I'm specialist in pediatrics. I completed my specialization at Fırat univercity Hospital in 2016. I worked at Harput Hospital between 2016-2019. I have been continuing studies at Balıkesir city hospital since 2019.

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An investigation into the relationship between serum vitamin D levels and the success rate of pregnancy in a cycle of in vitro fertilization

Nurgül Ulusoy[1], Ayşe Şeyma Küçükakça[2]

[1]Private Gynecology and Obstetric Clinic, Istanbul, Turkiye
[2]Department Gynecology and Obstetric, Istanbul Medipol University Çamlıca Hospital, İstanbul, Turkiye

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Corresponding Author: Nurgül Ulusoy, nculusoy17@gmail.com

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ABSTRACT

Aims: The significance of vitamin D in women's health is well-established, and numerous studies have explored its role in reproductive physiology. This examination aimed to delineate the association between serum vitamin D levels and the success rate of pregnancy in in vitro fertilization (IVF) cycles among infertile women aged 20-45.

Methods: This retrospective cohort study, conducted between March 2020 and August 2023, included 134 infertile women with insufficient vitamin D levels and 152 infertile women with sufficient vitamin D levels. The study aimed to investigate the impact of adequate vitamin D serum levels on the success of the IVF method. The threshold for determining insufficient vitamin D level was set at 30 ng/mL, measured using the ELISA method seven days before embryo transfer.

Results: The results revealed that gestational sac and fetal heart rate were significantly higher in women with sufficient vitamin D levels ($p<0.05$). Additionally, a statistically significant association was observed between the case and control groups regarding live births ($p<0.05$; 13.4% vs. 75.7%). Multiple logistic regression, adjusting for confounding variables, demonstrated a significant difference between the groups in terms of pregnancy success rate ($p<0.05$).

Conclusion: It is inferred that sufficient vitamin D levels increase the likelihood of success in IVF among Turkish infertile women.

Keywords: Infertile women, in vitro fertilization, IVF, vitamin D, pregnancy success

INTRODUCTION

Vitamin D deficiency represents a notable global health concern across various age groups, with a particular emphasis on pregnant women, adult females, and girls.[1] High rates of vitamin D deficiency have been demonstrated among scholars in Turkiye.[2] This deficiency has implications for immune system dysfunction, as well as its association with conditions such as cancer, psoriasis, diabetes, leukemia, and osteoporosis.[3] Considerable research has focused on exploring the impact of this vitamin on the reproductive system of females.[4]

Vitamin D comprises two principal isoforms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), with 1 and 25-hydroxyvitamin D3 representing the active form of the vitamin.[5,6] In this study, the focus is on 25-hydroxyvitamin (OH) D3. Vitamin D is present in various foods, including but not limited to fish, reindeer lichen, mushrooms, fish liver oils, cheese, beef liver, dark chocolate, fat spreads, fish fat, yogurt, milk, orange juice, breakfast grains, and eggs.[7] The concentration of 25 (OH) D in blood serum serves as a key determinant for evaluating vitamin D deficiency.[8,9] Numerous studies have proposed varying thresholds for the appropriate and acceptable level of vitamin D concentration in blood serum, with most research indicating adequacy at 30 nanograms per milliliter (ng/mL) or higher.[10]

Infertility poses numerous challenges for both couples and the healthcare system. Defined as the inability to achieve a successful pregnancy after 12 months of regular unprotected sexual intercourse, infertility affects approximately 8-12% of couples worldwide.[11] Among the various causes, factors contributing to infertility include issues related to ovulation, the uterine-tubal system, and male factors.[12] Over the past decades, the increasing age of marriage and the postponement of childbearing have emerged as significant contributors to infertility.[13] In vitro fertilization (IVF), an assisted reproduction treatment (ART) method, involves the combination of sperm and eggs in a laboratory setting. Many

couples have successfully addressed their infertility concerns through the application of this technique. Numerous researchers have explored factors influencing the success of IVF.[14] This study investigates the impact of vitamin D on the likelihood of IVF success.

Vitamin D deficiency represents a notable public health concern in Turkiye, with reported prevalence ranging from 58.9% to 66.6%.[2] Testing for vitamin D serum levels is relatively inexpensive and widely accessible, and the associated treatment is cost-effective.[15] Consequently, the diagnosis and treatment of vitamin D deficiency in women contemplating assisted reproductive methods may prove beneficial. The impact of vitamin D deficiency on women's reproductive health underscores the necessity for extensive and diverse studies addressing the increasing prevalence of this deficiency and its adverse consequences on the female reproductive system. This study aims to explore the correlation between vitamin D levels and IVF outcomes, marking what we believe to be the first investigation into this subject among Turkish women.

METHODS

This retrospective cohort study was conducted on patients between March 2020 and August 2023. Ethical approval was granted by the İstanbul Medipol University Non-invasive Researches Ethics Committee (Date: 26.10.2023, Decision No: 879). All procedures adhered strictly to ethical guidelines and the principles outlined in the Declaration of Helsinki.

Inclusion criteria encompassed infertile women within the reproductive age range (20-45 years) experiencing either primary or secondary infertility. The study focused on women undergoing their initial cycle of in vitro fertilization (IVF). Exclusion criteria comprised cases involving repeated pregnancy loss, ovarian hyperstimulation syndrome, autoimmune disease, chronic illness, cardiovascular problems, endocrine disorders, infertility attributed to severe endometriosis, and uterine abnormalities.

Infertile women meeting the study criteria received detailed information about the study's purpose and methodology. Subsequently, the researcher conducted interviews to complete a demographic profile questionnaire, and blood samples were collected from all participants seven days prior to embryo transfer to measure the serum level of vitamin D. The laboratory employed the ELISA method to measure vitamin D serum levels, ensuring uniformity by conducting all assessments in a single laboratory.

