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Iron vs non-iron containing oral contraceptive pills effect on iron status

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ABSTRACT

Background: Contraceptives are generally the deliberate use of artificial methods to prevent pregnancy as a consequence of sexual intercourse. They can be divided into two types: hormonal contraceptives and non-hormonal contraceptives. A contraceptive pill inhibits ovulation by preventing the ovaries from releasing the ovum. Around 30% of the iron in the body is stored as ferritin or hemosiderin in he spleen, bone marrow, and liver. Menstruating women are known to be at risk of iron insufficiency, and the addition of iron in oral contraceptives have the benefit of increasing iron stores by decreasing menstrual iron loss as a novel strategy to manage iron deficiency. Iron containing oral contraceptives have the potential to be a cost-effective solution for the prevention and/or treatment of iron deficiency. **Objectives**: This study aims to assess Iron status in women using iron-containing oral contraceptives compared to that of non-iron-containing oral contraceptive users. **Methods**: the study was conducted on 48 female volunteers regularly visiting gynaecology clinics during the 4-month period. The study involved a questionnaire in addition to a laboratory test (serum ferritin test). Information about the type and duration of oral contraceptives used, demographic data, co-administration of iron supplements, history of major blood loss, tobacco use, and others were collected for each woman through a questionnaire in a face-to-face interview. **Results**: Comparison of serum ferritin results between iron and non-iron-containing oral contraceptive users, smokers and non-smokers was statistically significant. However, the comparison of serum ferritin results between all the subjects who consume meat, fish, tea and/or coffee shows no statistical significance. **Conclusion**: There was a significant difference in serum ferritin levels between subjects using iron-containing contraceptive pills and those using non-iron-containing contraceptive pills. The iron-containing contraceptive pills users had higher serum ferritin as an extra benefit to the known oral contraceptives' general benefit of increasing iron stores by decreasing menstrual iron loss.

INTRODUCTION

Oral contraceptive pills have an estimated 922 million users worldwide to meet the great human need for birth control with unrivalled effectiveness, allowing for family planning and pregnancy prevention. According to the data compiled by the United Nations Report Contraceptive Use by Method 2019, approximately 16% of women use oral contraceptives (Hasanat et al., 2017) (Fischer, Sasai, & Karakochuk, 2021). Contraceptives are generally classified into two types: hormonal contraceptives and non-hormonal contraceptives(Fischer et al., 2021). Hormonal contraceptives contain an artificially created form of two hormones naturally produced in the body, oestrogen and progesterone, which regulate a woman's menstrual cycle. They could be combined hormonal contraceptives (estrogen and progesterone) in pill or injection form or progestational agents: Progesterone-only pills (POPs), depot medroxyprogesterone acetate injection (DMPA), subdermal contraceptive implants, and progesterone-releasing intrauterine devices are examples (Hasanat et al., 2017). A contraceptive pill inhibits ovulation by preventing the ovaries from releasing the ovum. They also thicken cervical mucus, making impending sperm entry into the uterus more difficulties(Hasanat et al., 2017). Women who take combined oral contraceptives (COC) do not ovulate, so the endometrium lining undergoes cyclical changes. The menstrual periods that occur each month while using COC are unnatural and are referred to as "pill periods." The pill period occurs as planned withdrawal bleeding after continuously receiving hormones for three weeks and then withdrawing them on the fourth week (Shrader & Dickerson, 2008). Oral contraceptives are typically packaged in packets of 21 hormonal tablets followed by seven inactive placebo tablets. These placebo pills have no medical effect and are given to mimic natural menstruation by causing a withdrawal bleed while allowing women to continue the habit of taking one tablet daily (Fischer et al., 2021). In recent years, there has been increased interest in the changes in various metabolic processes and trace element profiles associated with using OCs. Changes in lifestyle, environmental factors, dietary habits, and active ingredients in hormonal agents have all been shown to affect micronutrient status in the human body (Hasanat et al., 2017). The OCP creates a change in the body's iron levels. The most noticeable effect of OCs on iron status is the reduction in menstrual blood loss that occurs for approximately 60–80% of women who use them, potentially resulting in lower menstrual iron losses. Females lose between 20 and 35 ml of blood per month on average, which equates to 11 mg of iron, but this can be as high as 80 ml of blood per month in some cases. Iron can also be lost through other means of blood loss, such as nosebleeds and blood donation. According to evidence from studies by Thein et al. and Nilsson and Solvell, OC users may lose only one-third to one-half the menstrual blood iron of non-oral contraceptive users. A clear inverse relationship exists between serum ferritin levels and menstrual bleeding duration. So, serum ferritin level is high in OC users (Fischer et al., 2021) (Frassineii-Gunderson, Margen, & Brown, 1985; Greig, Palmer, & Chepulis, 2010; Hasanat et al., 2017; Yeasmin, Haque, Yeasmin, & Amin, 2010). Studies found that OC users had much shorter menstrual periods than individuals who used alternative contraception methods, such as hormonal intrauterine devices (IUDs). For the purpose of minimizing the risk of anaemia and iron insufficiency among women, several manufacturers have recently begun to provide supplemental iron in place of the placebo tablets traditionally included (consumed during the week of the

