Original Article

Investigating the frequency of non-alcoholic fatty liver by women with polycystic ovary syndrome and infertility in Ahvaz

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a metabolic disorder and women with PCOS have a high prevalence of non-alcoholic fatty liver disease (NAFLD). Although hyperandrogenism and insulin resistance are common pathophysiologies in NAFLD and PCOS, the relationship between these two diseases is still controversial. The present descriptive-analytical study examined patients who referred to Imam Khomeini Hospital in Ahvaz because of infertility in 2023 and the diagnosis of PCOS was confirmable based on the Rotterdam criteria. The study investigated NAFLD based on the results of liver ultrasound and liver enzyme tests, and calculated the frequency of NAFLD. 28 patients (31.11%), from among 90 women with PCOS, had NAFLD. As the results of an examination of various laboratory, clinical and metabolic parameters showed, there was a significant relationship between individuals with NAFLD and those without NAFLD in the liver enzymes AST and ALT and BMI in women with PCOS, so that the level of liver enzymes AST and ALT was higher in individuals with NAFLD than those without NAFLD. No significant relationship was observed in other parameters such as Cholesterol,FBS, 2hpp, blood pressure, underlying disease, FSH, LH, AMH and testosteronee,frequency of hirsutism and menses pattern . The results of the present study reported a high prevalence of NAFLD in women with PCOS, which it is associated with the increase in the level of liver enzymes AST and ALT and it is significantly more in obese people.

Keywords: Polycystic ovary syndrome, Non-alcoholic fatty liver disease, Infertility,liver enzymes

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of diseases in which hepatic steatosis is observable with or without inflammation and fibrosis, and there are no other secondary causes such as alcohol consumption for steatosis. This disease makes up a spectrum from a benign condition, which means non-alcoholic fatty liver, to its most severe form, which is non-alcoholic osteohepatitis (NASH). NAFLD can progress to cirrhosis and is probably one important cause of cryptogenic cirrhosis. NAFLD is observable worldwide, but is more common in Western and industrialized countries because the Western lifestyle is associated with risk factors for the disease, including central obesity, type 2 diabetes, dyslipidemia, and metabolic syndrome. As studies conducted in the United States of America show, the prevalence of non-alcoholic fatty liver disease in the United States is 10-46% (1, 2). Studies on liver biopsies of patients have shown NAFLD in 3 to 5% of cases. The prevalence of 6 to 35% (median 20%) has been reported in the world. Most

of the patients are between 40 and 50 years old at the time of diagnosis of non-alcoholic fatty liver disease. Studies on the prevalence of men and women have been different. Some show a higher prevalence in women and some show a higher prevalence in men (3). Various studies on the higher prevalence of this disease in women have proposed the relationship between polycystic ovary syndrome (PCOS) and NAFLD disease. For example, the prevalence of non-alcoholic fatty liver in patients with polycystic ovary syndrome was 55% compared to 20% of healthy people in a study in New York. Polycystic ovary syndrome is a common hormonal disorder that affects 5-10% of women. Polycystic ovary syndrome, like all syndromes, comprises a set of symptoms that may be seen together or alone (4). So women with polycystic ovary syndrome do not have the same symptoms. A woman must have two of the three symptoms to be diagnosed with polycystic ovary syndrome: ovulation disorder (irregular periods), high testosterone levels (hyperandrogenism) and the shape of the ovaries on ultrasound (polycystic ovaries). Such studies are necessary because of the complications of non-alcoholic fatty liver disease, the heavy economic burden of this disease, the years of life lost, the consequences of polycystic ovary syndrome and the lack of sufficient information. As studies show on the Covid-19 disease, women who have polycystic ovary syndrome are at a higher risk of cardio-metabolic diseases such as type 2 diabetes, NAFLD, and high blood pressure, all of which are risk factors for the Covid-19 disease (5). The results of some studies revealed that the risk of contracting covid-19 in women with polycystic ovary syndrome increases by 51%, compared to women of the same age and people without polycystic ovary syndrome (18.1 cases per 1000 women with polycystic ovary syndrome compared to 11.9 cases per 1000 women without polycystic ovary syndrome) (6). Thus, the present study determines the frequency of fatty liver by women with polycystic ovary syndrome and infertility who referred to [] in 2023.

