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RESEARCH ARTICLE

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Influence of oral contraceptives on lipid profile and paraoxonase and commonly hepatic enzymes activities

Katarzyna Kowalska | Milena Ściskalska | Anna Bizoń | Mariola Śliwińska-Mossoń | Halina Milnerowicz

Department of Biomedical and Environmental Analyses, Uniwersytet Medyczny im Piastow Slaskich we Wroclawiu, Wroclaw, Poland

Correspondence
Bizoń Anna, Uniwersytet Medyczny im Piastow Slaskich we Wroclawiu, Department of Biomedical and Environmental Analyses, Wroclaw, Poland.
Email: a_bizon@op.pl

Background: The aim of the study was to verify the influence of oral contraceptives (OCs) on lipid profile and the arylesterase, lactonase and phosphotriesterase activities of paraoxonase 1 (PON1). Also commonly hepatic enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyltranspherase (GGT) were measured.

Methods: Lipid profile and hepatic enzymes were determined using commercial available reagents. Paraoxonase activities were estimated using earlier published procedures. Blood samples were collected from 120 women of similar age (22.6±1.0 years) with similar BMI (20.71±2.20 kg/m^2). Participations were divided into two groups: 74 females do not take (group A) and 46 women taking OCs (group B).

Results: Higher triglycerides and lower low-density lipoproteins levels were observed in group B than in group A) (56.9±19.7 mg/dL. Castelli risk index I was significantly higher in group B when compared to group A (P<.0001), whereas we did not observe any statistically significant differences in Castelli risk index II value between studied groups. In group B, increase in ALT, AST and GGT activities were found, while the de Ritis ratio was lower in group B than in group A.

In group B, lower phosphotriesterase activity and higher arylesterase and lactonase activities were found when compared to group A.

Conclusion: Higher ALT, AST and GGT activities in serum as well as changes in lipid profile and PON activities can indicate that OCs usage can cause disorder in these parameters in the serum of women taking OCs.

KEYWORDS
hepatic enzymes, lipid profile, oral contraceptives, paraoxonase

1 | INTRODUCTION

Oral contraceptives (OCs) are the most widely used method of contraception,[1] therefore, information on the risks and benefits of therapies is critically important. It was shown that the use of OCs increases oxidative stress.[2] There are several hypotheses for this increase.[3] One of them is the need to metabolize the hormone load from the OCs with the help of liver enzymes.[3] The crucial liver enzymes are aspartate aminotransferase (AST) (EC 2.6.1.1), alanine aminotransferase (ALT) (EC 2.6.1.2)[4] and γ-glutamyltransferase (GGT) (EC 2.3.2.2).[5] γ-glutamyltransferase is additionally a marker of oxidative stress. In the blood of women, an increase in GGT was reported to be positively correlated with oral contraceptive use.[2]

Oral contraceptives have been shown to alter lipid profile among various population groups with different patterns of dyslipidemia.[6] OC effect on lipid profile through the genomic pathway, in which estrogen receptor alterations affect hepatic apolipoprotein upregulation.[6] It has been suggested that contraceptive steroids might exert

their metabolic effects related to the synthesis and/or turnover of lipids and lipoproteins, including total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), and low-density lipoproteins (LDL).[7]

Estrogens and progestrogens used in oral contraceptive changes also paraoxonase activities (PON) (EC 3.1.8.1).[8] PON is a group of proteins present in three forms (PON1, PON2, PON3).[8,9] PON-1 has phosphotriesterase, arylesterase, and lactonase activities; PON-2 and PON-3 have lactonase activity but practically no paraoxonase or arylesterase activity.[10]

PON1 is produced in the liver and secreted into the blood, where it is associated with HDL and is able to prevent LDL oxidation (ox-LDL).[11,12] PON1 present in liver microsomes may also protect against oxidized phospholipids, environmental lactones and metabolism of drug containing lactone or cyclic carbonate.[13,14]

Although millions of young women use contraceptive pills, the exact effects of these OCs on liver damage, including alterations to paraoxonase, have been poorly investigated to date.

The aim of the study was to verify the influence of OCs on the arylesterase, lactonase and phosphotriesterase activities of PON1 in the blood of healthy young women. There is no information about the influence of OCs on the PON1 phosphotriesterase, arylesterase, and lactonase activities. In order to evaluate their role as markers of liver function, the ALT, AST, GGT activities and a lipid profile were measured. De Ritis ratio (AST/ALT ratio), Castelli risk index I (TC/HDL) and Castelli risk index II (LDL/HDL) also were calculated.