withdrawal bleed)(Fischer et al., 2021). Iron Containing Oral Contraceptives (ICOC) can potentially be a cost-effective solution for the prevention and/or treatment of iron deficiency, one of the most common nutritional deficiencies worldwide, in some populations and/or circumstances (Fischer et al., 2021). Iron is a crucial element for almost all living organisms. About 65% of the iron in the body is bound with haemoglobin in red blood cells, and 4% is bound with myoglobin molecules. Around 30% of the iron in the body is stored as ferritin or hemosiderin in the spleen, bone marrow, and liver(Hasanat et al., 2017). Menstruating women are known to be at risk of iron insufficiency, and the addition of iron in oral contraceptives, a novel strategy to manage iron deficiency, is an alternative to iron or Iron Folic Acid (IFA) supplementation or fortification programs, could potentially help them. Nonetheless, more research is needed to determine the efficacy of ICOC in increasing haemoglobin concentration and iron status in terms of reducing and/or treating iron insufficiency. Given the extensive use of OCs worldwide, a thorough assessment of the advantages and risks of ICOC is required (Fischer et al., 2021).

METHODS

This study was conducted from January to April 2022 on 48 women, including 11 women who were attending the family planning clinic in Al-Wasiti health center to receive contraception, 9 OC users who were visiting their gynaecologist's clinic for a routine check-up in Kirkuk, and 28 women in Tikrit city participated in this study.

The study's inclusion criteria:

1. These women are currently married.
2. Ranging in age from 20 to 45.
3. Had to have used the OCs for at least 3 months before admission to the study.
4. No long-term iron supplement consumption
5. No recent major blood loss (trauma, surgery, etc.).

The study's Exclusion criteria:

1. Age under 20 or above 45 years.
2. Duration of oral contraceptives' use less than 3 months.
3. History of long-term iron supplement administration.
4. Women with recent major blood loss.

This study involved a questionnaire in addition to a laboratory test (serum ferritin test). Information about the type and duration of OC used, demographic data, co-administration of iron supplements, history of major blood loss, tobacco use, and others were collected for each woman through a questionnaire in a face-to-face interview. In setting the questionnaire's questions, the study relied on questionnaire data from another research (Haile, Teweldeberhan, & Chertok, 2016) with some modifications and adding applicable and more relevant questions to the study. At the interview, women's height and weight were measured. Blood samples were collected from groups. Serum ferritin was measured by the Immunofluorescence method for the rapid and quantitative determination of Ferritin using the test kit dedicated to the I-Chroma instrument (Boditech I-Chroma, Korea). Nineteen women were excluded. Seventeen of them had been taking iron supplements for a long period and had significantly higher serum ferritin than non-consumers, and two of them had recently suffered major blood loss. Leaving a total of 29 women for analysis.