Following embryo transfer, luteal phase support for all participants involved intramuscular progesterone injections of 50 mg every other day and vaginal progesterone suppositories of 400 mg every 12 hours.

Participants were categorized into two groups based on their serum vitamin D levels: insufficient (<30 ng/mL) constituted the case group, while sufficient (≥30 ng/mL) formed the control group. Sampling continued until the number of participants reached 134 in the insufficient vitamin levels group and 154 in the sufficient vitamin levels group.

Subsequently, participants were closely monitored, and assessments for intrauterine gestational sac and fetal heart rate were conducted at seven weeks of gestation.

Statistical Analyses

The study utilized mean (M) and standard deviation (SD) to present descriptive statistics for the data. Categorical variables were delineated using number and percentage and analyzed through the Chi-Squared test. The normality of quantitative data was assessed using the Kolmogorov-Smirnov test, revealing a normal distribution for all the data. Group comparisons were conducted using the Independent t-test, deemed appropriate for datasets with normal distributions. Exploring the significant relationship between vitamin D and IVF success involved employing multivariate logistic regression analysis. Statistical analysis was performed using SAS statistical software, and the threshold for statistical significance was set at a p-value less than 0.05.

The sample size for the study was determined using the G-Power 3.2 program. The calculation, based on Pearson's Chi-Square Test of Association, aimed for a power of 80%, an effect size of 40%, and a type 1 error of 0.25, resulting in a minimum requirement of 278 patients.[16]

RESULTS

The study encompassed two hundred and eighty-six infertile women, carefully matched for age (31.25±5.21) and body mass index (BMI) (26.62±4.45). **Table 1** provides a comprehensive statistical overview of maternal characteristics, gestational sac, fetal heart rate (FHR), vitamin D supplement usage, vitamin D levels, pregnancy test outcomes, and pregnancy results. Maternal characteristics, comprising age, BMI, husband's age, duration of infertility, type of infertility, smoking habits, and employment status, were presented for detailed analysis.

As indicated in **Table 2**, an Independent t-test revealed no statistically significant differences between the insufficient vitamin D group and the sufficient vitamin D group concerning age, husband's age, BMI, and duration of infertility ($p>0.05$). However, a statistically significant difference was observed between the case and control groups in terms of vitamin D levels ($p<0.05$). The mean and standard deviation (SD) of vitamin D levels in the case and control groups were 14.37±6.47 and 35.69±12.5, respectively.

As presented in **Table 2**, a chi-squared test identified a statistically significant difference between the insufficient vitamin D and sufficient vitamin D groups in terms of the presence of a gestational sac ($p<0.05$). Additionally, a statistically significant difference was observed between the case and control groups concerning fetal heart rate (FHR) ($p<0.05$). However, no statistically significant difference was found between the case and control groups regarding vitamin D supplements ($p>0.05$).

Furthermore, **Table 2** reports that the chi-squared test revealed a statistically significant difference between the insufficient vitamin D and sufficient vitamin D groups in

relation to the pregnancy test results (p<0.05). All infertile women in the control group exhibited positive results. Similarly, a statistically significant difference was noted between the case and control groups concerning pregnancy outcomes (p<0.05). The number and percentage of live births in the insufficient vitamin D and sufficient vitamin D groups were 18 (13.4) and 115 (75.7), respectively.

Table 3 provides insight into a logistic regression test conducted to explore factors influencing live births in pregnant women. Binary logistic regression was utilized to predict pregnancy outcomes using variables such as vitamin D, women's age, husband's age, and BMI level. Vitamin D emerged as a significant predictor of pregnancy outcomes (Exp(B)=1.083, p=<0.001, 95% CI [1.059, 1.107]). Additionally, the age of pregnant women proved to be a significant predictor of pregnancy outcomes (Exp(B)= 0.939, p=0.021, 95% CI [0.891, 0.991]). However, husband's age and BMI did not emerge as significant predictors of pregnancy outcomes (p>0.05).

Table 1. Statistical description of study parameters in infertile women (n=286)

Study parameters	mean ± SD (range) or n (%)
Maternal characteristics	
Age (years)	31.25±5.21 (20-44)
BMI (kg/m²)	26.62±4.45 (17.30-40.80)
Husband's age	35.59±4.69 (24-47)
Duration of infertility	3.08±1.25 (1-6)
Type of infertility	
Primary	236 (82.5)
Secondary	50 (17.5)
Smoking	
Yes	32 (11.2)
No	254 (88.8)
Employment status	
Employed	213 (74.5)
Unemployed	73 (25.5)
Gestational sac	
Zero	130 (45.5)
One	111 (38.8)
Two	45 (15.7)
Fetal heart rate (FHR)	
Yes	156 (54.5)
No	130 (45.5)
Use of Vitamin D supplement	
Yes	184 (64.3)
No	102 (35.7)
Vitamin D	
Insufficient	134 (46.9)
Sufficient	152 (53.1)
Pregnancy test results	
Positive	177 (61.9)
Negative	109 (38.1)
Pregnancy results	
Birth	133 (46.5)
Negative	109 (38.1)
Abort	44 (15.4)

"BMI: Body mass index, FHR: Fetal heart rate, SD: standard deviation, n: Number."

