ORIGINAL ARTICLE

Effect of Hormonal Contraceptives on Fibrinogen and Plasma Antithrombin

NEELAM MAZHAR[1*], AYESHA KHANUM[2], SUNDUS ARSHAD[3], JAVERIA FATIMA[4], SAIMA FARHAN[5], NAUMAN ASLAM MALIK[6], NISAR AHMED[7]
[1-5,7]Department of Haematology and Transfusion Medicine, CH &ICH LHR. Pakistan.
[6]Department of Haematology, PGMI LHR. Pakistan.
Correspondence: Dr. Neelam Mazhar, Email:neelam_mazhar@hotmail.com, Contact #: +923314083389

ABSTRACT

Aim: To determine the changes in the coagulation profile, fibrinogen level and anti-thrombin level in females on hormonal OCPs.
Methodology: This case control study was carried out at Family planning and fertility clinics, of three hospitals of Lahore. Females of age 16-49 years using hormonal contraceptives for at least 6 months were included in case group. In control group, 55 females matched for age who are not taking hormonal contraceptives were taken. PT, APTT and fibrinogen assay and anti-thrombin level estimation was done using standard laboratory procedures.
Results: The mean of age was 29.02+5.81 years, hemoglobin 11.74+0.96mg/dl, platelets 316.43+47.04, prothrombin is 11.76+0.922%, fibrinogen is 2.643+0.45g/L and antithrombin level is 87.36+5.71%. Haemoglobin levels were better in group not using hormonal contraceptive and a significant relationship between shortening of PT, APTT, increase in fibrinogen level and decrease in antithrombin level with hormonal contraceptives than controls.
Conclusion: Hormonal contraceptives are most commonly used method, but its effects on coagulation profile cannot be ignored. Prothrombin time and APTT were decreased, mild increase in fibrinogen but considerable lowering of antithrombin levels. We must educate about non-hormonal contraceptive method to minimize the risk.
Keywords: Contraceptives, Antithrombin level, APTT, Fibrinogen time, Thrombosis

INTRODCUTION

In our country, the use of various methods of contraception was 34% in the year 2008. Contraceptive methods include oral as well as other routes. Among the various methods of Oral contraception, oral pills are most common in our local population. Around 32% of the total female's using contraception for family planning in our population use oral pills; intrauterine devices IUDs (12%), injectable contraceptives (8%) and implants for prolonged contraception (4.3%)[1].

On basis of the nature of contraceptives, hormonal contraceptives are most commonly prescribed for pregnancy control in young girls and young adult age group. Other indications of hormonal OCPs include ovarian cyst, dysmenorrhea, endometriosis, dysfunctional uterine bleeding, and hormone replacement therapy.[2] Combined hormonal contraceptives containing estrogens and progesterone, possess an inherent risk of thrombogenic events like venous thrombosis[3]. Studies have shown that there is three to four times increase in the risk of thrombo-embolic phenomenon, mostly deep venous thrombosis of lower limbs[4].

Various methods of contractions have their advantages and disadvantages. Hormonal contraceptives are better in controlling family size and other issues related to birth control.[5] Almost all the women of child bearing age use them to suppress ovulation.[6] Methods of contraception currently in practice include various barrier methods; Hormonal OCPs (progestin-only pills, combined oral contraceptive pills). Almost all contraception methods have estrogen (typically ethinyl estradiol) along with progestin[7].

Received on 07-10-2020
Accepted on 17-02-2021

Thromboembolic phenomenon can occur after the use of oral contraceptive pills. It is one of the rare but life threatening consequence of hormone contraception use. Among the risk factors of coagulation dysfunction due to OCP use, advanced age is significant. Studies have shown that adolescents of age 15 to 20 years can have the lowest incidence of this complication (around 2 cases in a 10,000 exposure years).[8,9] Metabolic derangements have been reported in multiple studies along with disturbances in the coagulation profile, fibrinogen and platelet counts[10,11].

This study was planned to evaluate the various parameters of coagulation and antithrombin level, which can complicate into thromboembolic phenomenon. No local data is available in this regard currently. Conclusions at the end of this study can help in spreading awareness regarding risk of thrombotic events due to hormonal contraceptives. Changes in the hormone formulations used in OCPs can be done to minimize these adverse effects.