This study aims to assess the Iron status in women using iron-containing oral contraceptives (ICOC) compared to that of non-iron-containing OC users. Also, to assess the effect of smoking on serum ferritin in female subjects and to assess the relationship of weight with serum ferritin.

Table (1): Illustrates types of oral contraceptives used by study subjects.

Iron-containing	**Microgynon®**	**Combined Oral Contraceptive**	**Levonorgestrel 150mcg Ethinylestradiol 30 mcg**
Non-iron containing	Sunya®	Combined Oral Contraceptive	Gestodene 75mcg Ethinylestradiol 20mcg
	Yasmin®	Combined Oral Contraceptive	Drospirenone 3mg Ethinylestradiol 0.03mg
	Microlut®	Progesterone only pill	Levonorgestrel 30mg

Statistical analysis: Data were analyzed by SPSS software version 20. Normality tests (Kolmogorov-Smirnov[a] and Shapiro-Wilk tests), independent sample test (T test), ANOVA test, and LSD test were used. P value <0.05 was considered statistically significant.

RESULTS

Table (2): Demonstrates the demographic characteristics of the whole study sample.

Variables	Frequency (f)	Percentage (%)
Age Groups		
20-30	11	37.9
31-35	8	27.6
36-40	7	24.1
>40	3	10.3
Total	29	100
BMI		
Normal	8	27.6
Overweight	14	48.3
Obese	7	24.1
Total	29	100
Education		
None	3	10.3
Primary	12	41.4
Secondary	9	31.0
institution / College	5	17.2
Total	29	100
Socio-economic status		

Poor	1	3.4
Medium	18	62.1
Good	10	34.5
Total	29	100
Number of children		
1-3	13	44.8
>3	16	55.2
Total	29	100

Table (2) shows the demographic characteristics of the entire study sample. According to the table, the highest percentage of age group (37.9%) was between (20–30) years. In terms of women's BMI, the table shows that the highest percentage of them (48.3%) were overweight. According to the level of education of women in the whole study, the primary school formed the highest percentage (41.4%). About socio-economic status, the table shows that the majority of them (62.1%) were of medium socio-economic status. In terms of the number of children, more than half of the subjects (55.2%) had >3 children.

Table (3): Demonstrates behavioural characteristics of the whole study sample.

Variables	**Frequency (f)**	**Percentage (%)**
Breast Feeding		
No	25	86.2
Yes	4	13.8
Total	29	100
Cigarette Smoking		
No	22	75.9
Yes	7	24.1
Total	29	100

Table (3) shows the behavioural characteristics of the whole study sample. Regarding breastfeeding, most women (86.2%) were not breastfeeding. Regarding cigarette smoking, most of them (75.9%) were non-smokers .

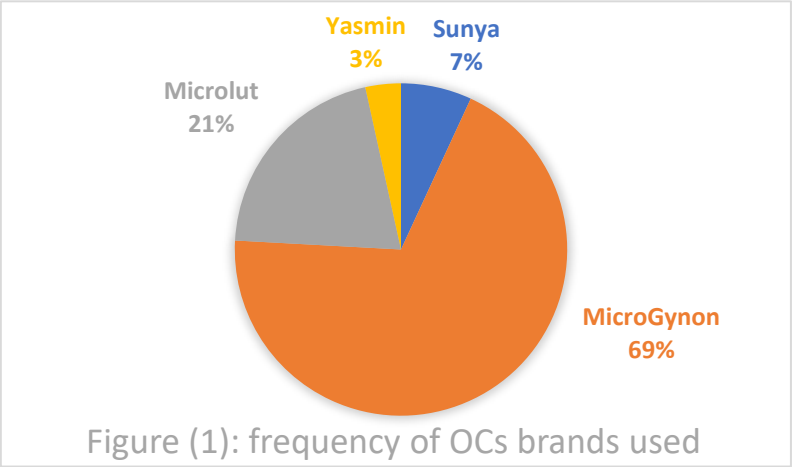

Figure (1): frequency of OCs brands used

Figure (1): Frequency of OCs brands used. This figure shows that most of the subjects (69%) have been taking the iron-containing type (Microgenon), with the remaining subjects have been consuming the non-iron-containing types; (21%) using Microlut, with only (7%) and (3%) using Sunya and Yasmin respectively.

