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EFFECT OF HORMONAL CONTRACEPTIVES ON INFLAMMATORY BLOOD BIOMARKER C-REACTIVE PROTEIN

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ABSTRACT: To compare the effect of combined oral contraceptive (COC) and progesterone-only injectable contraceptive (PIC) on the inflammation, we recruited 47 female participants (16 to 43 years old) in 3 groups: control participants (n=10), COC users (n=16) and PIC users (n=21). Using ELISA and Latex agglutination methods, we measured the effect of hormonal contraceptives on the inflammatory blood biomarker, C-reactive protein (CRP). Data were collected from July 2019 to January 2020 from Rajshahi Medical College and Hospital. The users of both COC and PIC had higher levels of CRP ($p<0.001$), as compared to the controls, and COC users had higher levels as compared to PIC users ($p<0.001$). We also found a correlation between the CRP data of contraceptive users and some socio-demographic variables. The CRP values of different demographic variables in the Elisa method but not in the Latex method were significantly correlated ($p<0.01$). There was a significant association between the types of contraceptives used, as measured both Latex and Elisa methods. Our data suggested that limiting hormonal contraceptives can decrease the high-sensitivity CRP in women. Longitudinal studies with a larger sample size are needed to better assess the inflammatory and agglutination response due to contraceptive use. CRP values in the Latex method were statistically insignificant ($p>0.05$), but the variations of CRP values in the Elisa method were statistically significant ($p<0.001$). Only the Elisa test is recommended for the measurement of CRP.

INTRODUCTION: Reproductive health has been a great concern for every woman in developing countries, especially in Bangladesh, as maternal mortality and morbidity are very high.

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Though Bangladesh has achieved remarkable progress in important aspects of health and family welfare, the overall health status, particularly in the reproductive health-related medications and the critical side effects those women are experiencing every single day, still remains unsatisfactory [1, 2]. Estrogen and progesterone are the two female sex hormones that regulate the female reproductive system. Estrogen regulates women's menstrual cycle, control cholesterol level and protects against bone decay [3]. Progesterone, a steroid hormone,

plays an important role in reproduction, including the monthly menstrual cycle. It is responsible for preparing endometrium implantation, maintaining the gestational sac in the uterine cavity, and regulating the maternal immune system [4]. Though COCs are accepted as an effective and safe contraceptive option, these methods are still underused, likely due to a lack of awareness about their availability and utility among women [5]. The CHC utilizes synthetic derivatives of naturally occurring female sex hormones (estrogen and progesterone) to inhibit ovulation and prevent pregnancy. Studies have shown that CHC use is linked to an increased risk of vascular events, including venous thromboembolism (VTE), myocardial infarction (MI) and stroke [6-11].

C-reactive protein (CRP) is a polypeptide molecule belonging to the family of pentraxins and is synthesized primarily by the liver in response to certain pro-inflammatory cytokines. It is a protein of acute systemic inflammation and is, therefore, a prime marker of inflammation [12]. In healthy women, elevated CRP is one of the most significant predictors of cardiovascular disease and heart attack risk [13, 14]. The circulating level of CRP is commonly used as an inflammatory marker to assess the risk for cardiovascular disease (CVD) and stroke [15-20]. The significance of elevated CRP as a marker of inflammation in the clinical setting has been suggested in the literature. The association between the cytokines and high-sensitivity CRP (Hs-CRP) and different events has also been demonstrated [17, 21, 22]. The use of hormonal contraceptives has been reported to increase the level of CRP. The high level of estrogen and progesterone affects physical and mental health in women [23]. Therefore, our objective was to assess the plasma levels CRP due to use of combined oral contraceptives (COC) and Progesterone-only injectable contraceptives (PIC). This study will help make some appropriate recommendations for the awareness of contraceptive use.

MATERIALS AND METHODS:

Users and Non-users of Contraceptives: In this study, reproductive women between 16 to 43 years of age were recruited in three groups: 1) Control or non-user subjects (n=10): women who had not been on any hormonal contraceptive for a minimum of six months, (2) COC users (n=16): women who have been using combined oral contraceptive pills for a minimum of six months and (3) PIC users (n=21): women who have been using progesterone-only injectable contraceptives for a minimum of six months. With the authority's approval, blood samples were collected over six months from the outpatient department of gynecology and obstetrics at Rajshahi Medical College and Hospital (RMCH), Rajshahi. IEC approval number 2597/4. With consent provided by the subjects, both the users and non-users were asked to fill out a standardized questionnaire describing their medical history, educational background, and familial history with their health status. This cross-sectional study was designed to compare the predictive value of the CRP level with some socioeconomic and demographical factors. Women's age, their educational level (illiterates, under-graduates, and graduates), duration of contraception use, age at the time of marriage, number of children, etc were considered in the questionnaire. The exclusion criteria included a recent history of viral or bacterial infection, history of recent surgery, history of chronic inflammatory diseases, history of malignancy, and history of pregnancy within the last six months prior to the study. Also a history of any kind of medications within one week prior to the study was known.

