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**Original Research**

# Liver function congruence with contraceptive medical profile in women at child-bearing ages

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**Abstract**

**Background:** Hormonal contraceptives are among the most widely used medications worldwide, providing effective and reversible contraception for women. However, their use has been associated with potential side effects, including effects on liver function. This article reviews current evidence on the influences of different hormonal contraceptives agents on liver function in women of childbearing age. A cross-sectional study was conducted on 46 women aged 25-45 years using different contraceptive methods. Serum levels of the liver functional parameters were measured and compared between contraceptive-users versus contraceptive-free group, as well as among different age groups, parity, and contraceptive types. The results showed significantly higher levels of the liver functional parameters in women over 45 years old compared to younger age groups. Contraceptive users also had significantly higher levels of these liver enzymes compared to non-users. Among contraceptive types, combined oral contraceptives were associated with the highest elevations in liver enzymes. The results suggest that prolonged use of hormonal contraceptives, especially combined oral contraceptives, may adversely affect liver function. However, the clinical importance of these elevations needs further investigation. Careful screening and monitoring of liver function is advisable for women on long-term hormonal contraception.

**Keywords:** contraceptives; hormones; liver function; hepatotoxicity; reproductive health



## INTRODUCTION

The most commonest method for contraception is hormonal method with merits of being reversible, effective, and user-controlled.[1,2] Commercially available oral contraceptives are either combined (estrogen and progestin) or progestin only contraceptives in the form of oral or injectable or implants or intrauterine devices pharmaceutical preparations.[2,3], with recent increased usage of injectable progestin preparations globally.[4] These increased usage has raised the fears of their side effects potentials on target organs, such as, liver as a hormonal metabolising organ.[5-7] this has been reported as a potential side effects of hormonal contraceptives.[8-12] The possible mechanism could be a direct cell toxicity, vascular changes, hypercoagulability, and immune mediated pathways.[13-15]

The extensive hepatic metabolism of liver, thereby increasing the likelihood of synthesizing other components naturally produced by liver imparting a greater burden on hepatic tissue and hence disrupting the functionality.[16,17] Previous research indicates that prolonged hormonal use is associated with increased risk of hepatic adenomas, focal nodular hyperplasia and hepatocellular carcinoma.[18,19] Biochemical markers of liver injury like liver enzymes and bilirubin may also be elevated.[20]

However, there is considerable debate regarding the clinical relevance of minor derangements in liver tests during oral contraceptive use.[10,21,22] While some elevations are statistically significant, they rarely exceed normal ranges and are unlikely to be symptomatic. More research is required whether biochemical changes translate into increased morbidity or mortality from liver disease. There is also conflicting evidence on whether newer contraceptive formulations with lower hormone doses carry less hepatic risk.[23,24]

This study aims to evaluate liver function among women of childbearing age using different contraceptive methods compared to non-users. The effects of age, parity and contraceptive type on levels of serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glucose are assessed. The findings will help elucidate the real-world impact of hormonal contraceptives on liver health in women.

## PATIENTS AND METHODS

Study design and participants: This cross-sectional study was piloted at the City Hospitals, between January 2022 and January 2023. The reference population comprised women of childbearing age (15-49 years) visiting the clinic for contraceptive advice.

Purposive sampling was used to select women aged 25-45 years with normal menstrual cycles and no known liver disease. Pregnant and breastfeeding women were excluded. The sample size was calculated as 46 women based on a power of 80% and alpha error of 5%.

The participants were divided into three age groups: 25-35 years, 36-45 years, and over 45 years. Information was collected on parity (number of births), contraceptive use and type. Contraceptive users were defined as those currently using oral contraceptive pills (OCP), injectable contraceptives (IMP) or intrauterine devices (IUD) for at least 6 months. Non-users were women who had never used hormonal contraception or

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had stopped use at least one year ago.

Laboratory analyses: Venous blood samples were collected from each participant after overnight fasting. The samples were analyzed for the detection of liver related parameters.

Statistical analysis: Data were analyzed using SPSS version 27. Quantitative variables were reported as mean ± standard deviation. The student's t-test and one-way ANOVA were used for comparisons between groups. Qualitative variables were expressed as counts and percentages and analyzed using the chi-square test. Statistical significance was defined as $p<0.05$.