Table (4): Demonstrates the alimentary habits of the whole study sample.

Variables	Frequency (f)	Percentage (%)
Consumption of meat at least once a week		
No	4	13.8
Yes	25	86.2
Total	29	100
Consumption of fish at least once a week		
No	8	27.6
Yes	21	72.4
Total	29	100
Vegetarian		
No	25	86.2
Yes	4	13.8
Total	29	100
Tea or Coffee consumption after taking placebo pills		
No	16	55.2
Yes	13	44.8
Total	29	100

Table (4) shows the alimentary habits of the whole study sample. For meat and fish consumption, the table shows that the highest percentage of the subjects (86.2%) meat and (72.4%) for fish eat meat and fish at least once a week. Only (13.8%) of women were vegetarian. Finally, regarding tea or coffee consumption after taking placebo pills, the highest percentage (55.2%) were non-consumers

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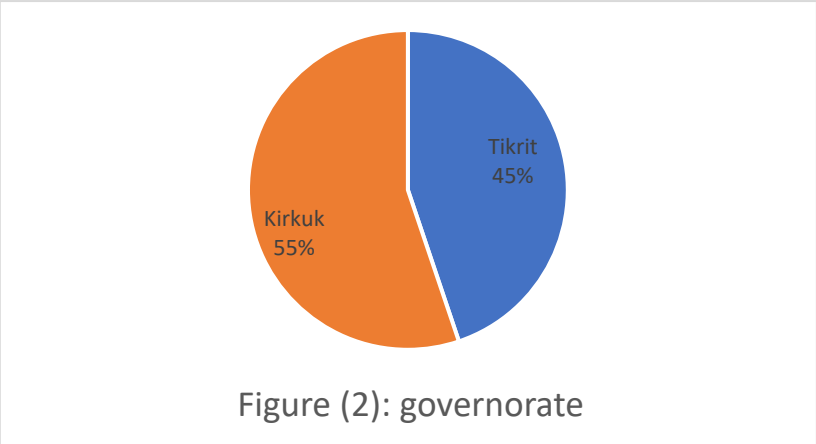

Figure (2): governorate

Figure (2): Governorate. The figure shows that most subjects (55%) were from Kirkuk.

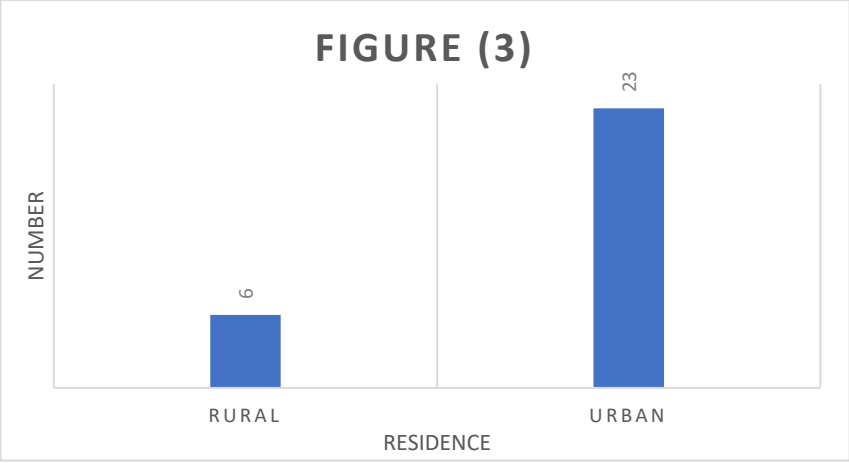

Figure (3): Residence. This figure shows that 79% (n=23) of subjects lived in urban areas.