Table 2. Comparison of insufficient vitamin D and sufficient vitamin D groups

Study parameters	Insufficient Vitamin D (n=134) mean ± SD (range)	Sufficient Vitamin D (n=152) mean ± SD (range)	p value
Age (years)	31.53±5.29 (21-42)	31±5.14 (20-44)	0.392*
Husband's age	35.86±4.9 (24-47)	35.36±4.5 (27-46)	0.396*
BMI (kg/m²)	27.01±4.63 (17.3-40.8)	26.28±4.27 (18.9-36.9)	0.170*
Duration of infertility	3.19±1.24 (1-6)	2.98±1.26 (1-6)	0.150
The serum vitamin D (ng/ml)	14.37±6.47 (2.3-31)	35.69±12.5 (5.3-95.2)	<0.001*
Gestational sac			<0.001**
Zero	113 (84.3)	17 (11.2)	
One	15 (11.2)	96 (63.2)	
Two	6 (4.5)	39 (25.7)	
FHR			<0.001**
No	113 (84.3)	17 (11.2)	
Yes	17 (12.7)	97 (63.8)	
Twin	4 (3)	38 (25)	
Use of Vitamin D supplement			0.409**
Yes	89 (66.4)	95 (62.5)	
No	45 (33.6)	57 (37.5)	
Pregnancy test results			<0.001**
Positive	25 (18.7)	152 (100)	
Negative	109 (81.3)	0 (0)	
Pregnancy results			<0.001**
Live birth	18 (13.4)	115 (75.7)	
Negative	109 (81.3)	0 (0)	
Abort	7 (5.2)	37 (24.3)	

*An Independent t-test. **A chi-squared test.

Table 3. Logistic regression test to investigate factors affecting pregnancy results

Study parameters	95% C.I.for EXP(B)		Exp(B)	p-value
	Lower	Upper		
Vitamin D n(ng/ml)	1.059	1.107	1.083	<0.001
Age	0.891	0.991	.939	0.021
Husband's age	0.931	1.047	.987	0.667
BMI	0.959	1.067	1.012	0.669

DISCUSSION

The primary objective of this investigation was to establish a connection between serum vitamin D levels and the success rate of pregnancy in an IVF cycle. The study encompassed 134 infertile women with insufficient and 152 infertile women with sufficient vitamin D serum levels. The research findings demonstrated a significant impact of serum vitamin D levels on the success of the IVF method in achieving pregnancy for infertile women. Over the past decades, numerous studies have delved into the physiological role of vitamin D in influencing outcomes in assisted reproductive technology. However, the results of these prior studies exhibit inconsistency and contradiction.[17] This disparity may be attributed to various factors influencing vitamin D, including sunlight exposure and dietary habits.[18]

In a cross-sectional study involving 848 Chinese infertile women, Liu et al.[19] discovered that vitamin D levels were not associated with the live birth rate and clinical pregnancy following IVF. Similarly, Cozzolino et al.[20] conducted a meta-analysis and systematic review, encompassing multiple articles, and concluded that serum

vitamin D levels do not impact clinical pregnancy, live birth, and ongoing pregnancy rates in conventional IVF or intracytoplasmic sperm injection outcomes. Franasiak et al.[21] in a retrospective cohort study involving 517 infertile women, found no significant relationship between serum vitamin D levels on the day of ovulation and implantation rate and clinical pregnancy in IVF.

The influence of race on the association between serum vitamin D levels and pregnancy rate after IVF was explored by a study conducted by.[22] They observed that in most studies involving Asians, the effect of adequate vitamin D levels on pregnancy outcomes was not evident.[23] Limited research has been conducted on Turkish women regarding the impact of vitamin D on assisted reproductive technology (ART) success. Yilmaz et al.[24] reported that serum vitamin D levels do not affect intrauterine insemination success in Turkish infertile women.

Contrary to the findings of the studies mentioned above, the present study revealed a significant relationship between vitamin D levels in Turkish infertile women and IVF outcomes, differing from the results reported in these studies.

The findings of this study align with those of several other studies. Garbedian et al.[25] reported that adequate levels of vitamin D increase the likelihood of clinical pregnancy following IVF and suggested vitamin D supplementation to enhance pregnancy rates in infertile women. Zhou et al.[26] echoed this recommendation for vitamin D supplementation to improve success in IVF. Previous studies have indicated that elevated follicular vitamin D levels are associated with higher pregnancy rates in IVF.[17,27] In a meta-analysis and systematic review, Iliuta et al.[28] found favorable outcomes in IVF for women with sufficient vitamin D status, while another systematic review by Shen et al.[29] suggested that vitamin D deficiency tended to reduce IVF pregnancy outcomes.

Vitamin D emerges as a significant factor in women's fertility, whether achieved spontaneously or with the assistance of assisted reproductive technology (ART) such as IVF. The ongoing discourse on the role of vitamin D in reproductive health underscores the need for further investigation. Conflicting research results on vitamin D and infertility emphasize the necessity for additional studies. Studies with larger sample sizes, involving thousands of women, are warranted to establish the vitamin D threshold influencing the reproductive process, which may differ from recommended amounts for bone health. The role of vitamin D in ART processes across diverse ethnic groups is another crucial area requiring further exploration. The primary contribution of this study lies in demonstrating a significant relationship between vitamin D and IVF outcomes in Turkish women. Discrepancies among studies conducted in different countries may be attributed to factors such as lifestyle, seasonal influences, or the involvement of other ovarian factors in the reproductive process. Vitamin D is linked to various factors, including geographic, demographic, and clinical parameters, which can influence its effects on women's fertility. Conducting randomized trials could yield more reliable answers.

Limitations

This study has both limitations and advantages. One limitation is its single-center nature, and future studies are recommended to utilize data from multiple centers. Additionally, exploring the role of vitamin D levels in men and their impact on IVF success is suggested for future research. Another limitation is the absence of data related to men. The study's substantial sample size stands out as one of its key strengths, enhancing the reliability of its results.