MATERIAL AND METHODS

This multi-center case control study, carried out at three centers: The family planning center in the Lahore General Hospital, Lahore; the department of pathology and hematology of the Postgraduate Medical Institute in Lahore; and the gynecology outpatient dept. at The CH &ICH Lahore. Data was collected in 12 months from January 2018 to December 2018. First aim of this study was to determine the changes in the coagulation profile, fibrinogen level and antithrombin level in females using hormonal contraceptive pills. Second aim of this study was to compare changes in the coagulation profile, fibrinogen level and antithrombin level in females taking hormonal OCPs versus female not taking hormonal OCPS.

Alternate Hypothesis of this study was that there is difference in the changes in coagulation profile, fibrinogen level and antithrombin level in females taking hormonal OCPs versus female not taking hormonal OCPS. Studies have shown that fibrinogen level increases while serum Anti-thrombin level decreases in women using hormonal OCPs.

Sample size of 110 was calculated using WHO sample size calculator with 5% expected risk of thromboembolic phenomenon in females not using hormone OCPs and 30% expected risk of thromboembolic phenomenon in females using hormone OCPs, taking the power of the study of 90%, with level of significance of 5% and confidence level of 95%. Sampling technique in this study was through non-probability purposive sampling.

All the females of the age of more than 15 years to less than 50 years using hormonal contraceptives for minimum of 3 months were included in the study. All those patients who were diagnosed with thrombophilic disorder before use of hormonal contraceptives, having coagulation disorder, recurrent abortions, venous thromboembolism, taking oral anticoagulants and those with evidence of disseminated malignancies were excluded from the study.

Strict criteria of selection of the patients was opted. Cases and control samples were coded. Status of patient's contraceptive method was concealed by giving ambiguous numbers. Data was collected from all the females included in the study after written consent; all responses were documented as per the pre-designed questionnaire.

In the control group, 55 females matched for age who are not taking hormonal contraceptives were taken and 55 taking them in the cases group. Of these 55 cases, 14 females were taking oral contraceptives (Microgynon 21) containing Levonorgestrel 0.15mg (progestogens) and Etinilestradiol 0.03 mg (estrogen). Injectable hormonal contraceptives were being used by 24 females, DEPO-PROVERA which contains 1.5mg/ml depotmedroxy – progesterone acetate (progestogens). Long acting subdermal, intradermal preparations were used by 17 females. Its either Jadalle: two implants each containing 75 mg of progestin-Levonorgestrel a total of 150 mg, with release rate of 100microgram/ day for first month then 40 micro gram / day at 12th month then 30 microgram for about 5 years or Implanon- Etonorgestrel implant which lasts for three years.

Laboratory investigations including prothrombin time (PT), APTT and fibrinogen assay and anti-thrombin levels were estimated. Three ml venous blood sample was taken in EDTA vial and sysmex hematology analyzer was used for complete blood count. Three ml venous blood sample collected in 3.8% trisodium-citrate anticoagulant viol using aseptic measures and coagulation studies were done. Samples were centrifuged for 15 mins at 2,500 g. All lab investigations were done within 3 to 4 hours of the collection of the specimen. For estimation of antithrombin level, plasma was stored at a temperature of -20 ºC. Samples were placed at a temperature of 37 ˚C for complete thawing; later Diagnostic Stago Compact was used to run tests. PT, APTT and fibrinogen levels were measured on semiautomated coagulometer sysmex CA-50.

All the collected data was recorded and processed in the SPSS 20 version. Descriptive data of continuous variable including age was analyzed to calculate mean and S.D. All the categorical variables with quantitative data including contraceptive method, their frequency of usage and percentage in control and cases were estimated. Data has presented using graphs, tables, diagrams. Antithrombin, PT, APTT and fibrinogen levels are compared in both groups, independent sample student t-test applied to test statistical significance. Proportions in both groups were applied chi-square test for comparison. P-value of less than 0.05 was considered as significant.