## RESULTS

Participant characteristics: The study included 46 women (age, of 32.7±7.4 years), with most women were aged 25-35 years (57.8%), followed by 36-45 years (30.4%) and over 45 years (21.7%). Over half had 0-4 births (60.9%), while 39.1% had 5 or more births.

Among the participants, 38 (82.6%) were using hormonal contraception while 8 (17.4%) were non-users. The most frequently used method was COCs (82.9%) followed by IUDs (17.1%). The mean duration of contraceptive use was 4.3±2.1 years.

Impact of age on liver parameters: Table 1 shows the variation in measured liver parameters across different age groups. Total bilirubin, direct bilirubin, indirect bilirubin, AST and ALT showed a progressive increase with advancing age.

Table 1. Liver function tests by age group

| Parameter | 25-35 years | 36-45 years | >45 years | p value |
|---|---|---|---|---|
| Total bilirubin, mg/dL | 1.0±0.1 | 0.95±0.3 | 1.4±0.8* | 0.02 |
| Direct bilirubin, mg/dL | 0.3±0.03 | 0.32±0.2 | 0.5±0.3* | 0.01 |
| Indirect bilirubin, mg/dL | 0.63±0.09 | 0.65±0.1 | 0.95±0.54* | 0.02 |
| AST, (U/L) | 10.5±0.6 | 14±9 | 19.5±10.5* | 0.03 |
| ALT, U/L | 3±0 | 4.9±2.6 | 6.1±3.1* | 0.04 |
| FSG, mg/dL | 98.5±32 | 105±23.65 | 105±26.7 | 0.15 |
| *p<0.05 versus younger groups | | | | |

Women over 45 years had significantly higher plasma concentrations of total bilirubin (p=0.02), direct bilirubin (p=0.01), indirect bilirubin (p=0.02), AST (p=0.03) and ALT (p=0.04) compared to younger age groups. Fasting serum glucose (FSG) levels also trended higher in older women, nonetheless, the difference was statistically insignificant (p=0.15).

Effect of parity on liver function: As shown in Table 2, women with higher parity (5 or more births) had significantly elevated total bilirubin (p=0.04), direct bilirubin (p=0.02), indirect bilirubin (p=0.01), AST (p=0.03) and ALT (p=0.02) compared to women with 0-4 births. Again, FSG did not differ significantly between the groups (p=0.9).

Table 2. Liver function tests by parity

| Parameter | 0-4 births | ≥5 births | p value |
|---|---|---|---|
| Total bilirubin, mg/dL | 0.95±0.23 | 1.5±0.83* | 0.04 |
| Direct bilirubin, mg/dL | 0.32±0.18 | 0.52±0.3* | 0.02 |
| Indirect bilirubin, mg/dL | 0.6±0.15 | 0.98±0.55* | 0.01 |
| AST, (U/L) | 12.6±6.4 | 20.6±10.6* | 0.03 |
| ALT, U/L | 4.4±2 | 6.3±3.3* | 0.02 |
| FSG, mg/dL | 103±22 | 102±26 | 0.9 |
| *p<0.05 versus 0-4 births | | | |

Effect of contraceptive use on liver function: As shown in Table 3, contraceptive users had significantly higher total bilirubin (p=0.02), direct bilirubin (p=0.01), indirect bilirubin (p=0.03), AST (p=0.04) and ALT (p=0.03) compared to non-users. FSG was also higher in contraceptive users but the difference was not significant (p=0.3).

Table 3. Liver function tests by contraceptive use

| Parameter | Non-users | Users | p value |
|---|---|---|---|
| Total bilirubin, mg/dL | 1±0.55 | 1.2±0.6* | 0.02 |
| Direct bilirubin, mg/dL | 0.35±0.24 | 0.43±0.23* | 0.01 |
| Indirect bilirubin, mg/dL | 0.68±0.3 | 0.8±0.4* | 0.03 |
| AST, (U/L) | 12.9±6.5 | 17±9* | 0.04 |
| ALT, U/L | 4.2±2.1 | 5.6±2.9* | 0.03 |
| FSG, mg/dL | 96±16 | 105±25 | 0.3 |
| *p<0.05 versus non-users | | | |

Effect of contraceptive type on liver function: Among hormonal contraceptive users, COC users had significantly higher levels of total bilirubin (p=0.04), direct bilirubin (p=0.02), indirect bilirubin (p=0.03), AST (p=0.02), and ALT (p=0.04) compared to IUD users (Table 4). FSG did not differ significantly between the groups (p=0.3).