2 | MATERIALS AND METHODS

2.1 | Materials

Blood samples were collected from 120 healthy people aged 21-28. The study protocol was approved by the Local Bioethics Committee of Wroclaw Medical University (KB-141/2015). All subjects were of a similar age (22.6±1.0 years) and had a similar BMI (20.7±2.2 kg/m^2). A personal interview about the participants' health and nutritional habits and their use of dietary supplements/medications was carried out. Women who did not report any diseases or special diet (eg, vegetarian, Mediterranean) as well as did not used any prescribed medication and dietary supplements were admitted to the study. Healthy status also included medical history, physical examination, vital signs measurements (blood pressure, heart rate, and body temperature) and clinical laboratory tests (morphology, glucose and insulin concentrations, high sensitivity C-reactive protein).

Additionally women exposed to active and passive tobacco smoke were excluded from the study. Cotinine concentration (Cotinine ELISA test; ref. No.: EIA-3242, DRG International Inc., Springfield Township, NJ, USA), a metabolite of nicotine, was measured to confirm the lack of exposure to tobacco smoke. In order to exclude alcohol abusers from the study, the level of carbohydrate-deficient transferrin, a biomarker for long-term alcohol consumption, was estimated by using CEofix CDT kit for Beckman Coulter P/ACE MDQ Series; ref. No.: 844111036.

Participants were divided into two groups: A and B. Group A consisted of 74 females who did not take OCs. Group B was composed of 46 females taking OCs for a period of more than 1 year (monophasic pills containing 0.02 mg ethinyl estradiol and 3 mg drospirenone).

2.2 | Sample preparation

Venous blood was collected in the morning, after 8 hours of fasting. Serum was obtained according to the standard procedure by taking venous blood in trace element-free tubes with serum clotting activator (ref. No.: 03.1524.001, Sarstedt, Nümbrecht, Germany), left at 25°C to complete thrombosis, and centrifuged at 1200 g for 20 minutes. In order to obtain the plasma, blood was collected into trace element-free tubes containing heparin (ref. No.: 04.1931.001, Sarstedt), immediately gently mixed, and centrifuged (2.500 g/15 min). The obtained serum and plasma were portioned out and stored in sealed tubes (ref. No.: 0030102.002, Eppendorf, Hamburg, Germany) at −80°C until analysis.

2.3 | Laboratory analysis

The marker of lipid peroxidation (MDA) was measured in plasma using thiobarbituric acid, according to method described earlier.[15] The amount of MDA was measured spectrophotometrically at λ=535 nm at 25°C, calculated using an extinction coefficient (ε=156 mmol^{-1}/L/cm^{-1}) and was expressed as μmol/L.

Total cholesterol was measured in the serum using a reagent (ref. No.: 5017.1; BioMaxima, Lublin, Poland). Cholesterol was determined using enzymatic method. One of the reactions by products, H_2O_2, was measured quantitatively in a peroxidase-catalyzed reaction that produces a color, of which the intensity was proportional to cholesterol concentration. Absorbance was measured at λ=500 nm at 25°C.

Triglycerides were determined in the serum using a reagent (ref. No.: 5031.1; BioMaxima). Triglycerides were hydrolyzed to produce glycerol, then glycerol was oxidized using glycerol oxidase, and H_2O_2, one of the reaction products, was determined as described above for cholesterol. Absorbance was measured at λ=500 nm at 25°C.

High-density lipoproteins concentration was determined in the serum using a direct method with the test (ref. No.: 10300060, BioMaxima). In this method, all cholesterol fractions except HDL were blocked. High-density lipoprotein was subjected to the enzymatic reaction that involves the formation of color compounds. The amount of color product was proportional to the HDL concentration in the sample. The absorbance was measured at λ=600 nm at 25°C.

Low-density lipoproteins concentration was calculated using the Friedewald formula.[16]

Castelli risk index I (TC/HDL ratio) and Castelli risk index II (LDL/HDL ratio) were calculated according to Asare et al.[6]

Alanine aminotransferase activity was measured in plasma using a commercial reagent (ref. No.: 12701 99 10021, DiaSys Diagnostic Systems, Holzheim, Germany). Alanine aminotransferase catalyzed transferrin, the amino group from L-alanine, to 2-oxoglutarate, which led to pyruvate and L-glutamate formation. Then, pyruvate was

converted to lactate dehydrogenase. During this reaction, reduced nicotinamide adenine dinucleotide (NADH) converted to oxidised nicotinamide adenine dinucleotide (NAD^+). The activity of this enzyme was determined based on the speed of decrease in NADH concentration, which was measured at λ=340 nm at 37°C.