Laboratory Methods: Following the subject examination, phlebotomy was performed to collect whole blood in serum separator Vacutainer tubes (Fuzhou Changgeng Medical devices Co, Fuzhon, China) containing sodium citrate and ethylenediaminetetraacetic acid (EDTA). The citrated blood samples were centrifuged at 1000 g for 15 min to collect plasma samples. The Serum separator tubes were allowed to clot for 30 minutes and then centrifuged at 1000 g for 15 minutes. All samples were appropriately aliquoted and labeled for storage at −80°C for further analysis.

A test for ultrasensitive CRP concentration was completed by the United Diagnostic Center clinical laboratory, Laxmipur, Rajpara, Rajshahi. Frozen plasma and serum samples were tested using the enzyme-linked immunosorbent assays (ELISA) and the Latex agglutination method. The ELISA tests were performed per manufacturer instructions (Genrui Biotech Inc., India). The Latex agglutination method is an *in-vitro* diagnostic assay

for the quantitative determination of CRP in human serum and plasma. The test is based on the immunological reaction between CRP as an antigen in the serum sample and polyclonal anti-CRP antibody coated on the surface of biologically inert latex particles, resulting in agglutination. Kinetic determination of CRP concentration by photometric measurement at 546 nm of antigen-antibody reaction between antibodies to human CRP bound to polystyrene particles and CRP present in the sample. The actual concentration is then determined by interpolation from a calibration curve prepared from calibrators of known concentration.

The increase in absorbance at 546 nm is proportional to the CRP concentration (Laboratory Procedure manual of Genrui Biotech Inc., India). According to the American Heart Association (AHA) and the CDC (Centers for Disease Control), Atlanta, USA, the following guidelines are recommended for the assessment of cardiovascular risk in regards to high-sensitivity C-reactive protein (hs-CRP) levels [24]:

The cardiovascular risk in regard to hs-CRP levels	
Risk	hs-CRP Level
Low risk	1 milligram (mg) per liter or less
Moderate risk	between 1 and 3 mg per liter
High risk	greater than 3 mg per liter
Acute plaque rupture (a stroke or heart attack)	greater than 10 mg per liter

Statistical Analysis: All continuous measurements were analyzed for departure from normality. For variables with relatively normal distribution, mean and standard deviation (mean ± SEM) were reported. The Independent sample t-test was used for comparison of continuous variables with the CRP scores. Analysis of variance (ANOVA) was used with multiple comparison tests to find the differences in the score of biomarker method among the reproductive women. Pearson's correlation coefficient was used to find the degree of relationship between two continuous variables. Statistical Package for Social Sciences (SPSS, IBM version 20) was used for analyzing our data. A value of $p<0.05$ was considered as statistically significant.

RESULTS: In total, 47 participants (10 control/non-user participants, 16 COC users, and 21 PIC users) were successfully enrolled in our study. The analysis of some demographic characteristics and duration of contraceptive use with CRP serum level for both lower and elevated levels are presented in **Table 1**.

Age, age at marriage, number of children, and the duration of contraceptive use were compared with the low and high-risk levels of CRP estimated by Latex and Elisa methods [24]. According to the Elisa method, 37 users out of 47 participants were found to have their CRP values in elevated level (≥3 mg/L), whereas 10 non-users were found in low risk level with the CRP values of ≤1 mg/L). The non-users were found significantly ($p<0.001$) younger (23.10 ± 0.657 year) than the users (31.30 ± 1.015 year) and the marital age of control group was found significantly higher than the users ($p<0.001$). They also had fewer children (0.90±0.100) than the user group (1.81±0.122). Moreover, the users have a significantly ($p<0.001$) higher duration of contraceptive use (6.54±0.400 year) than the non-user control group (2.20±0.467 years). In the Latex method, the variation of CRP values was not significant in respect of age, age at marriage, number of children and duration of contraceptive use ($p>0.05$). On the other hand, CRP values in respect to all variables were found highly significant ($p<0.001$), as the CRP was tested by the Elisa method **Table 1.**

