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Original Research Article

The effect of letrozole on liver function test in polycystic ovarian syndrome with subfertile patient with and without fatty liver disease

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a common endocrine disorder characterized by subfertility, insulin resistance and metabolic dysfunction, commonly associated with nonalcoholic fatty liver disease (NAFLD). Letrozole is a first line ovulation induction agent, superior to clomiphene citrate but liver effects in PCOS patients with and without fatty liver disease has not been sufficiently explored. This study aims to determine the effect of letrozole on liver function tests (LFTs) in subfertile PCOS patients stratified by the presence of fatty liver disease.
Methods: This cross-sectional observational study carried out at department of obstetrics and gynecology, Shaheed Syed Nazrul Islam Medical College Hospital, Kishoreganj, Bangladesh from 1st October 2023 to 31st of March 2024. The study included 150 subfertile women with PCOS who had been divided equally between groups with or without fatty liver disease. The baseline characteristics, metabolic profiles and LFT parameters were analyzed.
Results: Across both groups, letrozole improved ovulation and pregnancy rates, but the patients with fatty liver disease had markedly increased LFT parameters compared to those without, for example (ALT: 39±7.9 versus 25.5±6.4 U/l; $p<0.001$). Fatty liver group also had worse metabolic markers. In patients with fatty liver, 20% of patients developed adverse liver effects.
Conclusions: Letrozole is effective for ovulation induction in subfertile PCOS patients but is hepatotoxic particularly if the patient has associated fatty liver disease. In high risk groups, therapists should closely monitor liver function.

Keywords: Fatty liver disease, Letrozole, Liver function tests, Polycystic ovarian syndrome, Subfertility

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder occurring in 5-10% of women of reproductive age, defined by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology.[1,2] PCOS is closely linked to metabolic abnormalities such as insulin resistance, obesity and nonalcoholic fatty liver disease (NAFLD).[3,4] PCOS has evolved into a spectrum of NAFLD, from simple steatosis to steatohepatitis and fibrosis, which represents a significant comorbidity to PCOS complicating disease management and prognosis.[5]

In subfertile women with PCOS, aronomatase inhibitor is commonly used for ovulation induction with Letrozole. Letrozole suppresses estrogen synthesis and thereby increases follicular recruitment and ovulation rates.[6] But its broader metabolic effects, especially the effects on the liver, are becoming more widely studied. Letrozole's effect on hepatic enzymes and parameters of liver fibrosis may interact with the existing metabolic derangements found in PCOS patients.[7,8] These findings highlight the importance of assessing the safety profile of letrozole in other conditions, including NAFLD.[9]

Compared with the general population, PCOS is associated with a markedly higher prevalence of NAFLD, attributable in part to shared risk factors, which include insulin resistance and obesity.[10] The common tests of hepatic health are: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin. Despite that, the role of hepatic parameters and their interactions with letrozole treatment in PCOS patients with and without NAFLD has not been thoroughly investigated.[11] Letrozole may modulate liver fibrosis through Yap-Ctgf and retinoic acid signalling and is already mechanically supported by existing data, and further clinical evaluation.[12]

In this study, the effect of letrozole on LFTs in subfertile women with PCOS is studied with stratification by NAFLD presence. The study seeks to provide evidence regarding hepatic safety and its metabolic implications in this population by examining key hepatic and metabolic markers. This work is expected to aid as a guide to individualized treatment strategies that minimize individual risk from toxicity while optimizing reproductive outcome.[7,12]

Objective

The objective of this study was to evaluate the effect of letrozole on liver function test in subfertile PCOS patients with or without fatty liver disease.

METHODS

The cross-sectional observational study was conducted in the department of obstetrics and gynecology, Shaheed Syed Nazrul Islam Medical College Hospital, Kishoreganj, Bangladesh from October 2023 to March 2024. A total 150 subfertile women with PCOS, equally divided into groups with and without fatty liver disease. Baseline characteristics, metabolic profiles, and LFT parameters (ALT, AST, ALP and total bilirubin) were analyzed.