Aspartate aminotransferase activity was measured in the plasma using a commercial reagent (ref. No.: 12701 99 10021, DiaSys Diagnostic Systems). This enzyme catalyzed the transfer of amino groups from L-aspartate to 2-oxoglutarate and formed oxaloacetate and L-glutamate. Then oxaloacetate was converted to malate involving malate dehydrogenase. This was accompanied by the conversion of NADH to NAD^+. The AST activity was determined by the rate of decrease of NADH concentration, measured at λ=340 nm at 37°C.

The activity of GGT in serum was determined using a Reagent Kit (ref. No.: 1-228-0150, BioMaxima) with L-γ-glutamyl-3-carboxy-4-nitroanilide as a substrate and glycylglycine as an acceptor. The enzyme reaction was determined by the released yellow 5-amino-4-nitrobenzoate. The rate of absorbance increase measured at λ=405 nm was proportional to GGT activity. One U/L of GGT activity was defined as the amount of enzyme needed to catalyze 1 μmol substrate/L/min.

Phosphotriesterase activity of PON1 was determined at 37°C with paraoxon (ref. No.: 311-45-5; Sigma-Aldrich, Darmstadt, Germany) as a substrate, 100 mM Tris-HCl buffer (pH 8.5), 2 mM calcium chloride. Reaction was initiated by the addition of 100 μL of serum.[12] The enzyme assay was based on the estimation of p-nitrophenol at λ=405 nm. The molar extinction coefficient (18.053 $[\mu mol/L]^{-1}\ cm^{-1}$) was used to calculate enzyme activity. One unit of PON1 activity was expressed as 1 μmol of paraoxon hydrolyzed per minute at a temperature of 37°C.

Arylesterase activity of PON1 was determined according Eckerson et al. and Lixandru et al.[17,18] using phenyl acetate (ref. No.: 122-79-2; Sigma Aldrich, Germany) as a substrate at 37°C in a 100 mM Tris-HCl buffer (pH 8.0), 2 mM calcium chloride. The enzyme assay was based on the estimation of phenol production at λ=270 nm. The molar extinction coefficient (1310 $[mol/L]^{-1}\ cm^{-1}$) was used to calculate enzyme activity. One unit of PON1 activity was expressed as 1 μmol of phenyl acetate hydrolyzed per minute at a temperature of 25°C.

Lactonase activity of PON1 was determined by the method described previously,[19] using 1 mM dihydrocoumarin (ref. No.: 119-84-6; Sigma-Aldrich) in 50 mM Tris-HCl buffer (pH 7.0), 2 mM calcium chloride. The enzyme assay was based on the estimation of 3-(2-hydroxyphenyl)propionate production at λ=270 nm. The molar extinction coefficient, (1870 $[mol/L]^{-1}\ cm^{-1}$) was used to calculate enzyme activity. One unit of PON1 activity was expressed as 1 μmol of dihydrocoumarin hydrolyzed per minute at a temperature of 30°C.

The change in absorbance for phosphotriesterase, arylesterase and lactonase activities of PON1 was measured at 10 s intervals for 1-3 minutes using a spectrophotometer (SPECORD 40, Analytik Jena AG, Jena, Germany, ref. No.: 400280).

2.4 | Statistical analysis

The data was expressed as mean (standard deviation, SD) values. The normality of the variables was tested using the Shapiro-Wilk W test. Differences between groups were tested using the Student *t* test. When a lack of normal distribution and variance uniformity occurred, the differences between groups were analyzed by means of a non-parametric U Mann-Whitney test. Correlation was expressed by Spearman's rank correlation coefficients (*r*). In all instances, $P<.05$ was considered statistically significant. Statistical calculations were done using the Statistica Software Package, version 10.5 (Polish version: StatSoft, Krakow, Poland).