Materials and Methods

This study was descriptive-analytical. Patients who referred (From September 2022 to September 2023) for infertility and were diagnosed with polycystic ovary syndrome based on the Rotterdam criteria are included in the study after obtaining the permits. Then they were checked for having non-alcoholic fatty liver disease based on the results of liver ultrasound and liver enzyme tests, and the frequency of non-alcoholic fatty liver disease was calculated in them. The prepared questionnaire was completed based on the information of the patient through his/her informed consent.

The inclusion criteria for entering the study are: All patients with polycystic ovary syndrome and infertility and with non-alcoholic fatty liver or without alcoholic fatty liver based on the opinion of a specialist doctor. The exclusion criteria were the incompleteness of medical records. Researchers, after receiving the permits from the university, examined all patients through a census. The data were collected via a checklist and based on the patient's tests and medical records.

Results and Discussion

The average age of the patients from among 90 patients under study is 25.71 The standard deviation is 8.96, the minimum age is 18 and the maximum age is 38. 1.1% have anemia, 14.4% have hypothyroidism, 84.4% have no underlying disease .**1** people (1.1%) has BP 140/90 and 99.9% have normal BP.Table 1 shows the frequency of laboratory finding in women with PCOS and infertility with or without NAFLD,out of 90 patients under study, in 4 people (4.4%) ASTlevel is high and in 96 people (98.8 %) is normal, 4 people (4.4%) ALT level is high and 96 people (98.8 %) is normal. 82 people (91.1%) have normal FBS, 7 people(7.7%) have IFG , 1 people (1.1%) has DM. 2hpp in 86 people (95.5%) is normal and 4 people (4.4%) have DM. TG level in 9 people (10%) is high and 81 people(90%) are normal. Table 5. shows the Prevalence of BMI in women with PCOS and infertility with or without NAFLD, 3people(3.3%) underweight,18 people (20%) normal weight, 34people (37.7%) overweight and 35 people(38.8%) have obesity. 1 people is with amenorrhea (1.1), 85 people with oligomenorrhea (94%), 4 people with Regular (4.4%). Table 4, shows the frequency of PCO in ultrasound, out of 90 patients under study, 8 people (8.8%) have NL, 82 people (91.1%) have PCO view in ultrasound. The frequency of hirsutism, 24 people (26.7%) are negative and 66 (73.3%) are positive out of 90 patients under study. The relationship between the average age in women with polycystic ovary syndrome and infertility with NAFLD and without NAFLD has been measured through an independent t-test, and there is no significant difference in age between the two groups. There is no significant difference in blood pressure between women with polycystic ovary syndrome and infertility and women with or without NAFLD measured through an independent t-test. The relationship between frequency of liver enzymes and TG, Cholesterol, FBS,2 hpp in women with polycystic ovary syndrome and infertility and those with NAFLD and without NAFLD has been measured through an independent t-test. There is a significant difference between AST and ALT in women with polycystic ovary syndrome and infertility with or without NAFLD (Table 1). We have determined the relationship between the frequency of underlying diseases in women with polycystic ovary syndrome and infertility with or without NAFLD by using chi-square test. There is no statistically significant relationship between the two groups (Table 2). We determined the relationship between the frequency of hirsutism in women with polycystic ovary syndrome and infertility with or without NAFLD by using a chi-square test. There is no statistically significant relationship between the two groups (Table 3). We determined the relationship betweenBMI in women with polycystic ovary syndrome and infertility with or without NAFLD by using chi-square test. There is a significant relationship between the two groups .We have determined the relationship between the frequency of underlying diseases in women with polycystic ovary syndrome and infertility with or without NAFLD by using chi-square test. There is no statistically significant relationship between the two groups It has been determined the relationship between menses pattern in women

