TAJ December 2022; Volume 35 Number-2

ISSN 1019-8555
The Journal of
Teachers Association
RMC, Rajshahi

Original Article

Effect of Combined Oral Contraceptive Pill on Serum Bilirubin and Alkaline Phosphatase

Shamima Nazneen Rupa,[1] Bedowra Begum,[2] Sayeeda Sultana Jolly,[3] Farjana Kabir,[4] Shahnaz Akhter,[5] Zahid Hasan Khan,[6] Manik Chandra Nath [7]

Abstract

Background: Combined oral contraceptive is the most known and popular method of contraception. The combined oral contraceptive pill was the first oral contraceptive method and was commercially marketed in 1960. Earlier investigators reported that early oral contraceptive pills had many side effects. Despite the modifications on early OCPs in terms of content and dosage to lessen their side effects, newer contraceptives still have some hepatotoxic effects.

Aim and Objectives: The objective of this study was to investigate the effect of low-dose OCP on S. bilirubin and ALP- one of the most important liver enzymes.

Materials and Methods: This cross-sectional analytical study was conducted on 184 healthy women aged 20-45. Among them, 92 women were OCP users, and 92 were nonusers. BMI-matched non-OCP users women were recruited in the study for comparison of S. bilirubin and ALP. A systematic sampling technique was applied to select each respondent. Data collection was commenced after obtaining ethical clearance from the Ethical Committee and informed consent from the respondents.

Results: The results showed a significant decrease in serum Alkaline phosphatase among OCP users (p=0.001), but the ALP level was progressively increased with increased duration of OCP use. Serum bilirubin level was within the normal range, but the levels were slightly higher in OCP users but in. OCP users' serum bilirubin levels did not significantly increase with the duration of OCP use (P > 0.05). In summary, OCP users' women are associated with a decreased level of serum Alkaline phosphatase and a slightly increased level of serum bilirubin.

Conclusion: So regular monitoring of S. bilirubin and ALP should be done among OCP users women to avoid many unwanted complications.

Keywords: Alkaline phosphatase (ALP), Oral contraceptive pill (OCP).

TAJ 2022; 35: No-2: 133-141

Introduction

The Combined Oral Contraceptive Pill, usually called 'the Pill,' contains two hormones, estrogen and progesterone. The primary way the pill works is by stopping a woman's ovaries from releasing an egg each month, which means that a pregnancy cannot begin.[1] With perfect use, the Pill is 99.7% effective, which means if 100 women use it correctly for one year, less than one will become

[1] Assistant Professor (cc), Department of Physiology, Rajshahi Medical College, Rajshahi.
[2] Assistant Professor (cc), Department of Physiology, Rajshahi Medical College, Rajshahi.
[3] Assistant Professor, Department of Physiology, Khulna City Medical College, Khulna.
[4] Assistant Professor (cc), Department of Physiology, Pabna Medical College, Pabna.
[5] Assistant Professor, Department of Physiology, Islami Bank Medical College, Rajshahi.
[6] Assistant Professor (cc), Department of Physiology, Satkhira Medical College, Satkhira.
[7] Assistant Professor, Department of Physiology, BGC Trust Medical College, Chattogram.

pregnant. With typical or 'real life' use, it is less effective (91%), with up to nine women in every hundred becoming pregnant in a year.[2,3] It contains low doses of two synthetic hormones- progestin and estrogen- similar to the natural hormones in a woman's body. Combined oral contraceptives are safe, effective, reversible methods to prevent pregnancy and must be taken regularly. It offers couples a wide range of options for delaying, spacing, and limiting births. Oral Contraceptives (OCs) are the most influential family planning method used by over 100 million women worldwide.[4] Sukhi is supplied free of cost through government health centers and hospitals. Each strip of Sukhi contains 21 hormonal tablets and seven nonhormonal (iron) tablets. It has several non-contraceptive benefits, like protection against endometrial and ovarian cancer, iron deficiency anemia, polycystic ovarian syndrome, and endometriosis.