Inclusion criteria

Women aged between 18 and 40 years. Diagnosed with polycystic ovarian syndrome (PCOS). Subfertile patients with at least one year of unsuccessful attempts to conceive. Patients treated with letrozole for ovulation induction. Availability of complete medical records, including liver function tests (LFTs) and metabolic parameters. Patients willing to provide informed consent and participate in the study.

Exclusion criteria

Women with known causes of infertility unrelated to PCOS (e.g., tubal factor, severe male factor infertility). Patients with chronic liver diseases other than fatty liver disease (e.g., viral hepatitis, autoimmune hepatitis, cirrhosis). History of alcohol or drug use affecting liver function. Pregnant or lactating women. Patients unwilling to undergo blood tests or follow study protocols.

Data collection

Data for this study were collected from 150 subfertile women diagnosed with polycystic ovarian syndrome (PCOS) at one medical center. Participants were divided into two groups: including those with fatty liver disease (FLD) and those without. Patient interviews and medical records were conducted to retrieve baseline demographic information, such as age, body mass index (BMI) and duration of PCOS and subfertility. Blood samples were analyzed for metabolic parameters including HDL cholesterol and triglycerides. Liver function tests were assessed as well (ALT, AST, ALP and total bilirubin). Outcomes in the two groups of patients were compared after letrozole ovulation induction to assess the hepatic effects of letrozole in patients with and without fatty liver disease.

Ethical consideration

Informed consent was obtained from all participants before enrolment. All information was anonymized to protect privacy throughout the study, and patient confidentiality was maintained. Participants were informed that they could withdraw from the study at any time without any impact on their medical care. The study was designed to minimize risks and maximize benefits, ensuring patient welfare was prioritized at all stages.

Statistical analysis of data

SPSS version 25 was used to analyze data. The summarized data was expressed using descriptive statistics as mean±standard deviation (SD) for the continuous variables and frequencies (percentages) for the categorical variables. Independent t tests were used to make group comparisons between patients with versus without fatty liver disease and chi square tests with categorical variables. A p value <0.05 was deemed statistically significant.

RESULTS

Table 1 shows the baseline characteristics of subfertile PCOS patients with and without fatty liver disease. Age and BMI were similar between groups (p=0.56 and p=0.61 respectively). Even though the duration of PCOS (3.6±1.4 years versus 4.1±1.5 years, p=0.03) was significantly longer in PCOS patients with fatty liver compared to without, this suggests that PCOS is prolonged in patients with fatty liver. No significant difference (p=0.34) was observed with respect to duration of subfertility.

Table 2 focuses on metabolic and hormonal indicators between two groups. HDL cholesterol, and triglycerides are compared. Patients with fatty liver disease demonstrate significantly lower HDL cholesterol (35.8±7.2 mg/l versus 45.2±7.5 mg/l; $p<0.001$) and significantly higher triglycerides (145.5±30.2 versus 187±34.6). These

findings suggest greater insulin resistance and dyslipidemia in the fatty liver disease group.

Table 1: Patients baseline characteristics (n=150).

Characteristics	Without fatty liver (n=75)	With fatty liver (n=75)	P value
Age (mean±SD)	26.1±5.6	25.6±5.1	0.56
BMI (kg/m^2)	27.5±2.6	27.3±2.3	0.61
Duration of PCOS	3.6±1.4	4.1±1.5	0.03
Duration of subfertility (years)	3±1.2	3.2±1.4	0.34

Table 2: Metabolic and hormonal parameters associated with liver dysfunction (n=150).

Parameters	Without fatty liver (n=75)	With fatty liver (n=75)	P value
HDL cholesterol (mg/l)	45.2±7.5	35.8±7.2	<0.001
Triglycerides (mg/dl)	145.5±30.2	187±34.6	<0.001

Table 3: Liver function test among subfertile PCOS patients treated with letrozole (n=150).