TABLE 1: COMPARISON OF MEAN DIFFERENCE OF LOW-RISK LEVEL AND ELEVATED CRP LEVEL FOR DEMOGRAPHICS AND DURATION OF CONTRACEPTIVE USES

Variables	CRP Latex		P-value	CRP Elisa		P-value
	Low-risk level N=14 Mean ± SEM	High-risk level N=33 Mean ± SEM		Low-risk level N=10 Mean ± SEM	High-risk level N=37 Mean ± SEM	
Age	28.79±1.928	29.88±1.089	0.603	23.10±0.657	31.30±1.015	0.000*
Age at marriage	17.36±0.626	16.67±0.297	0.264	19.00±0.494	16.30±0.260	0.000*
No of children	1.43±0.173	1.70±0.141	0.278	0.90±0.100	1.81±0.122	0.000*
Duration of contraceptive use	5.14±0.851	5.82± 0.482	0.488	2.20±0.467	6.54±0.400	0.000*

CRP, C-reactive protein *1% level of significance.

The CRP level was compared between the contraceptive users and non-users, as shown in **Table 2** and **Fig. 1**. Both COC and PIC contraceptive users were found to have higher CRP level than control participants. Mean concentration of high-sensitivity CRP in COC and PIC users were 5.44 (SEM ±0.49) and 5.95 (SEM ±0.58) mg/L, respectively, and were significantly higher (six-fold) than that of non-users (0.50 mg/L, SEM ±0.04) in Elisa method (p<0.001).

As measured by the Latex method, the mean concentration of high-sensitivity CRP in COC (8.06 mg/L) and PIC (8.19 mg/L) users rose significantly and were about two-fold higher when compared to the non-users (5.6 mg/L). However, this difference was not statistically significant (p>0.05), because the latex method is not a quantitative technique, So, all data were close to each other and had no variation **Fig. 1.**

TABLE 2: COMPARISON OF CRP LEVELS BETWEEN CONTRACEPTIVE AND NON-CONTRACEPTIVE USERS IN TOTAL 47 HEALTHY WOMEN

		N	Mean ± SEM	Minimum	Maximum
CRP level in Latex method mg\l	Nonuser control group	10	5.60 ± 0.45	4.00	8.00
	COC	16	8.06 ± 0.79	5.00	12.00
	PIC	21	8.19 ± 0.74	5.00	12.00
	Total	47	7.60± 0.46	4.00	12.00
CRP level in Elisa method mg\l	Nonuser control group	10	0.50 ± 0.04	0.30	0.70
	COC	16	5.44 ± 0.49	3.00	9.01
	PIC	21	5.95 ± 0.58	3.00	10.00
	Total	47	4.61 ± 0.44	0.30	10.00

The variation within CRP values between the two types of contraceptive groups (COC and PIC) was analyzed by one-way ANOVA in the Latex and Elisa methods used in **Table 3**. The CRP values between COC and PIC groups as tested by the Latex method was found statistically insignificant (p>0.05), whereas that values between the two groups measured by Elisa method was found to be highly significant (p<0.001). The multiple comparison tests of CRP values between the contraceptive users and non-users was measured by Bonferroni *post hoc* analysis and revealed that both the COC (95% confidence interval: -7.87, -2.80) and PIC (95% confidence interval: -7.48, -3.42) groups were highly significant (p<0.001) when compared with the non-user control group. The *post hoc* analysis of CRP values was done only in the groups tested by Elisa method, as the difference of CRP values between the groups tested by Latex method was not significant.

TABLE 3: ANALYSIS OF VARIANCE (ANOVA) FOR ELISA AND LATEX TEST RESULTS

Variable	Sum of square		Degrees of freedom		Mean squares		F_{cal}	P value
	Between-group	Within-group	Between-group	Within-group	Between-group	Within-group		
CRP Latex	50.74	400.58	2	44	25.37	9.11	2.787	0.073
CRP Elisa	217.35	198.46	2	44	108.67	4.51	24.090	0.000*

*1% level of significance

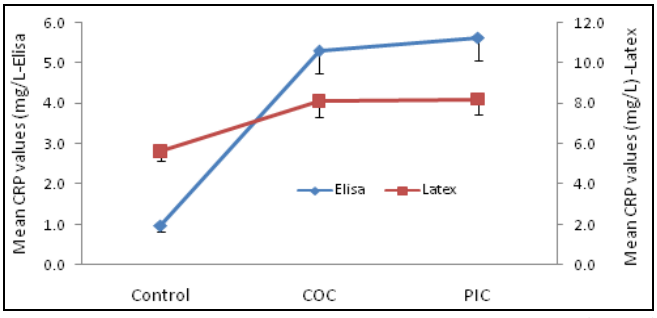

FIG. 1: MEAN CRP VALUES ± SEM OF COC (N=16) AND PIC (N=21) CONTRACEPTIVE GROUPS, AS COMPARED TO THE CONTROL NON-USER GROUP (N=10). CRP WAS MEASURED BY ELISA AND LATEX METHODS

