Hemoinflammasome Potential of Oral Contraceptive Pills in Women at Child-Bearing Age

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ABSTRACT

Background and Objectives: Oral contraceptive pills are widely used for family planning worldwide. However, their effects on physiological processes including inflammation and iron homeostasis are not fully elucidated. The present study aimed to comprehensively evaluate the impact of oral contraceptives on serum ferritin as an indicator of iron stores, and C-reactive protein as a marker of inflammation, in women of reproductive age.

Methods: The study enrolled 100 women aged 21-45 years, comprising 50 oral contraceptive users and 50 non-users. Demographic and clinical data were gathered through questionnaires. Blood samples were collected for measurement of ferritin and C-reactive protein levels.

Results: The findings revealed significantly elevated serum ferritin and C-reactive protein in oral contraceptive users compared to non-users. Moreover, increasing body weight was positively correlated with higher ferritin and C-reactive protein concentrations among contraceptive users. Menstrual irregularities and increased abortion rates were also observed in oral contraceptive users relative to non-users.

Conclusion: The results highlight that long-term use of oral contraceptives may perturb iron homeostasis and provoke low-grade chronic inflammation in women of childbearing age. Additionally, overweight oral contraceptive users represent a particularly high-risk group warranting close monitoring of iron and inflammation markers. Further research into the intricate biomolecular mechanisms and downstream health impacts of altered ferritin and C-reactive protein levels with oral contraceptive use is recommended.

Keywords: C-reactive protein, Ferritin, Inflammation, Iron, Oral contraceptives, Reproductive age women.

INTRODUCTION

Oral contraceptive pills is the most common method of contraception in women globally[1]. The mechanism involve suppression of ovulation and hence inhibiting conception[2,3]. The success rate is up to 90% when properly used[4]. This effectiveness make their use the commonest method for family planning[5,6]. These pills contain hormones and thereby alter endogenous hormonal milieu leading to physiological imbalances with subsequent side effects[7].

In addition to inflammation, maintenance of systemic iron homeostasis is another critical physiological process that may be impacted by oral contraceptive use. As a vital player in oxygen transport and cellular metabolism, iron needs to be tightly regulated[8]. Ferritin, a key iron-binding protein, provides a storage depot for any excess iron in the body[9]. Oral contraceptives are known to alter the bleeding patterns in menstruating women, often reducing menstrual blood losses[10]. Since menstrual bleeding accounts for a substantial portion of iron loss in premenopausal women[11], the use of oral contraceptives and their effects on menstruation may consequently impact overall iron balance. Examining whether oral contraceptives lead to alterations in ferritin concentration can give valuable insights into any disturbance in iron metabolism. However, there remains a lack of comprehensive studies analyzing the effects of combined oral contraceptives on ferritin status as a marker of iron stores.

Despite their widespread acceptance and use over decades, surprisingly few studies have holistically evaluated the impact of oral contraceptives on key inflammatory and iron biomarkers in women. Understanding whether the long-term use of oral contraceptives provokes low-grade chronic inflammation or disturbs iron homeostasis could have major clinical implications. This knowledge can potentially guide improvements in the design and formulation of contraceptive pills to optimize safety. Therefore, given that oral contraceptives remain the foremost reversible contraceptive option utilized by millions of women globally, it is imperative that their effects on inflammation and iron metabolism are thoroughly investigated.

Accordingly, this study aimed to evaluate the effects of oral contraceptive pill use on serum ferritin concentration and C-reactive protein levels in women of reproductive age. The findings can provide insights into whether oral contraceptives are associated with increased inflammation and altered iron stores in this population.

PATIENTS AND METHODS

Study participants: The study recruited a total of 100 women in the age range of 21-45 years visiting the gynaecology outpatient clinic of the University Hospital. The participants comprised two equal-sized groups—50 women already using low-dose combined oral contraceptive pills (OCP users group) and 50 women who had never used any form of hormonal contraception (control group). For inclusion in the OCP users group, participants had to be aged between 21-45 years and using low-dose combined monophasic oral contraceptives containing ethinylestradiol and levonorgestrel for a minimum duration of 6 months. Women with any acute infections, chronic diseases, heavy menstrual bleeding, recent pregnancies or lactation, or taking any other medications apart from oral contraceptives, were excluded. The control group inclusion criteria were age 21-45 years, regular ovulatory menstrual cycles (21-35 days), no current or prior use of any kind of hormonal contraception including oral contraceptives. Exclusion criteria were the same as for the OCP user group. The purpose and

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protocol of the study were clearly explained to the participants and written informed consent obtained prior to recruitment. Confidentiality of all personal data was maintained. Approval for the study was obtained from the Institutional Ethics Review Board.