CONCLUSION

This study underscores a significant correlation between serum vitamin D levels in infertile women and successful pregnancy outcomes in the IVF method. Women with elevated vitamin D levels exhibited a heightened probability of achieving live births and positive pregnancy test results. Given that vitamin D supplementation is both affordable and safe, it stands as a viable recommendation for infertile women undergoing IVF, offering potential benefits. The results, derived from large-scale studies conducted in Turkiye, contribute to shedding light on the precise mechanisms of vitamin D in the realm of fertility. To further enhance our understanding, future research endeavors should explore this relationship through comprehensive cellular and clinical studies for more accurate and nuanced results.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Balıkesir University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (Date: 23.08.2023 Decision No: 2023/114).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study had no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Nurgül Ulusoy

I graduated from Istanbul University, Istanbul Medicine Faculty in 1997. I'm specialist in gynecology and obstetrics. I completed my specialization at Bakırköy Women and Children's Diseases Training and Research Hospital in 2002. I worked at Gynecology and Obstetrics Department of Bakırköy Women and Children's Diseases Training and Research Hospital between 2002-2006 as chief assistant. Then I worked as a Gynecology and Obstetrics specialist at Private Avicenna Esenler Ensar Hospital between 2006-2016 and at Private Incirli Ethica Hospital between 2016-2017. I served at VM Medicalpark Florya Hospital as a Physician Lecturer at İstanbul Aydın University Gynecology and Obstetrics Department between March 2017-2020. As of 2023, I have been continuing my proffesional studies at my own private clinic (Bakirkoy, İstanbul) since January 2021.

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Original Article

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Vitamin D level in children with atopic dermatitis

Özlem Kemer Aycan, Özlem Özcanlı Çay, Demet Can

[1]Department of Pediatry, Faculty of Medicine, Balıkesir University, Balıkesir, Turkiye
[2]Department of Pediatry, Balıkesir City Hospital, Balıkesir, Turkiye
[3]Behçet Uz Children's Hospital, Department of Allergy Immunology, İzmir, Turkiye

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Corresponding Author: Özlem Özcanlı Çay, ozlemozcanli@yahoo.com

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ABSTRACT

Aims: Atopic dermatitis is a chronic relapsing skin disease that is mostly seen between the ages of 0-5. In our study, we aimed to reveal the difference in 25-OH vitamin D levels between the patient group diagnosed with atopic dermatitis and the control group.

Methods: It was carried out at the Pediatric Allergy Polyclinic of Balıkesir University Faculty of Medicine Hospital between 2018-2021. A control group consisting of 220 patients between the ages of 0-17 who were diagnosed with atopic dermatitis and who applied to the Pediatric Allergy outpatient clinic and 220 patients who were not diagnosed with atopic dermatitis were included. The diagnosis of atopic dermatitis was made using the Hanifin-Rajka criteria. Disease activity was measured by the scorad index.

Results: 25-OH vitamin D level and eosinophilia value in peripheral blood were found to be statistically significant between the patient and control groups. No significant difference was found between the patient and control groups in terms of parental age, parental education level, living place, weight, height, and body mass index (BMI).

Conclusion: 25-OH vitamin D levels were found to be lower and eosinophil levels were higher in patients with atopic dermatitis. No significant difference was found in terms of total IgE (kU/L) level. More extensive studies are needed to determine how 25-OH vitamin D (ng/dl) level affects atopic dermatitis.

Keywords: Pediatric, vitamin D, atopic dermatitis

INTRODUCTION

Atopic dermatitis is a recurrent, chronic and inflammatory skin disease that is mostly seen in childhood but can also affect adults.[1] Many environmental, metabolic and immunological causes are shown in the pathogenesis of atopic dermatitis. Generally, most symptoms begin within the first 5 years of age. Atopic dermatitis diagnosis is often[2] seen along with other allergic diseases such as asthma and allergic rhinitis. Its association with these diseases is approximately 50% and above.[3]

Vitamin D is a steroid hormone called cholecalciferol. Its main function is to ensure hemostasis of calcium phosphorus metabolism. It is also held responsible for many cardiovascular, neoplastic and immunological conditions. Vitamin D has 2 different synthesis pathways. It is synthesized in the skin by UVB rays from the sun or taken orally through plant (D2) and animal (D3) foods and added to the circulation. Vitamin D3 taken orally turns into 25-OH vitamin D in the liver and enters the circulation. 1,25 OH vitamin D is synthesized in the kidneys.[4-6]

METHODS

The study was carried out with the permission of the Balıkesir University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (Date: 23.08.2023 Decision No: 2023/114). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted at the Pediatric Allergy Polyclinic of Balıkesir University Faculty of Medicine Hospital between 2018 and 2021. A control group consisting of 220 patients between the ages of 0-17 who were diagnosed with atopic dermatitis and who applied to the Pediatric Allergy outpatient clinic and 220 patients who were not diagnosed with atopic dermatitis were included. The study was planned as retrospective, cross-sectional and descriptive. Atopic dermatitis was diagnosed according to the Hanifin-Rajka criteria. The patient group diagnosed with atopic dermatitis was not receiving active steroid treatment. The patient and control groups included people who had not taken vitamin D supplements in the

last 6 months. Physical examinations of these patients were performed and hemogram, total IgE, peripheral eosinophil count, and 25-OH vitamin D level parameters were recorded. Beckman at Balıkesir University Health Practice and Research Hospital Biochemistry Laboratory Chemiluminescence on Coulter DXI 600/800 Skin prick test was performed on the patient group diagnosed with atopic dermatitis and the control group who applied to the Pediatric Allergy and Immunology outpatient clinic. The patient group diagnosed with atopic dermatitis was evaluated with the scorad index. Scorad index: (A) extent (percentage of skin surface affected according to the rule of nine); (B) intensity (erythema, combination of edema/ papules, itching result, ooze/crust appearance, lichenification and dryness, six parameters evaluated from 0 to 3; 0: absent, 1: mild, 2: moderate, 3: severe); and (C) subjective symptoms (the severity of itching during the last three days, the effect of sleep, the effect of the general condition of the skin on daily life are questioned and the answers are evaluated from 1 to 10 and given as disease prevalence score/5+7xdisease severity score/2+patient symptoms. Scorad index was classified as mild if <25, moderate if it was 25-50, and severe disease if it was >50.7 Serum 25-OH vitamin D level of the patient and control group was classified as low if it was <20 ng/dl, medium if it was 20-30 ng/dl, >30 ng/dl is classified as high. The patient and control group reside in the same province and a similar effect is observed for sunlight exposure. The sociodemographic data of the patient and control group were asked and the occupation of the parents, education level of the parents, and place of residence were recorded.