The prevalence of contraceptive use among married women of the reproductive age group is 55.8%, according to BDHS 2007.[5] The pills have evolved from the first to the second generation, and now the third generation pills contain a reduced amount of the active hormones estrogen and progesterone are available.[6] The third-generation pills are safer and more affordable with fewer side effects[7]. However, the failure rate (9%) has been observed to be due to non-compliance.[4]

The mode of action depends upon the formulation of the pills. The pills inhibit ovulation by decreasing the formation of pituitary luteinizing hormone that renders the cervical mucus hostile to sperm penetration.[8] Many workers have suggested that contraceptive use is beneficial but has some side effects. The widespread use of hormonal contraceptives provides an opportunity for assessing the influence of estrogen and progesterone on various biochemical parameters among users. Combined oral hormonal contraception affects almost every system in our body.[9] Burkman et al.[10] observed that the metabolism of oral contraceptive pills among OCP users could cause disturbed liver function, as suggested by the increase in serum liver enzymes.

The liver is the structurally and functionally largest organ in the human body. It plays a significant role in metabolism and has several important functions in the body, including the efficient uptake of amino acids, carbohydrates, bile acids, cholesterol, proteins, lipids, and vitamins for storage and metabolism for subsequent release into bile and blood.[11] Disturbed hepatic function, therefore, affects several vital body processes, which are realized gradually. Because of this, the liver function test (LFT) performance becomes pivotal in assessing liver integrity. A wide range of tests are involved in LFT, but liver enzymes are the most common in our environment. Liver function tests are used to determine if the liver has been damaged or its function has been impaired. The liver filters the body's blood supply to clear and metabolize many compounds it perceives as poisonous, including medications. In addition, the liver metabolizes most drugs that we intake, including oral contraceptives. Thus it can be vulnerable to various kinds of drug-induced liver injuries.

Oral contraceptives can induce a variety of liver lesions. They can cause liver disease directly or exacerbate an underlying condition affecting the liver. The liver plays a vital role in the metabolism of estrogen and progesterone. It became evident that these substances can act directly or indirectly on the liver to produce a variety of biological effects which have both physiological and pathological significance. Hence, this study aimed to determine the effect of low-dose estrogen and progestin OCP on S. bilirubin and serum alkaline phosphate (ALP). Liver functionality is determined by the serum concentration of total and direct bilirubin, and serum alkaline phosphatase (ALP) activity is essential for biliary integrity.[20]

Alkaline phosphatase (ALP) mainly comes from the liver, bone, and placenta in pregnant women. If a person has elevated ALP, does not have bone disease, and is not pregnant, he or she may have a problem in the biliary tract system that makes and stores bile in our body.[21] The development of jaundice is the most prominent pathological alteration of liver function that brings patients under oral contraceptives to the doctor. The serum

bilirubin usually ranges from 3 to 10 mg/100 ml and is mainly conjugated.[22] Intrahepatic cholestatic Jaundice was the first reported adverse effect of oral contraceptives on the liver within the first six cycles. The most commonly adverse effects during the first one are anorexia, nausea, vomiting, fatigue, weight loss, and itching. Darkening urine and jaundice follow after a few days. There is no fever, rash, or abdominal pain. Serum conjugated bilirubin level is moderately elevated. Serum albumin and prothrombin time are generally within the standard limit.[12]

Three major categories of adverse hepatic effects have been linked to oral contraceptives: hepatic dysfunction, cholestatic jaundice, and benign hepatic tumor. Hepatic abnormality is linked to the use of oral contraceptives and is related to the relative interference of estrogen with the hepatic excretion of various organic anions, including bilirubin. Women whose first-degree relatives have oral contraceptive-induced cholestasis may be at increased risk and should be closely monitored while taking birth control pills.

Hussein[22] found that ALP is comparatively reduced in OCP users. Ekhator et al.[21] also observed that ALP and serum bilirubin levels were higher in the test group (OCP users) than in the control group. Larsson-Cohn[18] observed that jaundice occurred in one case but subsided within four days despite continued medication. So the present study has been designed to determine the effect of OCP on S. bilirubin and serum alkaline phosphate (ALP).

Materials and Methods

This cross-sectional analytical study was done in the department of Physiology in collaboration with the department of Biochemistry, Rajshahi medical college, Rajshahi, from July 2017 to June 2018. Data were collected from the Rajshahi model family planning clinic, Gynae outdoor of Rajshahi medical college hospital. The study population was healthy married women aged 20-45 years in Rajshahi City. Among them, 184 women were selected following a systematic sampling technique and maintaining eligibility criteria. OCP users women were recruited in one group (n=92), while OCP nonuser women were included in another group (n=92). Lactating mothers, diabetic women, women on any hepatoxic drug therapy, known acute and chronic liver disease cases, women under OCP less than six cycles, and interrupted OCP within six cycles were excluded from the study.