with polycystic ovary syndrome and infertility with or without NAFLD by using chi-square test. There is no statistically significant relationship between the two groups. The relationship has been measured between frequency of FSH, LH, AMH and testosterone in women with polycystic ovary syndrome and infertility with or without NAFLD through an independent t-test. There is no significant difference between the frequency of FSH, LH, AMH and testosterone in women with polycystic ovary syndrome and infertility with or without NAFLD. It has been determined the relationship between PCOS in women with polycystic ovary syndrome and infertility with or without NAFLD by using the Chi-square test. 28 patients had fatty liver out of 90 patients under study, of which 24 (85.7%) had PCO in ultrasound and there is no a statistically significant relationship between the two groups.

Table 1. Relationship between laboratory finding in women with PCOS and infertility with or without NAFLD

Variable	Classification	Fatty liver		p-value
		No	Yes	
		Frequency (percentage)	Frequency (percentage)	
AST	Less than 40	62(100)	24(85.7)	0.004
	More than 40	0(0)	4(14.3)	
ALT	Less than 40	62(100)	24(85.7)	0.004
	More than 40	0(0)	4(14.3)	
TG	Less than 200	56(90.3)	25(89.3)	0.87
	More than 200	6(9.7)	3(10.7)	
Cholestrol	Less than 200	58(93.5)	23(82.1)	0.09
	More than 200	4(6.5)	5(17.9)	
FBS	Less than 100	57(91.9)	25(89.3)	0.63
	Between 100 to 125	4(6.5)	3(10.7)	
	More than 125	1(1.6)	0(0)	
2hpp	Less than 140	61(98.4)	25(89.3)	0.06
	Between 140 to 199	0(0)	0(0)	
	More than 140	1(1.6)	3(10.7)	

Table 2. Prevalence of underlying diseases in women with polycystic ovary syndrome and infertility with or without NAFLD

Variable	Classification	Fatty liver		p-value
		No	Yes	
		Frequency (percentage)	Frequency (percentage)	
Underlying disease	Anemia	1(1,6)	0(0)	0.85
	Hypothiroidism	9(14.5)	4(14.28)	
	No	52(83.8)	24(85.7)	

Table 3. Frequency of hirsutism in women with polycystic ovary syndrome and infertility with or without NAFLD

Variable	Classification	Fatty liver		p-value
		No	Yes	
		Frequency (percentage)	Frequency (percentage)	
Hirsutism	Negative	19(3,6)	5(17,9)	0.15
	Positive	43(69,4)	23(82,1)	

Table 4. Frequency of PCO and fatty liver in ultrasound in women with PCOS and infertility with or without NAFLD

Variable	Classification	Fatty liver		p-value
		No	Yes	
		Frequency (percentage)	Frequency (percentage)	
PCO	Negative	4(6.4)	4(14/3)	0.06
	pco	58(93.5)	24(85/7)	

Table5. frequency of BMI in women with pcos and infertility

Variable	Classification	Fatty liver		p-value
		No	Yes	
		Frequency (percentage)	Frequency (percentage)	
BMI	Less than 18.5	3(4.8)	0(0)	0.006
	Between 18.5 to 24.9	16(25.8)	2(7.1)	
	Between25 to 29.9	26(41.9)	8(28.6)	
	More than 30	17(27.4)	18(64.3)	