Statistical Analyses

SPSS 23.0 package program was used for statistical analysis of the study. Descriptive statistics of continuous variables are shown with mean, standard deviation, median, minimum and maximum values, and categorical variables are shown with frequency and percentage. Suitability of continuous variables to normal distribution Shapiro It was examined with the Wilk test. One-way analysis of variance (ANOVA) was used for comparisons of normally distributed continuous variables between 3 or more groups. Mann Whitney U test was used for comparisons of variables that did not show normal distribution between 2 groups, and Kruskal Wallis test was used for comparisons of 3 or more groups. Pearson chi-square, Yates corrected chi-square and Fisher exact chi-square tests were used for group comparisons of categorical variables. In all statistical comparisons in the study, comparisons with a p value below 0.05 are considered statistically significant.

RESULTS

Among the patient and control groups included in the study, 244 were girls and 196 were boys. No significant difference was found in terms of gender. 57% of 25-OH vitamin D levels were <20 ng/dl and 32% were within the normal range (20-30 ng/dl). The average age of the groups was 5.14±3 years. No feature was detected in 71% of the groups in the skin prick test. The mean 25-OH vitamin D level was 19±8.5 ng/dl. The average total IgE value was found to be 149.6±12 kU /L (**Table 1**).

Table 1: 25-OH vitamin D distribution of patient and control groups

	25-OH vitamin D (ng/dl)			Total
	<20 ng/dl	20-30 ng/dl	>30 ng/dl	
Group				
Patient	178	28	14	220
Control	74	115	31	220
Total	252	143	45	440

Scorad index of patients with atopic dermatitis was reported as 42 mild, 106 moderate, and 72 severe. 25-OH vitamin D level and eosinophilia value in peripheral blood were found to be statistically significant. No significant difference was found between the patient and control groups in terms of parents' age, parents' education level, living place, weight, height, and body mass index (BMI) (p>0.05).

IgE level measured between the patient and control groups (p>0.05). 25-OH vitamin D levels were found to be significantly lower in patients with atopic dermatitis than in the control group (p=0.0). 65% of the control group consisted of patients diagnosed with allergic rhinitis and 30% with asthma. In our study, no significant relationship was found between 25-OH vitamin D level and scorad index (p<0.05).

Aeroallergen and food sensitivity were recorded by performing a skin prick test. No feature was detected in 71%. Pollen allergy was observed in 10%. Egg yolk positivity was the most common in the atopic dermatitis group.

Table 2: Statistical differences between the patient and control group (p<0.05*)

	Patient	Control	p
25-OH vitamin D (<20ng/dl)	178	74	0.00**
Gender			0.46
Girls	121	123	
Boy	99	97	
Height (3-25p)	83	62	0.13
Weight (3-25p)	71	68	0.78
BMI (3-25p)	72	69	0.86
Living place (city)	119	124	0.35
Eosinophil level in peripheral blood (4% -8%)	97	69	0.00**

DISCUSSION

Geographic differences play an important role in the development of all allergic diseases. In the study conducted by Lee et al.[8],it was concluded that allergic diseases develop more frequently in children living in apartments. This risk was found to be higher in atopic dermatitis. In our study, no significant difference was found between those living in urban and rural areas. This difference may be due to the fact that the study was conducted in a similar geographical region.

In our study, female gender diagnosed with atopic dermatitis was more common. This situation is compatible with the literature. 25-OH vitamin D levels were found to be lower in the atopic dermatitis group compared to other allergic diseases. In the study conducted by Çiçek et al.[9] 25-OH vitamin D levels were found to be significantly low in patients with atopic dermatitis, similar to our study. Again, in this study, eosinophil levels were found to be high, similar to our study, but no significant relationship was found between specific IgE levels.

In the study conducted by Raj et al.[3] no significant difference was found in the 25-OH vitamin D level in patients with atopic dermatitis, but the Scorad Index difference was measured between before and after vitamin D treatment, and 4.8 weeks and final measurements were made and a significant decrease in the Scorad index was observed. Vitamin D treatment is thought to directly increase the production of peptides with antimicrobial activity, such as cathecesins, in the skin. They suggested that corticosteroids used in the treatment of[10] atopic dermatitis reduce vitamin D synthesis.

CONCLUSION

We concluded that 25-OH vitamin D level is more important in atopic dermatitis compared to other allergic diseases. However, larger studies are needed to determine the effects of vitamin D.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Balıkesir University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (Date: 23.08.2023 Decision No: 2023/114).

Informed Consent

Since the study was designed retrospectively, no written informed consent forms were obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study had no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Özlem Kemer Aycan

I completed my undergraduate education at Manisa Celal Bayar University Faculty of Medicine in 2011. Between 2016 and 2020, I completed my assistantship at Balıkesir University Faculty of Medicine, Department of Child Health and Diseases. I completed my compulsory service as a Child Health and Diseases Specialist at Balıkesir Dursunbey State Hospital between 2021-2023. In 2023, I continue to work as a doctoral faculty member at Balıkesir University Faculty of Medicine, Department of Child Health and Diseases.

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Does autoimmune disease affect in vitro fertilization results in normo-responder cases?

Mehmet Ağar[1], Belgin Devranoğlu[2], Halime Çalı Öztürk[3]

[1]Private Clinic, Şanlıurfa, Turkiye
[2]Department of Obstetrics and Gynecology, Zeynep Kamil Women and Children's Diseases Training and Research Hospital, Health Sciences University, Istanbul, Turkiye
[3]Department of Obstetrics and Gynecology, Bezmialem University, Istanbul, Turkiye

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Corresponding Author: Halime Çalı Öztürk, drhalime@hotmail.com

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ABSTRACT

Aims: This study aimed to assess the effects of autoimmune disorders on pregnancy outcomes in infertile women undergoing in vitro fertilization (IVF) treatment.