After proper counseling, the study's aim, objective, benefit, risk, and procedure were explained in detail to the respondents. Complete history taking and physical examination were done and recorded in a preformed data sheet after informed consent. Then whole blood (about 5 ml) was collected from the anterior cubital vein by venipuncture technique using a 21-gauge hypodermic needle and collected in a sterile container. It was allowed to clot and centrifuged at 1200x 9 for 5 min at room temperature (29^0C-31^0C). Serum bilirubin and alkaline phosphatase (ALP) were estimated using a Randox reagent kit using 2, 4-dinitrophenylhydrazine substrate; activity was determined far biliary integrity with Randox reagent kit using nitrophenyl phosphate substrate.

All data were analyzed by using the 'Statistical Package for Social Sciences (SPSS)' software, 24-version. Categorical variables were summarized using numbers and percentages, while continuous variables were summarized by means ± standard deviation (SD). An independent t-test was used to compare continuous variables with two categories, and ANOVA test was used to compare continuous variables with more than two categories. In addition, a chi-square test was used to compare categorical variables with two categories. A p-value < 0.05 was considered statistically significant.

Results

The mean age of the OCP users women was 30.84±4.64 years, and non-OCP users women was 30.83±4.38 years. No significant difference was observed between the two groups in terms of age ($p > 0.05$). The mean pulse, systolic blood pressure, diastolic blood pressure & respiratory rate were 77.47±7.01 beats/min, 123.20±14.17 mmHg, 79.02±8.42 mmHg & 14.07±1.45 breaths/min, respectively among OCP users women and 78.00±6.11 beats/min, 123.15±11.66 mmHg, 77.71±7.42 mmHg & 14.17±1.47 breaths/min respectively among non-OCP users women. These parameters were not statistically significant between the two groups ($p > 0.05$) (Table 1). Regarding BMI, out of 92 OCP users respondents, 44(50.6%) had normal BMI, and 48(49.4%) were overweight. On the other hand, out of 92 non-OCP users women, 43(49.4%) had average weight, and 49(50.6%) were overweight (Figure-1). The mean bilirubin value of OCP users was 0.741±0.206 mg/dl, and of non-OCP users was 0.643±0.219 mg/dl. The mean Bilirubin level was higher in OCP users compared to non-OCP users. This difference is statistically significant and showed higher serum bilirubin value in OCP users (Figure II). The mean ALP value of OCP users was 107.68±17.14 IU/L, and of non-OCP users was 122.93±30.31 IU/L. The mean ALP level was higher in non-OCP users than OCP user group. A statistically significant difference was seen in the case of ALP, which showed a much higher value in non-OCP users (Table 4). OCP users women were categorized into five groups according to their duration of use, i.e., 1-12 months, 13-24 months, 25-36 months, 37-48 months, and 49-60 months. It showed that BMI changed with an increased duration of combined oral contraceptive use (Table 2). The ALP level was also progressively increasing with the increased duration of OCP use. However, in OCP users, serum bilirubin levels were not significantly increasing with the duration of use ($P>0.05$) (Table 3 & 5).

Table 1: General characteristics of the respondents (n=184)

Parameters	OCP Users (mean ±SD)	OCP nonusers (mean ±SD)
Age in years	30.84±4.64	30.83±4.38
Weight in kg	59.06±4.99	58.84±5.35
Height in cm	153.86±2.45	153.14±2.84
Pulse	77.47±7.01	78.00±6.11
Respiratory rate	14.07±1.45	14.17±1.47
Systolic blood pressure	123.20±14.17	123.15±11.66
Diastolic blood pressure	79.02±8.42	77.71±7.42