In our study, we attempted to measure the relative risk of CRP high sensitivity between the contraceptive users and non-users **Table 4**. In Elisa method, the percentage of the contraceptive users with high-sensitivity CRP concentrations ranging from <0.5 mg/L to <3.0 mg/L, 3.0 mg/L to <10.0 mg/L and 10.0 mg/L to >10 mg\L was 76.59% and 2.13 %, respectively. On the other hand, the percentage of high-sensitivity CRP of all non-users (n=10) ranging from 0.5 mg/L to <3.0mg/L was 21.27%. No woman had a high-sensitivity CRP more than 10 mg/L. Remarkably, contraceptive

users compared with the non-users had more frequently high-sensitivity CRP risk levels. In Latex method, the percentage of contraceptive users with high-sensitivity CRP concentrations varying from <6 mg/L to ≤12.0 mg/L was 10.64% (n= 5), 68.9% (n=32) respectively; whereas, the percentage of nonuser control group (n=10) with high-sensitivity CRP concentrations <6 mg\L was 21.27 %. Similar to the Elisa method, the Latex method also showed a lower risk CRP level for non-users, as compared to users.

TABLE 4: RELATIVE RISK BETWEEN CONTRACEPTIVE USERS (N=37) AND NON-USERS (CONTROL, N=10) FOR CRP HIGH-SENSITIVITY

Latex Test			Elisa Test		
CRP (mg/L)	**Variable**	**N (%)**	**CRP (mg/L)**	**Variable**	**N (%)**
<6 mg\L	Nonuser	10(21.27)	<0.5 mg/L to <3.0 mg/L	Nonuser	10(21.27)
	User	5(10.64)		User	0
≤ 12 mg\L	Nonuser	0	3.0 mg/L to <10.0 mg/L	Nonuser	0
	User	32(68.9)		User	36(76.59)
			≥ 10.0 mg\L	Nonuser	0
				User	1(2.13)
	Total	47(100)		Total	47(100)

Even though constrained by small sample sizes in our study, the Elisa values showed significant positive and linear associations between CRP and demographics (age, age at first marriage, and duration of contraceptive use) both in users and non-users. In the Elisa test group, the high sensitivity CRP was significantly associated with age (Pearson's correlation= 0.417, p<0.01), age at first marriage (Pearson's correlation= -0.313, p<0.01) and duration of contraceptive use (Pearson's correlation=0.364, p<0.01). However, as shown in the table, Pearson's correlation coefficient showed both positive and negative but insignificant associations between demographics and the CRP Latex results (p>0.05). Both the results are presented in **Table 5.**

TABLE 5: PEARSON'S CORRELATIONS (RS) BETWEEN CONCENTRATIONS OF HIGH-SENSITIVITY CRP (MG/L) AND VALUES OF DEMOGRAPHIC VARIABLES IN SUBJECTS

Variables	Latex		Elisa	
	Correlation coefficient (rs)*	**p***	**Correlation coefficient(rs)***	**p***
Age	0.188	0.207	0.417**	0.01
Age at first marriage	-0.049	0.786	-0.313	0.01
Duration of contraceptive use	0.033	0.825	0.364	0.01

* Correlation coefficients (rs) are presented according to two-tailed Pearson test. **. Correlation is significant at the 0.05 level (2-tailed).

To find out the association between CRP level and the types of contraceptives (COC and PIC), the Chi-square ($\chi 2$) test was used, as presented in **Table 6**. Since the p-value is less than our chosen significance level of 0.05%, we can conclude that there is a highly significant association between CRP level and the types of contraceptives used: Latex method- X^2 = 6.67, p<0.01 and Elisa method - X^2 = 48.65, p <0.001, which indicate that the variables were independent both in Latex and Elisa methods.