Methods: This retrospective cohort study was conducted between March 2022 and September 2023, involving 90 infertile women without autoimmune diseases as a control group and 96 infertile women with autoimmune diseases as a case group. The study investigated the impact of autoimmune diseases on IVF treatment outcomes. Single embryo transfer (ET) was performed on the fifth day in all patients. Autoimmune diseases included in this study as Hashimoto's disease, Rheumatoid Arthritis, Sjogren's syndrome, Systemic lupus erythematosus (SLE), Ulcerative Colitis, and Behcet's disease.

Results: There was no statistically significant association between the case and control groups regarding live birth rate ($p>0.05$). Similarly, no statistically significant association was found between the case and control groups concerning the clinical pregnancy rate ($p>0.05$). Our results revealed that total oocyte, pronuclear (PN), and metaphase II (MII) oocyte rates were statistically significantly higher in healthy infertile women ($p<0.05$). The number of attempts, anti mullerian (AMH) levels, total gonadotropin dose, and total days were similar between the groups ($p>0.05$).

Conclusion: Autoimmune diseases do not significantly affect pregnancy outcomes in women undergoing IVF. However, several factors, such as total oocyte, PN, and MII oocytes, clinical pregnancy rate (CPR), and live birth rate (LBR) levels, support the association between autoimmune diseases and IVF outcomes.

Keywords: Autoimmune disease, clinical pregnancy rate, in vitro fertilization, pregnancy outcomes, infertility

INTRODUCTION

Infertility is defined as the inability to achieve pregnancy after one year of unprotected and regular sexual relations.[1] Assisted reproductive technology (ART) has served as a solution to the problem of infertility since 1978.[2,3] Over the past few decades, ART has expanded and undergone significant improvements.[4,5] Despite the millions of recorded live births through ART, there remain numerous frustrated couples experiencing failed attempts.[6] The likelihood of successful live birth with in vitro fertilization (IVF) is contingent on various factors, including maternal age and the underlying cause of infertility.[7] The identification of factors influencing the success rate of IVF remains a contentious issue in obstetrics and gynecology studies.[8,9]

An autoimmune disease is characterized by the aberrant functioning of an individual's immune system, wherein the body produces antibodies that mistakenly target and attack its own tissues.[10] Cases of autoimmune diseases predominantly occur in youth and middle age, affecting at least 7% of individuals and exhibiting a higher prevalence in women than men.[11,12] In the early years of recognizing autoimmune diseases, it was advised that affected women should avoid pregnancy.[13] Scholars have posited that autoimmune diseases may exacerbate during pregnancy, potentially leading to adverse consequences for both the mother and the fetus.[13,14] Over time, substantial information has been gathered regarding the impact of various autoimmune diseases on pregnancy outcomes and the potential exacerbation of the mother's condition during pregnancy.[15] In the last 20 years, the management of these diseases during pregnancy and the overall quality of life for patients have undergone positive changes.[16]

The immune system plays a crucial role in the process of fertilization and the maintenance of pregnancy.[17] As half of

the fetus originates from the father, it is perceived as a foreign entity by the mother's body, prompting a response from her immune system. In a successful pregnancy, the mother's immune system undergoes adaptation to recognize, accept, and tolerate the developing fetus.[1] However, if the mother's immune system is compromised due to autoimmune diseases, it may struggle to adapt to the fetus. In such situations, there is a risk of preventing the embryo's implantation, ultimately leading to abortion.

This study explored the association between autoimmune diseases, such as Hashimoto's and Rheumatoid Arthritis, and the outcomes of IVF treatment. The primary objective was to investigate whether autoimmune diseases are linked to pregnancy outcomes following IVF treatment. Another aim was to determine whether these diseases should be routinely taken into account in the management of infertile women undergoing IVF.

METHODS

This retrospective study was conducted on infertile women between March 2022 and September 2023. Approval from the local ethics committee was obtained from Bezmialem Vakıf University Hospital Ethics Committee (Date: 06.11.2023; Decision No: 2023/291). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion criteria comprised infertile women of reproductive age (20-45 years) with primary or secondary infertility and those undergoing their first cycle of IVF. Exclusion criteria encompassed repeated pregnancy loss, ovarian hyperstimulation syndrome, chronic diseases, cardiovascular problems, endocrine diseases, infertility attributed to severe endometriosis, and uterine abnormalities.

Autoimmune diseases included in this study as Hashimoto's disease, Rheumatoid Arthritis, Sjogren's syndrome, Systemic lupus erythematosus (SLE), Ulcerative Colitis, and Behcet's disease. The case group comprised 96 infertile women with autoimmune diseases, while the control group consisted of 90 infertile women without any diseases.

IVF pregnancy is achieved through the following stages: egg collection, retrieval of a sperm sample, fertilization, embryo culture, and subsequent transfer of a fresh or frozen blastocyst to the uterus. A single embryo transfer was conducted on the fifth day for all patients. Parameters such as the number of attempts, anti mullerian hormone (AMH) levels, total gonadotropin dose, total days, total oocytes, fertilization-ready metaphase II (MII) oocytes, pronuclear (PN) status, and the number of cryopreserved embryos were measured in both the case and control groups.

Statistical Analyses

The normality of the quantitative data was assessed using the Kolmogorov-Smirnov test and histogram graphs. Upon reviewing the normality test results, a Mann–Whitney U test was employed to compare numerical parameter values between groups. Descriptive statistics for the data were reported using Median (M) and Interquartile Range (IQR). Categorical variables were described in terms of number and percentage and analyzed using a Chi-square test. Statistical analysis was performed using SAS statistical software, with the threshold for statistical significance set at a p-value of less than 0.05.