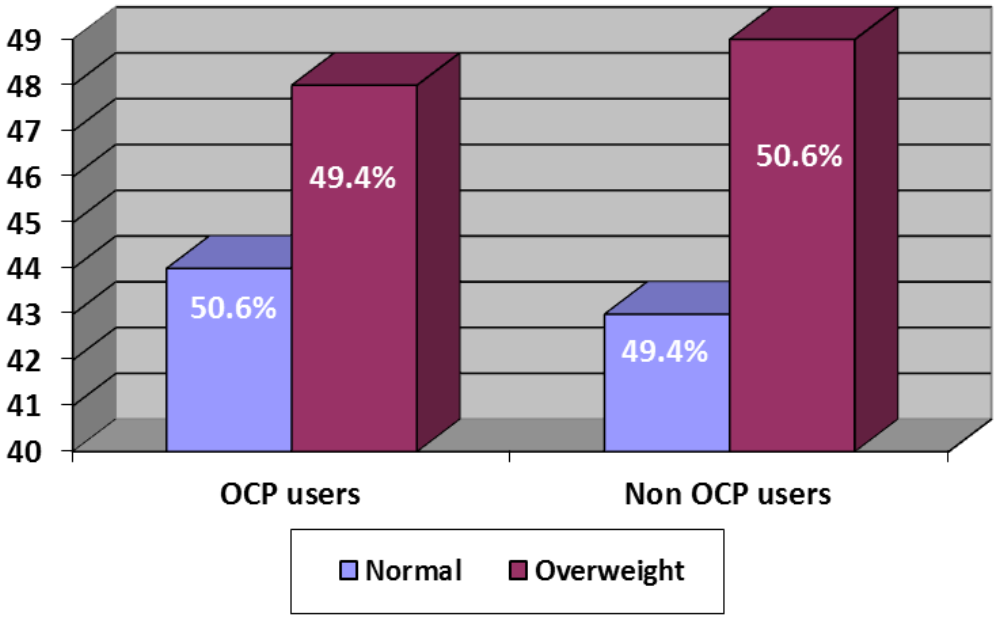

Figure 1: Body mass index of the respondents (n=92 in each group.

Table 2: Effect of duration of use of OCP on BMI (n=92 in each group).

BMI Kg/m^2	1-12 months	13-24 months	25-36 months	37-48 months	49-60 months
			Frequency (%)		
<22.99	3(21.4%)	3(21.4%)	4(28.6%)	4(28.6%)	0
23-24.99	5(16.7%)	5(16.7%)	11(36.7%)	9(30.0%)	0
25-26.99	2(6.9%)	4(13.8%)	4(13.8%)	14(48.3%)	5(17.2%)
>27	0	2(10.5%)	2(10.5%)	5(26.3%)	10(52.6%)

Data were analyzed using the Chi-square test and were presented as frequency and percentage.
χ^2=35.406, df=12, p=0.001

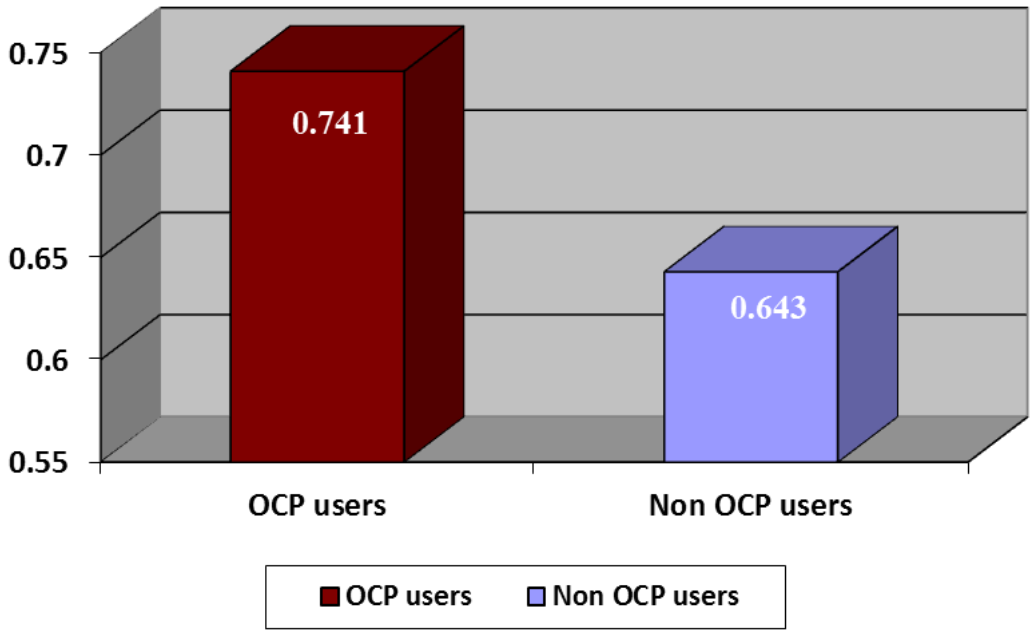

Figure II: Serum bilirubin level between OCP users and OCP nonusers (n=184)

Table 3: Effect of duration on serum bilirubin in OCP users.