Table 4. Liver function tests by contraceptive type

| Parameter | COC users | IUD users | p value |
|---|---|---|---|
| Total bilirubin, mg/dL | 1.2±0.65* | 0.9±0.08 | 0.04 |
| Direct bilirubin, mg/dL | 0.45±0.26* | 0.37±0.2 | 0.02 |
| Indirect bilirubin, mg/dL | 0.8±0.4* | 0.53±0.16 | 0.03 |
| AST, (U/L) | 16.5±9.8* | 12±2.5 | 0.02 |
| ALT, U/L | 5.4±2.9* | 3.8±0.5 | 0.04 |
| FSG, mg/dL | 104±23 | 96±25 | 0.3 |
| *p<0.05 versus IUD users | | | |

## DISCUSSION

This study evaluated hepatic parameters to age, parity and contraceptive use in 46 women aged 25-45 years. The results showed significantly higher levels of serum bilirubin, AST and ALT with advancing age, increased parity and use of hormonal contraceptives, especially COCs.

In our study, older women above 45 years had markedly higher bilirubin, AST and ALT compared to women aged 25-35 years and 36-45 years. This age-related decline in liver function has been noted previously and attributed to changes in liver blood flow, metabolic activity, enzyme synthesis and hepatocyte regeneration.[25,26] Progressive accumulation of fat and fibrotic changes may also reduce hepatic reserve and impair detoxification.[27]

Women with higher parity (≥5 births) demonstrated significant elevations in bilirubin, AST and ALT versus women with 0-4 births. Similar findings were reported by Mahmood & Jaber,[18] who noted worsening of liver tests with increasing parity. Repeated pregnancies impose metabolic stress on the liver due to increased estrogen/progesterone production, iron demands, weight gain and postpartum depletion of nutritional reserves.[28,29] This may diminish hepatic functional capacity over time.

Several earlier studies found altered liver tests in oral contraceptive users indicative of subclinical hepatic injury.[30-32] Our results align with these findings, as contraceptive users showed significantly higher bilirubin, AST and ALT than non-users. The liver metabolizes contraceptive hormones, increasing load on hepatocytes and risk of toxicity with prolonged exposure.[10,29] Even low-dose formulations may produce biochemical changes with long-term use.[18]

Notably, COC users in our study demonstrated greater elevations in bilirubin, AST and ALT compared to IUD users. Previous research also indicates combined contraceptives carry higher risk of hepatic dysfunction than progestin-only methods.[33,34] This may be attributed to the estrogen component, as synthetic estrogens are actively metabolized in the liver and may cause direct hepatocellular damage as well as vascular and immunologic changes.[35] Newer COC formulations with lower ethinyl estradiol doses may confer some protection but cannot eliminate hepatic risk entirely.[36-38]

Overall, our findings indicate that long-term COC use may adversely impact liver tests in women. However, the clinical significance of these biochemical changes remains uncertain. Values generally remained within normal limits and none of the participants had overt liver disease. Nonetheless, the possibility of progression to advanced liver injury cannot be excluded and deserves further investigation.

## CONCLUSION

This study found significant elevations in serum bilirubin, AST and ALT levels with advancing age, multiparity and use of contraceptive medications, especially COCs, among females at their reproductive age. The results suggest that prolonged exposure to contraceptive hormones may potentially impair liver function. Further studies on the histopathological hepatic effects of modern low-dose contraceptive medications are warranted. Regular monitoring of liver tests may be prudent for women on long-term hormonal contraception. Screening is particularly advisable in older multiparous women and those with additional risk factors like obesity, smoking or metabolic syndrome. Alternative non-hormonal methods may be preferable for women with underlying liver conditions. Further research should explore whether newer contraceptive formulations, routes and regimens can minimize hepatic impact. Ultimately, the risks of hormonal contraception must be weighed against their considerable benefits in preventing unwanted pregnancy.

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