RESULTS

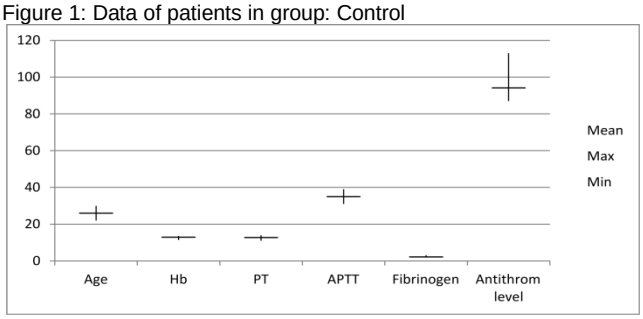
In this study, 110 patients were enrolled. Data analysis showed that the mean age of patients in control group was 26.02 years, oral group is 28.43 years, injectable group 30.42 years and long lasting injectable group 27.53 years. Analysis of other descriptive variables showed that mean and standard deviation of age was 29.02+5.81 years, hemoglobin is 11.74+0.96mg/dl, platelets is 316.43+47.04, prothrombin is 11.76+0.922, fibrinogen is 2.643+0.45 and antithrombin level is 87.36+5.71% (Table 1).

Analysis of mode of treatments showed that 14(25.5%) take oral treatment, 24(43.6%) take injectable and 17(30.9%) take long duration intradermal preparation. Analysis of duration of treatment showed that 18(32.7%) cases took treatment for less than 6 months, 16(29.1%) used treatment between 6 month to 1 year and 21(38.2%) took treatment for more than one year.

The mean hemoglobin of control group was 12.95g/dl, oral group is 11.42g/dl, injectable group 11.91g/dl and long lasting injectable 11.75g/dl. And mean platelet count of control arm was 244.49 $x10^3$/micro litre, orally taken is 338.29 $x10^3$/micro litre, injectable group 294.42 $x10^3$/micro litre and long lasting injectable 329.53 $x10^3$/micro litre.

Figure showing mean±SD of all the descriptive Statistics of patients in the case and control groups

Figure 1: Data of patients in group: Control



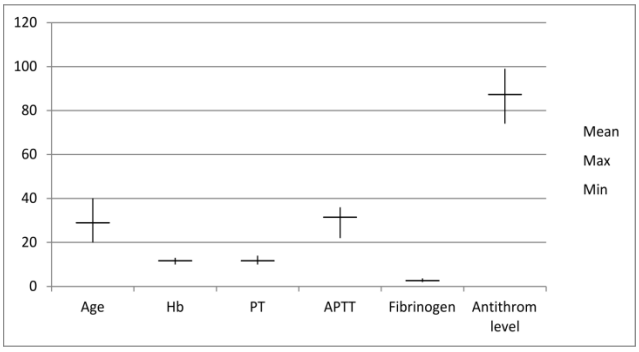


Table 1: Comparing mean of all descriptive variables of case and control Group

Variables	Treatment categories	Mean	STD. Deviation
Age (Years)	Not Taking	26.0	3.19
	Taking	29.0	5.81
Hemoglobin g/dl	Not Taking	12.95	0.40
	Taking	11.74	0.96
Platelets Count	Not Taking	244.49	41.1
	Taking	316.43	47.05
Prothrombin Time (PT) Seconds	Not Taking	12.8	1.20
	Taking	11.8	0.92
Activated Partial Thromboplastin time (APTT) Seconds	Not Taking	35.2	1.86
	Taking	31.5	2.48
Fibrinogen (mg/dl)	Not Taking	2.2	0.35
	Taking	2.6	0.46
Antithrombin level (%age)	Not Taking	94.2	7.43
	Taking	87.4	5.72

There is significant relationship between Hb level and exposure to hormonal contraceptives with confidence interval 0.012 (0.002-0.055) as shown in this analysis. Haemoglobin levels are better in group not using hormonal contraceptive. Similarly, significant relationship was seen between shortened PT and hormonal contraceptives with CI of 0.061(0.013-0.277) than controls. Significant shortening of APTT was seen with use of hormonal contraceptives with CI 0.052 (0.017-0.165) as compared to controls.

Odds ratio shows significant relationship between increase levels of fibrinogen and hormonal contraceptives with confidence intervals 3.115 ((2.27-4.276). Fibrinogen levels were found to be increased in cases than controls.