Duration of OCP use (months)	Frequency	Mean±SD	p-value, F
Users			
1-12	10	0.4100±0.22828	
13-24	14	0.57±0.33	
25-36	21	0.69±0.13	> 0.05,
37-48	32	0.69±0.169	0.002
49-60	15	0.70±0.17	
Total	92	0.64±0.21	

The significance of the difference was calculated using the ANOVA test.

Table 4: Serum Alkaline phosphatase (ALP) level between OCP users and OCP nonusers (n=184)

Parameters	OCP Users Mean±SD	Non-OCP users Mean±SD	p-value
Serum Alkaline phosphatase (ALP) level(U/L) (Normal value 45-115 U/L)	107.68±17.14	122.93±30.31	0.001*

*Significant

The significance of the difference was calculated using an unpaired 't-test.

Table 5: Effect of duration on Serum Alkaline phosphate (ALP) level in OCP users.

Duration of users (months)	No	Serum Alkaline phosphate (ALP) level	p-value
1-12	10	94.20±12.76	
13-24	14	103.92±16.42	
25-36	21	102.85±18.47	p=0.001
37-48	32	111.09±14.12	F=50.039
49-60	15	119.66±16.30	
Total	92	107.68±17.14	

The significance of the difference was calculated using the ANOVA test.

Discussion

This cross-sectional analytical study aimed to determine the effect of low-dose use of oral contraceptives on liver function by conducting S. bilirubin and Serum Alkaline phosphatase (ALP). This study also determined the effect of long-term OCP use on liver function tests. This study mainly highlighted the effect of second-generation monophasic combined oral contraceptives, which are commonly used in Bangladesh. The study included the measurement of S. bilirubin and Serum Alkaline phosphatase (ALP) to assess the effect of the combined oral contraceptive pills on liver function.

The study was conducted on 184 women aged 20-45 years who took combined oral contraceptive pills. The pills that were used in the present study were Sukhi, containing 30 µg Ethinyl estradiol and 150µg levonorgestrel. This Pill is the only Pill that is given to the OCP user in the model family planning clinic of Rajshahi Medical College Hospital. The user group was categorized into five groups according to their duration of using these pills.

Jaundice is the clinical manifestation of an elevated level of serum bilirubin. Intrahepatic cholestatic jaundice was the first reported adverse effect of oral contraceptives on the liver.

In this study, serum total bilirubin levels are higher in OCP users in comparison to non-OCP users. This observation coincides with Osifo[13], KATZ[14], Dickerson, et al.[15], Rahim et al.[16], and Heikel and Lathe[17]. Larsson Cohn et al.[18] observed that serum bilirubin level was within the standard limit after taking OCP. OCP-related jaundice usually appeals within 1st six months of pill use and disappears without sequelae 1 or 2 months after termination of pill use. Half (50%) of women developing jaundice with pill use had experienced intrahepatic cholestasis of pregnancy. They should be closely monitored when taking birth control pills.[19] The estrogen component of oral contraceptives is responsible for invading cholestasis.[20] Some researchers found that estrogens and progesterones inhibited basal bile flow and bile flow of bilirubin in the body. However, the dosage required to produce these effects was much with progesterones (40 mg/kg) than with estrogens (5 mg/kg). The rise in serum bilirubin must be either increased escape from the liver cells, a diminished storage capacity, or reduced transport into bile canaliculi.[17]

The effect of OCPs on liver functionality indicated via total bilirubin and direct bilirubin demonstrated that administration of low doses of synthetic OCPs may have the potential for red blood cell destruction in a dose-dependent fashion.[21]

Alkaline phosphatase is another liver enzyme that is an indicator of biliary integrity. In this study, serum alkaline phosphatase levels were within average in both OCP and non-OCP users. However, the levels were higher in non-OCP users. This observation coincides with Hussein et al.[22]. For females who used estrogen-containing oral contraceptive pills, the PTH (Parathormone) activity is inhibited, and ALP is significantly reduced. Steroids of the contraceptive Pill are potent inhibitors of PTH (Parathormone), which is the driving force of the ALP to rise from the bones in our body. Thus continuous administration of OCP may lead to reduced bone loss and reduced ALP activity.[21]