TABLE 1 Influence of oral contraceptives (OCs) on lipid peroxidation marker and lipid profile in women's blood

Parameters	Non-users OCs (group A)	Users OCs (group B)
MDA (μmol/L)		
Median	1.2	2.1*
Range	0.2-5.4	1.2-5.7
TC (mg/dL)		
Median	171.1	162.1
Range	82.0-254.7	122.4-213.7
TG (mg/dL)		
Median	61.2	75.3*
Range	31.6-127.0	44.8-122.2
HDL (mg/dL)		
Median	49.7	59.8
Range	16.2-102.4	14.2-97.8
LDL (mg/dL)		
Median	106.9	93.3*
Range	45.9-198.9	51.0-146.4
Castelli risk index I (TC/HDL)		
Median	1.2	2.9*
Range	0.2-6.0	2.1-11.1
Castelli risk index II (LDL/HDL)		
Median	2.3	1.6
Range	0.2-9.6	0.9-9.1

Reference range/value for: TC <200 mg/dL; TG 35-160 mg/dL (detection limit 10 mg/dL); HDL >35 mg/dL.
MDA, malondialdehyde; LDL, low-density lipoproteins; HDL, high-density lipoproteins; TC, total cholesterol; TG, triglycerides.
*Significant ($P<.05$) when compared to group A.

3 | RESULTS

3.1 | Blood biochemistry in study groups

Changes in lipid peroxidation and lipid profile in serum women taking or not take OCs were observed. MDA concentration was higher in group B when compared to group A. Statistically significantly higher TG concentrations were observed in group B ($P<.008$) than in group A, while LDL levels showed a statistically significant decrease in group B in comparison to group A ($P<.0369$). TC and HDL levels remained unchanged between women taking or not take OCs. When we have

analyzed Castelli risk index I (TC/HDL) we have found higher value in group B when compared to group A ($P<.0001$), whereas we did not observe any statistically significant differences in Castelli risk index II (LDL/HDL) (Table 1).

A statistically significant increase in ALT ($P<.007$) as well as AST activities in group B (OC users) when compared to group A, while the de Ritis ratio was lower in group B than in group A ($P<.025$). Higher GGT activity was found in serum of women taking OCs (group B) when compared to women not take OCs (group A) (Table 2).

There were observed changes in PON1 activities in women using OCs. The PON1 phosphotriesterase activity in group B was statistically lower ($P<.003$) when compared to group A, while a statistically significant increase in both PON1 arylesterase and PON1 lactonase activities in group B was observed ($P<.040$) (Table 3).

TABLE 2 Influence of oral contraceptives (OCs) on AST, ALT and GGT activities in women's blood

Parameters	Non-users OCs (group A)	Users OCs (group B)
AST (U/L)		
Median	17.9	30.5*
Range	3.4-38.4	9.4-148.8
ALT (U/L)		
Median	18.00	22.4*
Range	3.1-43.7	3.0-148.8
De Ritis ratio (AST/ALT)		
Median	1.0	0.6*
Range	0.2-4.4	0.1-5.8
GGT (U/L)		
Median	25.1	39.2*
Range	1.2-79.2	1.3-77.4

Reference value for: AST (for women) <31 U/L; ALT (for women) <31 U/L; GGT (for women) <32 U/L.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; the de Ritis ratio, AST/ALT ratio; GGT, γ-glutamyltransferase.
*Significant ($P<.05$) when compared to group A.

TABLE 3 Influence of oral contraceptives (OCs) paraoxonase activities in women's blood

Parameters	Non-users OCs (group A)	Users OCs (group B)
PON1 phosphotriesterase activity [U/L]		
Median	125.2	78.6*
Range	35.4-234.7	43.2-223.0
PON1 arylesterase activity [U/L]		
Median	166.6	188.4*
Range	133.5-217.1	141.6-281.9
PON lactonase activity [U/L]		
Median	9.2	12.3*
Range	5.4-15.2	6.0-19.6

*Significant ($P<.05$) when compared to group A.

3.2 | Correlation coefficients in oral contraceptives users

A positive correlation between TC and TG or LDL levels were found. Higher LDL level was correlated with lower HDL level. A negative correlation between HDL level and ALT or GGT activities were detected. Higher LDL level was accompanied by higher GGT activity. Higher ALT activity decreased the value of de Ritis ratio (AST/ALT ratio).

We noted positive correlation coefficients between PON1 phosphotriesterase activity and TC level, as well as between PON1 arylesterase activity and LDL level.

Negative correlation coefficients were observed between: PON1 phosphotriesterase activity and ALT activity, PON1 phosphotriesterase activity and de Ritis ratio and LDL and malondialdehyde (MDA) level (Table 4).