Table (5): Independent T-Test for serum ferritin level between two groups for different parameters.

Parameter	P value	95% Confidence
Non-Iron containing OC Vs Iron Containing OC	0.024	< 0.05 S
Smokers & non-smokers	0.00005	< 0.05 S
Meat consumers & non-consumers	0.293	> 0.05 N.S.
Fish consumers & non-consumers	0.366	> 0.05 N.S.
Tea & coffee consumers & non-consumers	0.975	> 0.05 N.S.
S= Significant, N.S.= No Significance		

Table (5) shows the independent T tests' results. The data were normally distributed and independent T test for the comparison of serum ferritin levels between iron and non-iron containing oral contraceptive users were applied. The p value was (0.024 < 0.05) which was significant.

T test for comparison of serum ferritin levels between smokers and non-smokers, it shows that p value (0.00005 < 0.05) was statistically significant.

T test for comparison of serum ferritin levels between subjects who consume meat and fish at least once a week and the non-consumers shows no statistical significance, p values for meat, and fish were (0.293 > 0.05) (0.366 > 0.05) respectively.

T test for Comparison of serum ferritin levels between two groups, subjects who consume tea or coffee after administration of the placebo pill and non-consumers shows no statistical significance with p value of (0.975 > 0.05).

Table (6): ANOVA tests' results.

Parameter	P value	95% Confidence
Age groups & serum ferritin	0.188	> 0.05 N.S.
Weight & serum ferritin	0.026	< 0.05 S
S= Significant, N.S.= No Significance		

Table (6) shows the ANOVA test for serum ferritin levels compared between age groups. It shows no statistical significance (P value 0.188 > 0.05) between age groups. It also shows the ANOVA test's result for serum ferritin levels compared between weight groups. Shows statistical significance (P value <0.05) between groups, so it would be appropriate to interpret the results of the LSD test.

Table (7): least significant difference (LSD) test for serum ferritin levels compared to weight groups.

Parameter	P value	95% Confidence
serum ferritin levels compared to weight groups (normal/obese)	0.008	<0.05

Table (7) shows the lowest difference (LSD) test for serum ferritin levels compared to weight groups. Shows statistical significance (P value 0.008 < 0.05) in (normal/obese) weight groups.

DISCUSSION

Oral contraceptives, in general, have the benefit of increasing iron stores by decreasing menstrual iron loss. Menstruating women could benefit from adding iron to oral contraceptives pills to help with managing iron deficiency, which is one of the most common nutritional deficiencies globally (Camaschella, 2019); in many situations, ICOC may present themselves as a good substitute or additive to iron supplementation or fortification programs for women in reproductive age. As they are more reliable to have lower iron levels because of blood loss during menstrual cycles. Considering that 16% of ovulating women already use pills as a method of contraception Field (Nations, 2019), merging birth control and iron supplementation strategies can provide an easy, practical, and cost-effective solution for family planning and iron replacement. The study aimed to examine the evidence evaluating the use of ICOC and its effect on serum ferritin as a biomarker for iron status. Regarding the negative effects of using iron, available brands of iron-containing contraceptive pills, mainly (Microgynon fe), contain 75mg ferrous fumarate, equalling about 25 mg elemental iron. Which is not likely to cause any serious side effects regarding iron overload for any non-pregnant, 20-45 years old woman taking it only 7 days each month. Other minor negative effects are nausea and gastric upset from iron. In the ICOC group (n=20), there was a higher serum ferritin level mean (93.2 ng/ml, SD 44.0) compared to the non-ICOC (n=9) had a mean of (54.7ng/ml, SD 28.8), and there was statistical significance (P value 0.024 < 0.05) for the difference between the two groups. A significant difference in serum ferritin levels was found between subjects using iron-containing contraceptive pills and those using non-iron-containing contraceptive pills. The iron-containing contraceptive pills users had higher serum ferritin as an extra benefit to the known oral contraceptives' general benefit of increasing iron stores by decreasing menstrual iron loss. Another study by J.A.J. Fisher et al. 2021, suggested no effect of added iron in placebo pills but was limited to comparing haemoglobin (Hb) levels. In another study, S. Gebremedhin et al. 2018 suggested a benefit of OCP in improving Hb levels compared to other means of contraception. But did not compare the two types, ICOC vs non-ICOC. Iron is a micronutrient that is required for almost all aspects of normal cell function. But simultaneously, it could be a potentially dangerous element. Its ability to catalyze the formation of reactive oxygen species can pose a health risk by causing oxidative stress and cellular membrane damage. For this reason, the iron balance must be finely regulated (Lee et al., 2016; Zafon, Lecube, & Simo, 2010). Cigarette smoke contains