The G-Power 3.2 program was utilized to estimate the sample size. The calculation for the difference between two independent proportions was conducted using a Mann–Whitney U test with a power of 80%, effect size of 50%, and a type 1 error of 0.05, requiring a minimum of 146 patients.18

RESULTS

This investigation included one hundred eighty-six age-matched (32, range: 30.75-36) and body mass index (BMI)-matched (24, range: 23-25) infertile women. Table 1 provides a statistical description of age, BMI, number of attempts, AMH, total gonadotropin dose, total days, total oocytes, MII oocytes, PN status, the number of cryopreserved embryos, clinical pregnancy rate (CPR), and live birth rate (LBR).

As depicted in **Table 1**, the frequency of autoimmune diseases in the current study is as follows: Hashimoto (85.5%), Rheumatoid Arthritis (5.3%), Sjogren's syndrome (2%), SLE (3.2%), Ulcerative Colitis (2%), and Behcet (2%).

Table 1. Statistical description of study parameters in infertile women (n=186)

Study parameters	Median (IQR) or n (%)
Age (years)	32 (30.75-36)
BMI (kg/m²)	24 (23-25)
Number of attempts	1 (0-2.25)
AMH (ng/ml)	1.40 (1.3-1.6)
Total gonadotropin dose	2250 (2000-2250)
Total days	10 (9-11)
Total Oocyte	10 (8.75-11)
MII	9 (8-9)
PN	9 (8-9)
The number of cryopreserved embryos	2 (2-2)
Clinical pregnancy test results	
Positive	110 (59.1)
Negative	76 (40.9)
Live birth	
Yes	99 (53.2)
No	11 (5.9)
The autoimmune disease frequency	
Hashimoto	82 (85.5)
Rheumatoid Arthritis	5 (5.3)
Sjogren's syndrome	2 (2)
SLE	3 (3.2)
Ulcerative Colitis	2 (2)
Behcet	2 (2)

SD, standard deviation; n, number; BMI, body mass index; AMH, anti Mullerian hormone, MII, metaphase II; PN, pronuclear; SLE, systemic lupus erythematosus

As shown in **Table 2**, the Mann–Whitney U test did not identify a statistically significant difference between normo-responder women with autoimmune diseases and healthy women in terms of age and BMI (p>0.05). There was no statistically significant difference between infertile women with autoimmune diseases and the control group regarding AMH levels (p>0.05). The median and interquartile range of AMH levels in the case and control groups were 1.4 (1.3-1.6) and 1.4 (1.3-1.52), respectively. The number of attempts,

AMH, total gonadotropin dose, total days, and the number of cryopreserved embryos were similar in the two groups (p>0.05). However, total oocytes, MII oocytes, and PN status were significantly higher in the control group (p<0.05).

As presented in **Table 2**, the chi-squared test did not identify a statistically significant difference between normo-responder patients with autoimmune diseases and healthy women in terms of CPR (p>0.05). The CPR in the groups with autoimmune diseases and the healthy groups were 53 (55.2%) and 57 (63.3%), respectively.

Similarly, as indicated in **Table 2**, the chi-squared test did not find a statistically significant difference between normo-responder women with autoimmune diseases and healthy women in terms of LBR (p>0.05). The LBR in the groups with autoimmune diseases and the healthy groups were 46 (47.9%) and 53 (58.9%), respectively.

Table 2. Comparison of the normo-responder women with autoimmune diseases and healthy groups

Study parameters	Case group (n=96) Median (IQR) n (%)	Healthy group (n=90) Median (IQR) n (%)	p-value
Age (years)	31 (30-36)	33 (31-36.25)	0.162*
BMI (kg/m²)	24 (22.25-25)	24 (23-25)	0.720*
Number of attempts	1 (0-2)	1 (0-3)	0.738*
AMH	1.4 (1.3-1.6)	1.4 (1.3-1.52)	0.833*
Total gonadotropin dose	2250 (2000-2250)	2250 (2000-2250)	0.876*
Total days	10 (9-11)	10 (9-11)	0.821*
Total oocyte	9 (8-10)	10 (9-11)	0.001*
MII oocytes rate	8 (8-9)	9 (8-10)	<0.001*
PN	8 (8-9)	9 (8-9.25)	<0.001*
The number of cryopreserved embryos	2 (2-2)	2 (2-2)	0.12*
Clinical pregnancy			0.260**
Positive	53 (55.2)	57 (63.3)	
Negative	43 (44.8)	33 (36.7)	
Live births			0.296**
Yes	46 (47.9)	53 (58.9)	
No	50 (52.1)	37 (41.1)	

* A Mann–Whitney U test **A chi-squared test. n, number; BMI, body mass index; AMH, anti Mullerian hormone, MII, metaphase II; PN, pronuclear; SLE, systemic lupus erythematosus

In **Figure 1**, the bar chart depicts the number of positive clinical pregnancies and the live birth rate between infertile women with autoimmune diseases and healthy groups. It is evident that the CPR decreased slightly from 63.3% to 55.2% in women with autoimmune diseases. The LBR is relatively lower in women with autoimmune diseases compared to healthy women (47.9% vs. 58.9%).

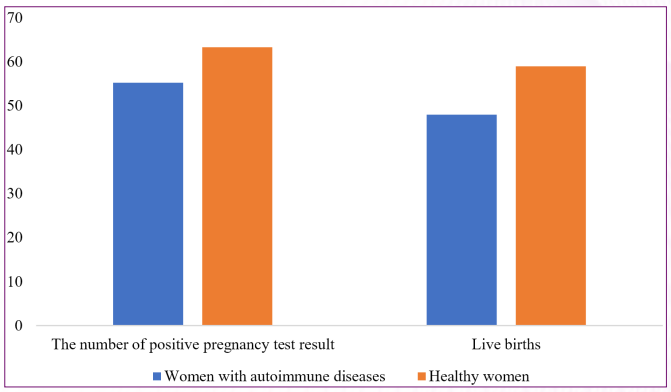

Figure 1. Comparison of CPR and LBR between groups

DISCUSSION

In our study, CPR and LBR were relatively higher in healthy women; however, this difference was not statistically significant. The autoimmune diseases + group exhibited a significantly lower rate of MII oocytes, PN status, and total oocytes. In this study, autoimmune diseases had no significant effect on IVF treatment outcomes.