Odds ratio shows significant relationship between decrease in anti-thrombin level and the females with hormonal contraceptive use and CI was 2.833 ((2.27-4.276) than controls.

Table 2: Showing statistical analysis (Independent Sample t-Test) results of two groups

	t-test for Equality of Means		
Study parameters	T	Degree of Freedom	P-value
Age (Years)	-3.36	83.82	0.001*
Hemoglobin g/dl	8.57	72.32	<0.001*
Platelets Count	-8.46	108	<0.001*
Prothrombin Time (PT) Sec.	5.16	101.7	<0.001*
Activated Partial Thromboplastin time (APTT) Sec.	8.79	108	<0.001*
Fibrinogen (mg/dl)	-5.11	100.42	<0.001*
Antithrombin level (%age)	5.41	108	<0.001*

*means its significant

Table 3 showing the odds ratio to determine the relation of various factors with use of OCPs

Relationship between hemoglobin and hormonal contraceptives						
Variables		Treatment		Total	Odds Ratio (95% CI)	P-Value
		Not Taking	Taking			
Hb	Up to 12.5	2(4.5%)	42(95.5%)	44	0.012* (0.002-0.055)	< 0.001*
	Above 12.5	53(80.3%)	13(19.7%)	66		
Total		55	55	110		
Relationship between prothrombin time and hormonal contraceptives						
Variables		Treatment		Total	Odds Ratio (95% CI)	P-Value
		Not Taking	Taking			
PT	Up to 13 Sec	34(39.1%)	53 60.9%	87	0.061* (0.013-0.277)	< 0.001*
	Above 13 Sec	21(91.3%)	2(8.7%)	23		
Total		55	55	110		
Relationships between aptt & exposure to hormonal contraceptives						
Variables		Hormonal contraceptive methods		Total	Odds Ratio (95% CI)	P-Value
		Not Taking	Taking			
APTT	Up to 34 Sec	22(30.1%)	51(69.9%)	73	0.052* (0.017-0.165)	< 0.001*
	Above 34 Sec	33 (89.2%)	04(10.8%)	37		
Total		55	55	110		
Relationships between fibrinogen and exposure to hormonal contraceptives						
Variable		Hormonal contraceptives		Total	Odds Ratio (95% CI)	P-Value
		Not Taking	Taking			
Fibrinogen	Up to 2.05	28(96.6%)	1(3.4%)	29	3.115* (2.27-4.276)	< 0.001*
	Above 2.05	27(33.3%)	54(66.7%)	81		
Total		55	55	110		
Relationship between Antithrombin level and Treatment						
Variables		Treatment		Total	Odds Ratio (95% CI)	P-Value
		Not Taking(controls)	Taking (cases)			
AT	Till 86%	1(4%)	24(96%)	25	2.833* (2.125-3.778)	<0.001*
	Above 86%	54(63.5%)	31(36.5%)	85		
Total		55	55	110		

*Significant

DISCUSSION

This research was performed to see the effect of hormonal methods of contraception on thrombotic tendency by accessing PT, APTT, Fibrinogen level and Anti thrombin levels in females using hormone OCPs and those not using hormone OCPs. Our study showed significant fall in PT and APTT and slight increase in the fibrinogen level with significant fall in anti-thrombin levels. These results are supported by various other studies.

A similar survey of 70 females aging 18 to 30 years old having BMI ranging from 19 to 30 kg/m^2 and some using hormone OCPs for last 6 months and some not using hormone OCPs. PT, Factor VII, APTT, Factor XII, fibrinogen, Factor 1and 2, Protein C, Protein S, antithrombin, D-dimers, and plasminogen activator inhibitor-1 were estimated. Females using progestogen containing OCPs showed changes in PT close to that in the group not using hormonal contraceptives. Remarkable changes in PT, APTT, fibrinogen, D-dimers and protein S were seen in patients using OCPs with DRSP/20EE. The data supported the presence of a hypercoagulation state in these females. OCPs with DRSP/30EE and LNG/30EE also lead to hypercoaguable state due to changes in PT and protein C and S.[12]