TABLE 6: CHI-SQUARE (X2) TEST BETWEEN CRP LEVEL USING LATEX AND ELISA METHOD AND TYPES OF CONTRACEPTIVE USERS

Variable		Latex method				Elisa method			
Types of contraceptive users	Total n (%)	CRP risk level, n (%)				CRP risk level, n (%)			
		Normal	High	X^2	P value	Normal	High	X^2	P value
Non-user	10(21.3)	6(60)	4(40)			10(100)	0		
COC	16(34.0)	2(12.5)	14(87.5)	6.67	0.036	0	16(100)	48.65	0.000
PIC	21(44.7)	6(28.6)	15(71.4)			1(9.1)	20(90.9)		

DISCUSSION: The plasma level of CRP is considered a marker of hepatic protein response to acute inflammation, as it exists in very small amounts in human serum and its serum

concentration increases rapidly with the onset of acute inflammation. In this study, the effect of COC and PIC on the inflammatory blood biomarker CRP was evaluated in 47 healthy women of reproductive ages. Our results suggest that minimum 6 months of use of COC and PIC caused a significant increase in serum CRP concentration, which is very similar to a work using OCP for three months that caused a significant increase in serum CRP concentration and homocysteine levels [25]. Additionally, previous studies demonstrated an association between increased hs-CRP and risk of cardiovascular disease in women [13, 14].

It is suggested that the use of COCs and PICs in our study could have damaged the CRP metabolism and induced the formation of free radicals, which in turn stimulated CRP and homocysteine synthesis. It is not precisely known if hormonal contraceptives directly affect hepatic CRP synthesis. However, several factors are known that are involved in the elevation of CRP levels in COC users [26]. The significantly increased oxidative stress in oral contraceptive users could lead to an elevated cardiovascular risk, such as thromboembolism. Also, in another study, the increased level of lipid peroxides (+176 %) and oxidized low-density lipoproteins (+145 %) in 32 oral contraceptives (OC) users were found when compared to 30 non-OC users [27]. However, the mechanisms leading to the elevation of hydroperoxides by contraceptive use still need to be clarified.

We found that hormonal contraceptives have a major effect on hs-CRP levels such that both the COC and PIC users increased CRP six times when compared to non-users, as tested by Elisa method. However, CRP increase in contraceptive users was two-fold higher in the Latex method than in non-users and the increase was statistically insignificant. Surprisingly, we also found that the contraceptive users, compared to non-users, were much less likely to have protective hs-CRP levels less than 0.5 mg/L. The small sample size in our study might have reduced the power of the interpretation of the results and increased the margin of error. However, acknowledging that limitation, we used Bonferroni post hoc analysis to correct the experiment-wise type I error rate following analysis of variance (ANOVA). Interestingly, both the COC and PIC groups were found significant ($p<0.01$) when compared with the non-user control group in 95% confidence interval, suggesting that there were noticeable differences between the user and non-user control groups in respect of the elevated CRP level. Another finding in our study was the insignificant outcome of the Latex agglutination method. In this study, using two different methods, Elisa and Latex, the CRP level between the contraceptive and non-contraceptive users following Latex agglutination method appeared insignificant ($p>0.05$).

Additionally, as measured by Latex, Pearson's correlation coefficient showed positive and negative but insignificant associations between demographic variables and CRP concentration ($p>0.05$). At the same time, the variation within the CRP level in respect of minor changes were not detectable, indicating that the qualitative latex method is not the proper method to analyze serum CRP level.

We observed that hs-CRP was positively correlated and had a linear association with the variables of demographics: age (Pearson's correlation= 0.417, $p<0.01$), age at first marriage (Pearson's correlation=-0.313, $p<0.001$) and duration of contraceptive use (Pearson's correlation=0.364, $p<0.001$), meaning the increasing value of participant's age and duration of contraceptive use simultaneously increases the serum CRP level. Moreover, highly significant association was also found between the CRP level and the types of contraceptives used, indicating that the variables were independent. As a consequence, our data suggest that the only modifiable risk factor to decrease hs-CRP in women may be limited to the reduction of hormonal contraceptive use. Increased average hs-CRP concentration in oral contraceptive users has also been observed in other research works [28-32].

CONCLUSION: Our study shows that many young, healthy hormonal contraceptive users have elevated concentrations of hs-CRP, demonstrating that they are potentially at higher disease risk than non-users. Consequently, the hormonal contraceptive effect may have implications for the development of cardiovascular disease and others. Also, a significant positive and linear association

between CRP and demographics, such as age, age at first marriage, and the duration of contraceptive use, has been observed. Further research is needed to extend our results to clarify the biochemical pathways leading to increased plasma C-reactive proteins in COC and PIP users.

Author Contributions: SSL conceived, designed, collected data and wrote the manuscript. FH analyzed data. AMJ provided diagnostic and laboratory support. SAL and MI collected data. RH designed and supervised the study and improved the manuscript through careful review and helpful suggestions.

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CONFLICT OF INTEREST: Authors declare no conflict of interest concerning the research reported herein.

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