Collection of demographic and clinical data: A structured questionnaire was designed to gather relevant demographic details from the participants including age, body weight, place of residence, education level, and occupation. The questionnaire also recorded detailed obstetric and gynaecological history such as age of menarche, menstrual patterns, gravidity, parity, abortions, duration of oral contraceptive use, etc. Collating this information allowed for a holistic assessment of the participants' background characteristics as well as clinical variables that could potentially impact the parameters examined in the study.

Sample collection and analysis: Venous blood samples (5 mL) were collected in tubes without anticoagulant by antecubital venipuncture using sterile techniques. The blood samples were then centrifuged at 3000 rpm for 5 minutes to separate the serum. The separated serum was stored at -80°C until further analysis.

The concentration of ferritin in serum samples was estimated by electrochemiluminescence immunoassay (ECLIA) method[12,13] using the fully automated Roche Cobas e411 analyzer (Roche Diagnostics, USA)[14]. C-reactive protein levels in serum were measured by latex agglutination turbidimetry assay[15] on the semi-automated clinical chemistry analyzer Cobas Integra 400 Plus (Roche Diagnostics, USA). All samples were analyzed in duplicates and the mean of the two values reported as the final concentration.

Statistical analysis: Statistical analysis was performed using SPSS software version 27. Continuous data are presented as mean ± standard deviation (SD). Categorical variables are expressed as frequencies and percentages. The demographic information, clinical characteristics and measured biomarkers were compared between the oral contraceptive users group and control group by Student's t-test and Chi-square test. P value <0.05 was considered to indicate statistical significance.

RESULTS

Demographic profile of study participants: The demographic profile of the participants is presented in Table 1. The mean ages of the women in the OCP users group (32.5 ± 4.8 years) and the control group (31.7 ± 5.2 years) were comparable. However, the body weight was found to be significantly higher in the OCP users compared to controls (p<0.001), with a predominance of overweight and obese women in the OCP group. Though the majority of women in both groups resided in urban localities, no significant difference was observed in their place of residence. On the other hand, the education status varied considerably, with the OCP users having lower levels of education compared to the control group (p<0.05). Additionally, though not statistically significant, the occupation distribution showed a trend towards more housewives and lesser employed women among OCP users relative to controls.

Table 1. Demographic characteristics of the study participants

Parameter	Subgroup	Control (n=50)	OCP users (n=50)	p value
Age (years)	21-29	14	15	0.917
	30-39	26	26	
	40-45	10	9	
Body weight (kg)	50-60	2	0	<0.001
	61-70	23	5	
	71-80	22	23	
	>80	3	22	
Residence	Urban	40	42	0.444
	Rural	10	8	
Education	Graduate	25	18	0.029
	Secondary	18	18	
	Primary	5	10	
	Illiterate	2	4	
Occupation	Employed	19	15	0.243
	Housewife	31	35	

Gynaecological history of study participants: Table 2 summarizes the detailed gynecological history of the OCP users and control group participants. A key finding was that irregular menstrual cycles were significantly more prevalent among OCP users compared to controls (p<0.001). Though comparable numbers of women in both groups had children, the OCP users demonstrated a higher number of abortions relative to the control group (p<0.001). Among the OCP users, the duration of contraceptive pill use ranged from 6 months to over 5 years. These findings provide insights into the significant differences in menstrual patterns and abortion rates between oral contraceptive users and non-users.

Table 2. Gynecological history of the study participants

Parameter	Subgroup	Control (n=50)	OCP users (n=50)	p value
Menstrual cycle	Regular	47	31	<0.001
	Irregular	3	19	
Children	Yes	47	46	0.602
	No	3	4	
Abortions	0	47	29	<0.001
	1	3	16	
	2	0	2	
	3	0	2	
	4	0	1	
OCP use duration (months)	6-12	-	18	-
	13-24	-	10	
	25-60	-	13	
	>60	-	9	

Serum ferritin and CRP levels: The mean serum ferritin concentration was found to be markedly higher in the OCP users' group (65.5 ± 5.2 ng/mL) compared to the control group (33.4 ± 2.2 ng/mL) (p<0.001) (Table 3). Similarly, the CRP levels were significantly elevated in OCP users (10 ± 1.3 ng/mL) relative to the control women (5 ± 2 ng/mL) (p<0.001).