We did not observe any statistically significant differences between Castelli risk index I or II and analyzed parameters.

4 | DISCUSSION

The risk-benefit profile of any pharmacologic agent must be evaluated against risks connected with the events to be avoided.[20] OCs are metabolized in the liver and may have some adverse effects on the physiology and biochemistry of this organ.[4] The most useful biomarkers of hepatoxicity are ALT, AST and GGT. OC users had higher ALT, AST

TABLE 4 The correlation between estimated parameters in oral contraceptives (OCs) users

Correlated parameters	Correlation coefficient	
TC (mg/dL)—LDL (mg/dL)	$r=.7$	$P=.003$
TC (mg/dL)—TG (mg/dL)	$r=.5$	$P=.040$
HDL (mg/dL)—LDL (mg/dL)	$r=-.5$	$P=.044$
ALT (U/L)—HDL (mg/dL)	$r=-.5$	$P=.031$
ALT (U/L)—de Ritis ratio	$r=-.8$	$P=.001$
LDL (mg/dL)—GGT (U/L)	$r=.8$	$P=.002$
HDL (mg/dL)—GGT (U/L)	$r=-.6$	$P=.021$
PON1 phosphotriesterase activity (U/L)—ALT (U/L)	$r=-.9$	$P=.008$
PON1 phosphotriesterase activity (U/L)—de Ritis ratio	$r=-.6$	$P=.005$
PON1 phosphotriesterase activity (U/L)—TC (mg/dL)	$r=.5$	$P=.041$
PON1 arylesterase activity (U/mL)—LDL (mg/dL)	$r=.5$	$P=.040$
MDA (μmol/L)—LDL (mg/dL)	$r=-.8$	$P=.040$

LDL, low-density lipoproteins; HDL, high-density lipoproteins; TC, total cholesterol; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase the de Ritis ratio, AST/ALT ratio; GGT, γ-glutamyltransferase.

and GGT activities than non-users. According to other studies,[21] ALT and AST increased in the serum of OC users. However, the AST serum activity is considered a less specific biomarker of liver function than ALT activity.[22] Furthermore, the de Ritis ratio declined in OC users. Higher ALT activity was negatively correlated with value of de Ritis ratio (r=−.80). The usage of these steroid hormones has been shown to produce profound effects on the liver, although these effects are more physiological than pathological and they often return to normal soon after stopping treatment.[23]

γ-glutamyltransferase is a stronger predictor of disease risk than these other symptoms and markers.[24] γ-glutamyltransferase induces oxidative stress in the artery wall in the presence of free iron, and GGT also likely is an indicator of depleted supply of glutathione, especially in the liver,[24] which leads to a cascade of problems related to increased oxidative stress, therefore higher GGT activity in serum of OCs can indicate higher risk for development of diseases.

Progestogens and estrogens in OCs have many effects on lipid metabolism.[25,26] Alterations to serum lipids during OC intake depend on dosage; the hormonal components, ethinyl estradiol and progestogen; and the (anti-)androgenic activity of progesterone. Both constituents have counteracting effects on serum lipids. Estrogen may increase the production of TG and lipoproteins such as HDL, while it may decrease LDL levels.[26] Progestogens with androgenic activity can shift lipid and lipoprotein metabolism in a potentially unfavorable way.[27] Therefore, the novel progestogen drospirenone (DRSP), a 17α-spirolactone derivative with anti-androgenic properties, has been developed to reduce the impact on lipids when used for hormonal contraception.

High-density lipoproteins reduces the risk of atherosclerosis and has a cardiovascular protective effect, whereas LDL is thought to be a major contributor to heart disease.[28]

The study conducted in the blood of 1391 Pakistani women showed that long-term usage of OC containing progesterone (depomedroxyprogesterone acetate-DMPA) resulted higher TC, TG and LDL levels and lower HDL level in the blood, which could be associated with higher risk of cardiovascular diseases in the future.[29] Giribela et al.[30] have shown that taking OC containing estradiol and drospirenone during 6 months resulted a significant increase in TC and TG levels, but a non-significant changes in HDL and LDL levels when compared to non-OC users.