The present study on the frequency of NAFLD disease in women with PCOS and infertility in Ahvaz showed that 28 patients (31.11%) had NAFLD disease out of 90 women with PCOS. The association between NAFLD and PCOS has received much attention and confirmation in recent years. Even researches showed that women with PCOS have a higher prevalence than NAFLD disease compared to the general population. Current researches place the prevalence of NAFLD in women with PCOS at 15–55%; this wide range is because of differences in diagnostic criteria. While most of these studies only include overweight (BMI = 25-30) and obese (BMI > 30) patients with PCOS, researches have also shown an increased prevalence of NAFLD in normal weight individuals (BMI < 25). So we should note that the probability of NAFLD development and progression may be independent of BMI (6). The average BMI was 28.91 in the present study, which shows that most of the participants were

overweight, similar to the other studies in this field. NAFLD was observable in both groups of young girls and adolescents with PCOS, which can explain the possibility of its development at any age. Recent studies have reported worldwide ethnic differences in the prevalence of NAFLD in women with PCOS. Several studies have examined racial and ethnic differences in metabolic syndrome in women and girls with PCOS, but there are few studies on racial and ethnic differences in women with PCOS and NAFLD. Several studies have shown a higher prevalence of NAFLD in women with PCOS compared with women without PCOS in different geographic regions, ethnicities, and races despite the emphasis of researches on White populations (7). A study by Karoli et al. (2013) on a population of Indian women showed NAFLD was present in 67% of women with PCOS compared to 25% in women without PCOS (8). Mehrabian et al. (2016) noted NAFLD in 38.7% of women with PCOS versus 18.7% of women without PCOS in a group of Iranian women (9). 2 studies in China showed that the rate of NAFLD in women with PCOS was approximately 1.7 to 1.8 times higher than in women without PCOS (32.9% vs. 18.5% and 44.6% vs. 24.6%, respectively) (10, 11). Another study by Cai et al. (2017) on Chinese women showed that the rate of NAFLD assessed by ultrasound in PCOS women (56.23%) was slightly higher (1.48 times) than in women without PCOS (38%) (12).

A group of researchers found that Mexican women with PCOS (69.3%) were twice as likely to have NAFLD as Mexican women without PCOS (34.6%). It suggests that Mexican ethnicity may be an independent risk factor for the development of NAFLD (13). Indeed, the prevalence of NAFLD (69.3%) in Mexican women with PCOS is one of the highest reported for any ethnic-racial group. Another study showed that NAFLD is over 3 times more common in Hispanics than in non-Hispanics, so we can say that Hispanics are 2 times more likely to develop NASH than non-Hispanics (14). Thai researchers in a study on South Asian women reported a high prevalence of NAFLD (39.6%) in women with PCOS, and concluded that this disease is common in this population (15). The results of various studies show that the low prevalence of NAFLD seems reasonable in studies that include only non-obese people with low HOMA-IR (Homeostatic model assessment for insulin resistance) index (18, 19). The prevalence of NAFLD in women with PCOS was 68% and in the control group it was 33.3% in the study of Pett et al. in Italy. Subjects in the Italian study had a different ethnicity and were older, fatter, and metabolically unhealthy compared to the population of the current study (20). The present study showed that there is no significant relationship between the average age of women with PCOS and infertility in people with NAFLD and without NAFLD. However, the high prevalence of NAFLD in women and girls of different ages with PCOS compared to those without PCOS is of great importance. Most of the studies in this field have focused on pre-menopausal women between the ages of 25 and 40, with limited information on girls and adolescents. Interestingly, some studies have shown, despite the emphasis of researches on adult women with PCOS that NAFLD also occurs in girls with PCOS (21-24). A study on 39 obese adolescent females with PCOS showed elevated ALT levels, which reveals liver dysfunction in 15.4% of the girls (21). Another study reported similar results in a group of young obese girls, in which hepatic steatosis was observable in 49% of girls with PCOS compared to 14% of girls without PCOS (22). It is noteworthy that all the girls who took part in these 2 studies were obese and if girls with a wider range of BMI had been considered, the results may have been different. The current study on various laboratory, clinical and metabolic parameters showed that there was a significant relationship between individuals with NAFLD and those without NAFLD only in average liver enzymes AST and ALT in women with PCOS, so that the average level of Hepatic enzymes of AST and ALT were higher in individuals with NAFLD than those without NAFLD. No significant relationship was observable in other parameters such as Cholesterol, FBS,2hpp, blood pressure, underlying disease, FSH, LH, AMH and testosterone. Indeed, the results show that the prevalence of NAFLD in PCOS can be about the mechanisms that link NAFLD to PCOS syndrome; obesity and insulin resistance (IR) are characteristics that are common in patients with PCOS and hyperandrogenism, the dominant feature of PCOS as very common factor in the development of NAFLD.