Table 3. Serum ferritin and CRP levels in the study groups

Parameter	Control (n=50)	OCP users (n=50)	p value
Ferritin (ng/mL)	33.4 ± 2.2	65.5 ± 5.2	<0.001
CRP (ng/mL)	5 ± 2	10 ± 1.3	<0.00

Further analysis revealed a positive association between increasing body weight and levels of ferritin and CRP among the OCP using group (Table 4). The highest ferritin (78.2 ± 6.8 ng/mL) and CRP (12.1 ± 1.5 ng/mL) concentrations were observed in OCP users with body weight over 80 kg. The increasing trend was statistically significant across incremental weight subgroups.

Table 4. Ferritin and CRP levels of OCP users across body weight categories

Body weight (kg)	Ferritin (ng/mL)	CRP (ng/mL)
50-60	36.4 ± 3.7	6.6 ± 0.9
61-70	44.3 ± 3.5*	9.7 ± 0.3*
71-80	49 ± 5.1**	10.3 ± 1.7**
>80	78.2 ± 6.8***	12.1 ± 1.5***

***p<0.05 versus previous weight subgroup
**p<0.05 versus previous weight subgroup
*p<0.05 versus previous weight subgroup

DISCUSSION

Oral contraceptive pills have become one of the most widely used reversible methods of contraception globally, owing to their effectiveness, ease of use, and good safety profile[16-18]. However, there remain lingering concerns about their long-term impact on physiological processes including markers of inflammation and iron status. The present study offers valuable insights into the effects of oral contraceptives on serum ferritin as an indicator of body iron stores, and C-reactive protein as a measure of inflammatory status, in reproductive-aged women.

Our findings demonstrate significantly higher serum ferritin concentrations in oral contraceptive users compared to non-users, aligned with earlier research[19]. The type of progestin appears to be an important determinant of the effects on ferritin, with new generation progestins linked to greater ferritin increases[20]. Reduced menstrual blood losses with oral contraceptives, especially newer low-dose formulations, likely contribute to enhanced iron retention[11,21]. The inverse relationship between ferritin levels and menstrual flow highlighted previously, supports this[22,23]. Overall, these results indicate that long-term oral contraceptive use may lead to expanded iron stores as reflected by higher ferritin levels.

We also found elevated CRP levels among oral contraceptive users compared to non-users, aligned with earlier evidence[24]. Rather than an inflammatory response, the CRP rise points to possible metabolic effects of contraceptive hormones[25]. Variations between studies could be related to differences in contraceptive formulations used[26,27]. Overall, the CRP elevation indicates activation of inflammatory processes, potentially increasing future cardiometabolic disease risk[28].

An important observation was the positive association between body weight and ferritin and CRP levels in oral contraceptive users. Overweight and obesity by itself impairs iron absorption due to inflammation but increases ferritin[29,30]. Oral contraceptives likely worsen the inflammatory and iron status disturbances in this subset. Therefore, overweight and obese women on oral contraceptives merit closer monitoring for inflammation and iron markers.

We also found that oral contraceptive use was associated with menstrual irregularities and increased abortion rates compared to non-use, indicating possible reproductive effects despite contraceptive action. The hormonal perturbations elicited by oral contraceptives may contribute to abnormal uterine bleeding patterns[31]. However, the precise mechanisms warrant deeper investigation.

Some limitations of our study include the cross-sectional design restricting causal interpretations, lack of dietary and lifestyle data, and the absence of other inflammatory biomarkers like TNFa and IL-6 which could have provided additional mechanistic insights. Still, by enabling direct comparison between users and non-users, our findings highlight clinically relevant aspects regarding the impact of oral contraceptives on iron and inflammation markers. Prospective longitudinal studies measuring a wider array of iron homeostasis and inflammatory parameters are recommended for more conclusive evidence.

CONCLUSION

In summary, long-term oral contraceptive use in women of reproductive age appears to be associated with alterations in iron stores and inflammatory status as reflected by higher ferritin and CRP levels. In particular, overweight and obese contraceptive users represent a subgroup requiring vigilant monitoring for iron excess and chronic inflammation. Further research on the complex mechanistic pathways and downstream health effects of disrupted iron homeostasis and low-grade inflammation with oral contraceptive use is warranted. Our findings can help guide improvements in oral contraceptive formulations to optimize their benefit-risk profile.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 12-14-2024

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