In the present study, a decrease in LDL levels was observed in the serum of OC users, which is in accordance with previous studies.[31-33] It was shown that the estrogen component of OCs enhances removal of LDL cholesterol and raises levels of high-density lipoprotein cholesterol.[29,34] Another reason for the decrease in LDL concentration may be its oxidation, because in the plasma of OC users, we observed an increase of MDA concentration, the marker of lipid peroxidation. The study conducted by Cauci et al.[35] showed increased oxLDL and lipid peroxides levels in the blood of OC users compared with non-OC users, which indicates that OC usage can increase oxLDL not strictly LDL.

There were no changes in HDL levels between users and non-users of OCs, as in other studies,[28,36] which may mean that DRSP does not affect the level of this lipoprotein. Lower LDL was negatively correlated with HDL levels, which indicated favorable relationship between these parameters in the blood of OC users.

We found that TC levels did not change, but when we have analyzed the ratio between TC and HDL (Castelli risk index I) we have found statistically significant higher value of this ratio, which may be risk factors for cardiovascular disease.[37] Also Dilshad et al.[29] have observed higher Castelli I and II index in the group of women taking OC when compared to non-OC users.

In present study higher TG level in serum of OC users was found. A similar rise in TG levels was observed previously.[31,32,34] Estrogen increases lipogenesis, which results in elevated levels of TG. Increased triglyceride levels are considered a marker for cardio-metabolic diseases, and it has been suggested that long-term use of OCs might increase the risk of acute metabolic syndrome.[38]

Lipoproteins are closely associated with PON1. PON1 is HDL-associated and plays a vital role in the prevention of microvascular complications due to oxidative stress and against various toxic chemicals. Comprehensive structure-reactivity studies of PON1 have demonstrated that its native activity is lactonase and additionally that its arylesterase and phosphotriesterase activities are promiscuous.[39]

In the present study, an increase in PON1 arylesterase activity in the serum of OC users was observed. A previous study has reported that arylesterase activity reflects serum PON1 concentration.[40] It has been reported that PON1 has an important role in lipoprotein metabolism and its primary physiological responsibility is to protect LDL from oxidative stress modification.[11] The stress modification may be due to higher copper levels in women using OCs.[41] Estrogen induces ceruloplasmin synthesis in the liver, which leads to an increase in Cu levels in plasma. Cu initiates the oxidative stress and leads to the peroxidation of lipids. Therefore, the higher PON1 arylesterase activity may be associated with increased exposure to oxidative stress.

The present study showed lower PON1 phosphotriesterase activity in serum of women taking OCs in comparison to the women not taking OCs. Similar results were obtained by Ferre et al. (Ferré i in. 2002). Serum PON1 phospotriesterase activity have an important feature in that the measured value is inversely related to the degree of liver derangement, that is, it decreases while most of the standard laboratory test values increase with the extent of the disease.[42] In our study, PON1 phospotriesterase activity was negatively correlated with ALT activity and the de Ritis ratio. Furthermore, as mentioned above, the increase in plasma malondialdehyde concentration, a marker of oxidative stress, was observed in women using OCs. The PON1 active site for lipid peroxide hydrolysis requires a free sulfhydryl group at cysteine 284, and lipid peroxides react covalently with this site, leading to enzyme inactivation.[43]

The data on higher lactonase activity of PON1 in OC users when compared to non-users is new. It is known that PON1 metabolizes a number of drugs and pro-drugs via its lactonase activity,[44] which may be the cause of the increase in PON1 lactonase activity.

Serum PON1 activity has a high diagnostic accuracy when distinguishing patients with liver disease from control subjects and, when

added to a standard battery of liver function tests, increased the overall sensitivity.[45] Since standard biochemical tests for liver dysfunction are insufficiently sensitive for a reliable indication of the presence or absence of liver disease, PON1 phosphotriesterase activity may add especially valuable information in the assessment of liver damage.

In our study, higher ALT, AST and GGT activities in serum as well as changes in lipid profile and PON activities can indicate that OC usage can cause disorder in these parameters in the serum of women taking OCs.

5 | CONCLUSIONS

1. Higher activities of ALT, AST and GGT in the plasma of OC users confirm the adverse impact of OCs on the liver.
2. AST and ALT activities in the blood of contraceptive users should be monitored every year.
3. High AST/ALT value in the blood of contraceptive users is an important reason for discontinuation of oral contraception.
4. OCs using increase TG and decrease LDL levels in the serum.
5. Taking of OCs change PON1 activities in serum and resulted increase in lactonase (responsible for the detoxification of compounds containing aromatic rings) and arylesterase (which has an antioxidative function) activities and decrease phosphotriesterase activity.

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