Some studies have shown that Ortho Evra-subdermal patch the risk of increased thrombotic activity is higher than that of after using combined OCPS probably due to significant rise in the estrogen delivery. However, some other studies found that there was no significant rise of risk as compared to 35-µg EE/ norgestimate COCs and levonorgestrel COCs. As there is conflict between the two studies, one showing no risk of hazard while other concluded a twice the expanded risk, it is difficult for the physicians and consultants practicing in family planning to choose the appropriate OCP. Some authors are of the conclusion that the transvaginal or intra uterine hormone delivery systems might have relatively less chances of developing thrombotic problems as compared to oral preparations, but still studies should be done to prove this for different populations of different regions and races.[2]

Anti-thrombin levels in our study are significantly reduced in hormonal contraceptive users as compared to controls who are not using hormonal contraceptives. Out of controls only one patient (4%) is having antithrombin levels below 86% and rest of 54 controls have values above 86% with mean of 94.2%. 24 cases of our study (96%) have values of antithrombin below 86% while 31(36.5%) have above 86% level. Odd ratio is 2.833(95%) with CI (2.125-3.778). Mean values for OCP users were 87.5+/- 2.5, injectable hormonal method users have mean antithrombin levels of 87.17%, long acting sub-dermal hormonal contraceptive users have mean value of 87.53 which is showing that all have lower normal values as compared to controls.

Another study giving strong evidence that the users of progestin-only OCPs had similar thrombotic problems as that caused in non-users. Data analyses of lab results of coagulation profile of females using injectable progestin method for contraception have no expanded risk of development of thrombotic activity.

A study on post-operative thrombosis showed that only 1 of 122 cases not using any preventive contraception versus 0 of 99 cases on hormonal contraceptive OCPs had post-op thrombosis. This shows that there is no extra-ordinary risk of post op thrombosis in relation to the use of OCPs. In another study, plasma antithrombin activity was estimated before a procedure in around 81 patients half were using hormone OCPs and other half were placed in control group. Analysis of all the lab investigation of the two groups showed significant fall in antithrombin level, antithrombin action, and anti-factor Xa activity. Maximum fall was in the anti-factor Xa activity (103 $\pm$ 24% to 81 $\pm$27%). It was reported that 15% patients using the hormone OCPs[13]

A study on plasma levels of FVII, Factor X, and fibrinogen in females on hormone OCPs showed changes similar to those seen in our study. They concluded that type and quantity of estrogen and progesterone doesn't matter.[14] Fibrinogen levels rise along with shortening of APTT.

A study conducted in Physiology department in Dhaka in 2012 on healthy females taking OCPs for more than 6 months and compared them with healthy control group of females not taking OCPs. They concluded that mean total platelet count was higher ($P<0.001$) in females on contraceptives along with fibrinogen level. Researchers ended up with the conclusion that OCP users have increased tendency of hypercoagulable state and thromboembolism.[15]

In the current study, use of either mode of hormonal contraceptives has led to increased tendency of thrombosis in terms of shortened PT and APTT, while increase in fibrinogen and lowering of antithrombin levels in all three groups.

Babatunde AS, et al reported that mean values of platelet count and fibrinogen were prominently increased, while PT and TT reduced significantly after 3 months of contraceptive usage but APTT values were not significant before and after oral contraceptive use. Monitoring of haemostatic parameters in women using contraception is important.[16]

Elsayid M, et al reported significant fall in in TT and rise in APTT compared to controls, and changes in PT and fibrinogen level were not significant. Analysis of data in this study showed that the outcome variables were not affected with age, type and duration of use of OCP.

On the contrary, no significant difference was seen in these blood parameters (p value was not significant). Un-like ours, they concluded combined OCPs use have minor effects on PT, APTT and fibrinogen levels when compared with healthy controls.[17]

Zia A, et al reported that among all the participants on OCPs, 60% were in hyper-coagulable state. They concluded that use of OCPs lead to a state of hypercoagulability by activating protein-S system. Various factors including both the Genetic and non-genetic ones determine the intensity of the increase in hypercoagulability. Further studies should be done to see these changes in our local female population.[18]

CONCLUSION

Hormonal oral contraceptive pills lead to disturbance in the coagulation profile of the users. Significant shortening of PT, APTT with increase in the fibrinogen and decrease in

antithrombin levels were seen in our study. The use of non-hormonal contraceptives should be promoted and regular monitoring of the females taking hormone OCPs should be done for any thrombogenic tendency.