numerous oxidants and prooxidants that can generate free radicals and increase oxidative stress. Previous research has suggested that cigarette smoking influences iron status by demonstrating cigarette smoke-induced release of iron from ferritin by aqueous extracts of cigarette smoke and that this iron mobilization acts as a specific prooxidant mechanism during smoking. In addition to other studies showing increased lavage iron stores in smokers, Ghio et al. suggested an alteration in iron homeostasis from cigarette smoke exposure in their animal experiments. They have demonstrated that such exposure causes iron accumulation that is dependent on particulates in smoke and that this change affects oxidative stress, which is responsible for tissue inflammation after smoking. They hypothesized that the complexation of host iron by particulate matter in cigarette smoke's tar phase would alter iron homeostasis in the lung and throughout the body. Lung epithelial cells can rapidly increase ferritin protein expression to regulate iron-catalyzed oxidative stress The study showed that smokers (n=7) had higher serum ferritin than non-smokers (n=22). Ferritin acts as an antioxidant protein by limiting iron's ability to generate reactive oxygen species and free radicals through iron sequestration. Ghio et al. used human lavage samples to show that ferritin concentrations were significantly higher in healthy smokers and smokers with COPD when compared to healthy non-smokers (Lee et al., 2016). In previous research, its observations confirmed that high red meat intake was associated with metabolic syndrome and higher serum ferritin levels, as red meat contains large amounts of total fat, saturated fatty acids, and heme-iron(Huang et al., 2020). The total iron content in oily fish is generally very low, with negligible heme iron content. Nevertheless, fish contains the “meat factor”, which increases iron absorption and counterbalances its low iron content (Navas-Carretero et al., 2009). This study found no association between regular meat consumption, fish consumption and serum ferritin levels. Small sample sizes and time limitations may participate, limiting the study results. Tea is a potent inhibitor of iron availability, with reports indicating inhibition of up to 90% of intestinal iron inhibition (Hurrell, Reddy, & Cook, 1999). From the results of the study, they showed no association between serum ferritin and tea consumption after the administration of iron-containing placebo pills. The results of a study suggested that the ferritin level can increase with ageing as a part of the ongoing asymptomatic chronic systemic inflammatory state called inflammation(Cankurtaran et al., 2012). In our study, there was no association of serum ferritin between age groups. Regarding obesity, according to one study, obese people have high ferritin and C- reactive protein levels but low serum iron and transferrin saturation. Fat cells play an important role in producing acute-phase reactants like ferritin, which may not be the gold standard for assessing iron status in obese people (Alam, Memon, & Fatima, 2015). The study results confirmed that high serum ferritin was observed in obese subjects.

CONCLUSION

Many companies worldwide are producing ICOC despite little being known about where ICOC are superior to non-ICOC in improving iron status, with studies focusing on Hb rather than Biomarkers for iron status. Study data showed that subjects from Tikrit using ICOC had higher serum ferritin than those from Kirkuk; it may be attributed to lifestyle differences or variations in the duration of the pill use. The observations confirmed that smoking and obesity increase the levels of serum ferritin.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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