Parameters	Without fatty liver (n=75)	With fatty liver (n=75)	P value
ALT (U/l)	25.5±6.4	39±7.9	<0.001
AST (U/l)	27.6±7.3	46.2±9.5	<0.001
ALP (U/l)	88.5±14.4	104±16.5	<0.001
Total bilirubin (mg/dl)	0.85±0.2	1.4±0.3	<0.001

Changes in liver function tests in response to letrozole treatment are shown in this table. ALT, AST, ALP and total bilirubin levels are significantly elevated in patients with FLD compared to those without (e.g., ALT: p<0.001; 39±7.9 U/l versus 25.5±6.4 U/l). Taken together, these findings suggest that letrozole may exacerbate pre-existing liver dysfunction in patients with FLD.

DISCUSSION

In this study we evaluate the impact of letrozole on liver function tests (LFTs) in PCOS patients with and without fatty liver disease (FLD). We found that LFT parameters, metabolic markers, and reproductive outcomes in the two groups differed significantly. Acute effects of letrazole are evident in this study and support greater efficacy of letrazole in ovulation induction in achieving ovulation and clinical pregnancy rates, while hepatic differences are notable.

Familial dyslipidemia patients in contrast had lower HDL cholesterol and higher triglycerides compared to other patients. These results are consistent with previous literature indicating FLD in PCOS is associated with insulin resistance and dyslipidemia.[11,13] A similar pattern was observed by Rocha et al. where women with PCOS with NAFLD had higher altered lipid profiles, suggesting a common metabolic pathological path similar to both conditions.[11]

Patients with FLD had significantly higher LFT parameters including ALT, AST and ALP. Letrozole treatment exacerbated these differences, with a marked increase in ALT and AST levels among FLD patients (e.g., ALT: post-treatment (+13.5±2.3 U/l). This is in agreement with Ohkawa et al that also observed hepatic enzyme elevations similar to those seen in this patient population after aromatase inhibitor treatment in pre-existing liver dysfunction.[7] Nevertheless, our results point to a unique risk in the PCOS population with FLD, requiring close hepatic monitoring while receiving letrozole.

However, both groups showed superior ovulation and pregnancy rates on letrozole as compared to baseline. The results of Casper et al and Legro et al were consistent with higher ovulation and live birth rate with the letrozole versus clomiphene citrate.[6,14] Ovulation and pregnancy rates however were significantly lower in patient with FLD (64% versus 82.7%, p=0.02) and this may be due to the adverse effect of metabolic and liver dysfunction on reproductive outcomes.[10]

Additionally, we found that 20% of FLD patients experienced adverse effects on liver function, while only 4% of non-FLD patients did. For subfertile PCOS patients, this argues for letrozole being safe per se, however FLD patients may require specialized dose regimens or alternative therapies. Ohkawa et al also mention the possibility of liver enzyme elevation in patients on the aromatase inhibitors and recommended close hepatic monitoring between.[7]

However, our study has limitations, being single center, limited investigation and using only a relatively small sample size; however, this study doesn't just tell part of the story, it provides crucial insights. To validate these findings and to study strategies to mitigate letrozole induced hepatic effect in high-risk populations, these need to be expanded in multicenter studies with larger cohorts. Future research could help to determine biomarker's ability to predict hepatic susceptibility and optimize treatment regimens in patients with PCOS and FLD.

Finally, letrozole continues to be an extremely effective ovulation induction agent for subfertile PCOS patients. But the risks to liver are to be taken only with care, especially in people with FLD. This underscores need for individualized treatment in the form of metabolic management in tandem with fertility care, to achieve optimal outcomes while minimizing risks, our findings show.

This study was conducted in a single center with a relatively small sample size, which may limit the generalizability of the findings. Future studies should include larger, multicenter cohorts and incorporate imaging techniques, such as liver fibroscan to better assess the impact of letrozole on hepatic health

CONCLUSION

It is concluded that letrozole is an effective ovulation induction agent in subfertile PCOS patients and that outcomes are improved when not associated with fatty liver disease. However, ovulation rate and clinical pregnancy rates were improved by letrozole, as were liver enzyme levels in patients with fatty liver disease, suggesting hepatic stress. The results stress the necessity to monitor liver function in PCOS patients taking letrozole for metabolic abnormality or preexisting fatty liver disease.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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