REFERENCES

1. Majeed T, Qadir U, Mahmood Z. Prevalence of Contraceptive Methods and Factors Influencing the Choice of Temporary Vs Permanent Methods of Contraception - A Multicentre Urban Study [online] Available at <http://pjmhsonline.com/AprJune2012/prevalence_of_contraceptive_methods%20and%20factors.html
2. Trenor CC, Chung RJ, Michelson AD, Neufeld AJ, Catherine M. Hormonal Contraception and Thrombotic Risk: A Multidisciplinary Approach. Pediatrics. 2011; 127(2):124-136
3. Brandy KR, Rachel M, Meyer BS. Evaluation of the Coagulation Profile Among Oral and Vaginal Combined Hormonal Contraceptive Users Using Sonoclot Coagulation Analyzer. Clin. Appl. Thromb. Hemostat. 2012;18(6):576-581
4. Elsayid M, Elbasheer M, Elgari MM, Elfaki TE. The Effect of Contraceptive Pills on Coagulation Tests among Sudanese Women in Khartoum StateSudan. IJSR 2016;
5. Rodrigues RC, Belham FS, Garcia A, Satler C, Tomaz C, Tavares MC. Continuous Use of Combined Hormonal Contraceptive and the Effect on Blood Coagulation Factors in Female Capuchin Monkeys (Sapajus libidinosus) Intern J Endocr, 2019; 2019:ID 2047803, 9 pages.
6. Liu H, Yao J, Wang W, Zhang D. Association between duration of oral contraceptive use and risk of hypertension: A meta-analysis. J Clin Hypertens. 2017; 19: 1032– 1041. https://doi.org/10.1111/jch.13042
7. Woods GM, Kerlin BA, O'Brien SH, Bonny AE. A Review of Hormonal Contraception and Venous Thromboembolism in Adolescents. J Pediatr Adolesc Gynecol 2016; 29:402e408
8. Lidegaard O, Lokkegaard E, Svendsen AL. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009; 339:b2890
9. Lidegaard O, Nielsen LH, Skovlund CW. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011; 343:d6423
10. Akhter QS, Akhter N, Begum UN, Rahman F. Assessment of coagulation disorder in women taking oral contraceptives. J Bangladesh Society of Physio. 2014;9(1):1-5.
11. Manzoor S, Ganie MA, Amin S, Shah ZA, Bhat IA, Yousuf SD, et al. Oral contraceptive use increases risk of inflammatory and coagulatory disorders in women with Polycystic Ovarian Syndrome: an observational study. Scientific reports. 2019 Jul 15;9(1):1-8.
12. Stucco B, Helen F, Silvio A, Edson Z, Marzocchi-Machado M. Comparative study of the effects of combined oral contraceptives in hemostatic variables. Medicine. 2015;94(4):385
13. Gallus AS, Chooi CC, Konetschnik F, Goodall KT. Oral contraceptives and surgery: reduced antithrombin and antifactor Xa levels without postoperative venous thrombosis in low-risk patients. Thrombosis Research, 1984;35(5):513-526
14. Weiss C, Walter B, Micha F. Fibrinolytic response to exercise in women using third-generation oral contraceptives. Blood Coagulation and Fibrinolysis. 2006;17:563–568
15. Akhter QS, Atiquzzaman N, Naima BU, Rahman F. Assessment of Coagulation Disorder in Women Taking Oral Contraceptives Bangladesh Soc Physiol. 2014; 9(1): 1-5
16. Babatunde AS, Olatunji PO. Short-term effect of oral contraceptive pills on some haemostatic parameters in healthy Nigerian women. Niger Postgrad Med J. 2004 Dec;11(4):246-50. PMID: 15627149.
17. Salman ST, Hussein AA, Saadi RK. Effect of Combined Oral Contraception on Coagulation Profiles in Women Attending Fertility Control Clinic In Baqubah City- Iraq.
18. Zia A, Callaghan MU, Callaghan JH, Sawni A, Bartlett H, Backos A, et al. Hypercoagulability in adolescent girls on oral contraceptives-global coagulation profile and estrogen receptor polymorphisms. Am. J. Hematol., 2015;90: 725-731