The production of various antibodies can lead to immune system disorders. Previous studies have explored the impact of these antibodies on implantation failure and IVF treatment outcomes, yielding contradictory results. Antinuclear antibodies (ANA) target normal proteins in the nucleus of the body's cells and may indicate autoimmune diseases such as dermatomyositis, scleroderma, SLE, rheumatoid arthritis, and Sjögren's syndrome.[19]

Berestoviy et al.[20] reported that antiphospholipid, antithyroid, and ANA in recipients of oocyte donations did not affect their pregnancy results. Chen et al.[21] in a prospective cohort study with 3763 women, found no association between ANA, anti-thyroperoxidase, and antithyroglobulin antibodies and IVF/ intracytoplasmic sperm injection (ICSI) outcomes, aligning with our results. Li et al.[22] in a case-control study with 380 women, observed an association between ANA and poor IVF-ET treatment outcomes. Li et al.[23] suggested that ANA positivity might pose a risk factor for IVF/ICSI treatment but may not be the sole reason for poor outcomes.

Contrastingly, Zhu et al.[24] reported adverse effects of ANA on IVF-ET treatment outcomes and recommended prednisone plus low-dose aspirin adjuvant treatment to increase the implantation rate in IVF-ET. Ying et al.[25] highlighted the detrimental impact of ANA in follicular fluid on IVF outcomes. These studies present varying results compared to the current study.

Ticconi et al.[26] in a comprehensive meta-analysis and systematic review, investigated the potential relationship between ANA and IVF treatment outcomes and pregnancy complications. They reported lower implantation and pregnancy rates among ANA-positive women compared to healthy women, suggesting that ANA may have a detrimental effect on IVF results. However, in some studies, such as the results of the present study, this effect may not reach statistical significance.

Thyroid autoimmunity occurs when the body produces antibodies that target the cells in the thyroid. The detrimental impact of these antibodies on ART results has been reported in previous studies.[27] However, in recent years, there has been no consistent relationship between this condition and IVF outcomes, and the findings are conflicting.

Weghofer et al.[28] demonstrated that thyroid autoimmunity has a negative effect on live births and CPR results in IVF treatment outcomes. In contrast, Busnelli et al.[27] found that thyroid autoimmune disease does not influence implantation and clinical pregnancy rates, although live births and the risk of miscarriage increased in women with thyroid autoimmune disease. A large retrospective cohort study by Bliddal et al.[29]

reported that thyroid autoimmunity in infertile euthyroid women was not associated with LBR or embryo quality. Rao et al.[30] reported that thyroid autoimmunity in women was not linked to live births or embryo quality following IVF/ICSI. Similarly, the retrospective cohort study by Hamad et al.[31] showed that thyroid autoimmune disease did not adversely affect CPR.

In summary, the current study suggests no detrimental impact of autoimmune diseases such as Hashimoto and Rheumatoid Arthritis on IVF outcomes in Turkish infertile women. However, certain factors, including CPR and LBR levels, lean towards a potential association between autoimmune diseases and IVF/ICSI outcomes. The findings reveal relatively higher CPR and LBR in healthy women. The apparent absence of a significant relationship between autoimmune disorders and pregnancy outcomes suggests that testing for autoimmune diseases may not be necessary for women undergoing their first IVF treatment.

Nevertheless, further investigation with a larger sample size and randomized controlled trials is necessary to substantiate the potential impact of autoimmune diseases on IVF results. Additional studies involving normal pregnant women are also essential to comprehensively understand the relationship between autoimmune diseases and infertility. These results have reignited the discussion, prompting scientists to conduct more substantial investigations to gain deeper insights into the matter.

Limitations

The current study has several limitations. Firstly, the study size is small, and data were collected from a single center, underscoring the need for future studies with larger participant pools and conducted across multiple centers. While the study investigated the impact of autoimmune diseases on the female reproductive system of infertile Turkish women, it is recommended that future research explore each autoimmune disease separately. This approach would allow for a more detailed and accurate examination of their respective effects on IVF treatment outcomes.

CONCLUSION

The findings of the current study suggest that autoimmune diseases do not have a significant impact on pregnancy outcomes in women undergoing IVF. However, certain indicators, such as CPR and LBR levels, somewhat support a potential association between autoimmune diseases and IVF/ICSI outcomes. While CPR and LBR were relatively higher in healthy women, the differences were not statistically significant. The results of this investigation may offer valuable insights when formulating treatment programs for women undergoing IVF. Nonetheless, further studies are crucial to enhance our understanding of the effects of autoimmune diseases on the success rate of IVF.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Bezmialem Vakıf University Hospital Ethics Committee (Date:06.11.2023; Decision No:2023/291).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study had no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Mehmet Ağar

I graduated from Cerrahpaşa Faculty of Medicine in 1997. In the same year, my residency program years started at Bakırköy Maternity, Women and Children's Health Hospital. Between 2001 and 2002, I worked as a research fellowship at Temple University (Philadelphia-USA) for a year to conduct studies on urogynecology and high-risk pregnancies. After becoming an obstetrics and gynecology specialist in 2003, I worked at Private Şanmed Hospital in Şanlıurfa, then I went to Acıbadem University Hospital for endoscopy and robotic surgery training, and to Memorial Hospital for IVF and reproductive endocrinology training. I have been working in my own clinic since 2018.