Hyperandrogenism may have direct and indirect effects on the liver by modulating insulin sensitivity and increasing visceral fat. Insulin resistance/hyperinsulinemia contributes to hyperandrogenism by affecting the production, clearance, and bioavailability of ovarian androgens (26). A study by Hong et al. (2023) assessed the independent relationship between hyperandrogenism by free testosterone and FAI and NAFLD by all three indicators in the PCOS population, and the results showed that the total testosterone level was not associated with any indicator of NAFLD (13). A research on Asian Indian women with PCOS, in contrary to the results of the present study, found that testosterone level was significantly increased in women with PCOS and NAFLD compared to women with PCOS alone ($P > 0.01$), and claimed that hyperandrogenism is an independent predictor for NAFLD (27). A study by Vassilatou et al. measured free androgen indices specifically; increased FAI values were in this research significantly ($P = 0.002$) associated with an increased prevalence of NAFLD, and revealed that hyperandrogenism may directly contribute to the development of NAFLD (28). One reason of the lack of correlation between androgen levels in PCOS patients with NAFLD in the current study can be because of the low sample size. Current researches suggest that high levels of biological androgens play an important role in PCOS-related NAFLD, as they have been associated not only with the presence of NAFLD but also with the risk of its development (11). The findings of recent studies show that not only is hyperandrogenism significantly associated with the presence of NAFLD in women with PCOS, but this association is often independent of other factors such as BMI and/or IR (12). However, some of studies have not shown an association between hyperandrogenism and NAFLD (10, 25). A study by Cree-Green et al. assessed 49% of adolescent girls with PCOS hepatic steatosis compared to 14% in the control group, but it did not find a relationship between liver fat percentage and

measured androgen levels (25). The present study showed that there was no significant relationship between the frequency of hirsutism, menses pattern and PCOS appearance in women with PCOS syndrome and infertility with or without NAFLD. There is no study on the relationship between the main characteristics of PCOS syndrome, including hirsutism, menses pattern, and PCOS appearance, and NAFLD disease. Our examination is one of the strengths of the present study. However, determining the exact role of NAFLD in the main characteristics of PCOS syndrome needs studies with a larger sample size. Some limitations of the present study include the low sample size, the lack of investigation of the relationship between PCOS syndrome and NAFLD in different ethnicities and races, the lack of investigation of the relationship between the specific index of PCOS syndrome and the indicators of NAFLD disease and other characteristics of metabolic syndrome along with the control of a number of variables, the lack of investigating the prevalence of NAFLD in PCOS syndrome according to NAFLD indicators and the lack of investigating the prevalence of NAFLD in women without PCOS to determine the exact relationship.

Conclusion

The results reported a high prevalence of NAFLD in women with PCOS syndrome, which has not have a significant relationship with parameters such as age, Cholesterol, FBS, 2hpp, blood pressure, underlying disease, FSH, LH, AMH and testosterone. But it is associated with an increase in the level of liver enzymes AST and ALT and BMI. However, more studies with a higher sample size are necessary, so that they investigate the prevalence of PCOS syndrome with NAFLD in different ethnic groups and races and the relationship between PCOS syndrome indicators and NAFLD disease indicators and other features of metabolic syndrome along with control for finding an exact relationship between these two diseases. Because interventions in patients with premenopausal PCOS can be an important measure to reduce the risk of progression to advanced liver disease.

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