However, many researchers found increased Alkaline phosphatase levels in OCP users. These results are compatible with Ekhator[20], KATZ, et al.[13], Hargreaves[23], Dickerson, et al.[15], and Larsson-Cohn et al.[17]. The increased ALP level could be described by cellular degeneration of myocardial, neuronal, and liver cells.[20]

Alkaline phosphatase is located in the excretory surface of the liver and has been considered highly specific for hepatic disorders, especially in Intra-hepatic cholestasis. These observations suggest that the raised alkaline phosphatase level after administration of estrogen and progesterone may be of hepatic origin and may be related to functional alterations of hepatic excretory mechanism.[22]

Cullberg et al.[24] mentioned that liver cell damage accords well with the repeated observation of elevated transaminase during treatment with OCP. However, the alkaline phosphatase level was reported to be expected in several of these cases, suggesting that the cytotoxic effect may be more pronounced than the cholestatic effect.

Shrikanth et al.[25] mentioned that oral contraceptives and anabolic steroids are associated with cholestasis, vascular lesions, and hepatic neoplasm. Chronic use of oral contraceptives is associated with the development of hepatic adenoma, benign tumors typically observed only in women of childbearing age. These can be resolved entirely with drug withdrawal, and the removal of the risk factors depends upon the duration of the drug exposure. Both estrogen and progesterone are metabolized in the liver and excreted in large part in the urine. Large doses of estrogen and progesterone steroids must enter the liver to achieve adequate levels at the target tissues. The exposure of the liver to high levels of estrogen and progesterone via portal circulation puts this organ at risk for the adverse effects of these drugs.[26]

OCPs induce alterations in liver cellular integrity as well as the biliary tract. These alterations are the sequel of the significance of serum concentrations of hepatic enzymes and that these markers leak into the circulation when there is necrosis or damage to the hepatic cells.[20] The incidence of OCP-induced cholestasis is 1 per 10,000 women worldwide.[27]

Based on the results of this study, OCP use has challenged the liver's normal physiological function and integrity. Thus, taking low doses of OCP may affect the function and cellular integrity of the liver and biliary systems in a dose-dependent manner.[20]

One of the weaknesses of our study was that we did a cross-sectional study. So longitudinal study should be done to confirm our findings. After starting OCP, regular monitoring can give accurate results. The effect of OCP on different age groups should be evaluated. Furthermore, we have included only the women of Rajshahi city.

One of the strengths of our study was that our sample size was larger, i.e., 184. This sample size can predict relatively accurate findings of our parameters. On the other hand, we have collected the OCP user from the model family planning clinic of Rajshahi medical college hospital. Here regular registration of OCP users is recorded. So there is no chance of dropping out of these samples.

Based on our findings, we predict that OCP significantly affects some liver function tests, i.e., serum bilirubin. ALP levels are within standard limits for both OCP users and OCP nonusers. Our study suggests that the estimation of liver enzymes should be done before starting OCP, and regular monitoring is necessary to prevent liver damage.

Conclusion

Most women suffer from adverse effects if high-dose formulations of oral pills are used. Hepatobiliary complications are considered to be one of the most important adverse reactions. This study found that serum ALP was decreased and S. bilirubin level was slightly increased in OCP users. So it is wise to avoid OCP use in patients suffering from liver problems, and screening of every female before initiating OCP is necessary. It is also necessary to monitoring of liver function in females taking OCP for a prolonged period.

Conflict of interest: None declared

References

1. de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev. 2014 Mar 3;(3):CD010813.
2. Arowojolu AO, Gallo MF, Grimes DA, Garner SE. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2004 Jan 1;(3):CD004425.

3. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005 Dec 15;353(24):2550–2558.
4. Bhawan. Ministry of Health and Family Welfare. Reference Manual on Oral Contraceptive Pills. 2016.
5. Chowdhury RI, Islam MA, Gulshan J, Chakraborty N. Delivery complications and healthcare-seeking behavior: The Bangladesh Demographic Health Survey, 1999-2000. Health Soc Care Community. 2007 May;15(3):254–264.
6. Long ME, Faubion SS, MacLaughlin KL, Pruthi S, Casey PM. Contraception and hormonal management in the perimenopause. J Womens Health (Larchmt). 2015 Jan;24(1):3–10.
7. Lete I, Cuesta MC, Marín JM, Guerra S. Vaginal health in contraceptive vaginal ring users - A review. Eur J Contracept Reprod Health Care. 2013 Aug;18(4):234–241.
8. Naz F, Jyoti S, Akhtar N, Siddique YH. Effect of oral contraceptive pills on the blood serum enzymes and dna damage in lymphocytes among users. Indian Journal of Clinical chem. 2016; 31(3):294-301.
9. Malhotra N, Malhotra J, Saxena R, Bora NM. Jeffcoate's principles of gynaecology. books.google.com; 2018.
10. Burkman R, Schlesselman JJ, Zieman M. Safety concerns and health benefits associated with oral contraception. Am J Obstet Gynecol. 2004 Apr;190(4 Suppl): S5–22.
11. Braet F, Wisse E. Structural and functional aspects of liver sinusoidal endothelial cell fenestrae: a review. Comp Hepatol. 2002 Aug 23;1(1):1.
12. Valla D, Benhamou JP. Liver diseases related to oral contraceptives. Dig Dis. 1988;6(2):76–86.
13. Igberase E, Osifo P, Ofomaja A. The adsorption of copper (II) ions by polyaniline graft chitosan beads from aqueous solution: equilibrium, kinetic and desorption studies. Journal of environmental chemical …. 2014; 2(1): 362-369.
14. Katz R, Tushman ML. A longitudinal study of the effects of boundary spanning supervision on turnover and promotion in research and development. Academy of management Journal. 1983; 26(3).
15. Dickerson J, Bressler R, Christian CD. Liver function tests and low-dose estrogen oral contraceptives. Contraception. 1980 Dec; 22(6):597–603.
16. Rahim SA. Activities of some liver enzymes in serum of woman receiving oral contraceptives, injection and Cu-IUD. EurAsian Journal of BioSciences. 2020; 14(2): 5355-5360.
17. Heikel TA, Lathe GH. The effect of oral contraceptive steroids on bile secretion and bilirubin Tm in rats. Br J Pharmacol. 1970 May;38(3):593–601.
18. Larsson-Cohn U. Oral contraception and liver-function tests. Br Med J. 1965; 1(5447): 1414–1415.
19. Sabatini R, Cagiano R, Rabe T. Adverse effects of hormonal contraception. Journal für Reproduktionsmedizin und Endokrinologie. 2011; 8(1): 130-156.
20. Kreek MJ, Weser E, Sleisenger MH. Idiopathic cholestasis of pregnancy: The response to challenge with the synthetic estrogen, ethinyl estradiol. New England Journal of physiology 1967; 277(26):1391-5.
21. Ekhator CN, Osifo UC, Akpamu U. Effect of oral contraceptive pills (containing low doses of synthetic hormones) on liver function in adult female rabbits. 2014; 6(1): 15-20.
22. Hussein HJ. Physio-chemical study of some liver enzymes in the province of Najaf women s used low dose compound oral contraceptives pills (COCs). Int J Rec Sci Res. 2016.
23. Hargreaves T. Oral contraceptives and liver function. J Clin Pathol. 1969 Jan 1; s1-3(1):1–10.
24. Cullberg G, Lundstroem R, Stenram U. JAUNDICE DURING TREATMENT WITH AN ORAL CONTRACEPTIVE, LYNDIOL. Br Med J. 1965 Mar 13;1(5436):695–697.
25. Srikanth BA, Manisree V. Oral contraceptives induced hepatotoxicity. International Journal of Basic & Clinical …. 2013; 2(1):91.
26. Lindberg MC. Hepatobiliary complications of oral contraceptives. J Gen Intern Med. 1992 Apr;7(2):199–209.
27. Mawri S, Gildeh E, Joseph N, Rabbani B, Zweig B. Cardiac dysrhythmias due to oral contraceptive. Rep Cardiol. 2017 Jun 5; 2017:6250312..

All correspondence to
Shamima Nazneen Rupa
Assistant Professor (cc)
Department of Physiology
Rajshahi Medical College, Rajshahi
E-mail: shamimarupa43@gmail.com.