EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 1
01-10
Year: 2019

ISOLATED EFFECT OF PROGESTOGEN-ONLY CONTRACEPTIVES ON SOME COAGULATION PARAMETERS OF WOMEN ATTENDING FAMILY PLANNING CLINICS IN KADUNA STATE, NIGERIA

***[1]Egbunah M. O., [1]Eze E. M., [1]Ebirien-Agana B. S. and [2]Jeremiah Z. A.**

[1]Department of Medical Laboratory Science, Rivers State University, Nkpoluoroworukwu Port Harcourt,
[2]Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Bayelsa State, Nigeria.

***Corresponding Author: Egbunah M. O.**
Department of Medical Laboratory Science, Rivers State University, Nkpoluoroworukwu Port Harcourt.

Article Received on 25/10/2018 **Article Revised on 15/11/2018** **Article Accepted on 05/12/2018**

ABSTRACT
Progestogen-only contraceptives (POCs) contain different types and doses of progestogens and are widely used to prevent unwanted pregnancy. However, these steroids may be associated with some adverse effects. This is a cross-sectional study conducted among a total of 250 reproductive aged women comprising150 injectable and implant progestogen-only users and100 non-users, attending the family planning clinic of Yusuf Dantsoho Memorial Hospital and Primary Health Centre, in Kaduna State of Nigeria. The aim of this study was to assess the effect of these contraceptives on some coagulation variables. 4.5mls of venous blood was collected from each participants using standard venipuncture technique into 0.5mls of 31.3g/L trisodium citrate solution for PT, APTT and Fibrinogen concentrations using reagent kits. All standard operating procedures were adhered to. The data obtained were analyzed using R 3.03 software. The mean±SD of PT (15.06±1.58s) and APTT (31.74±3.99s) for contraceptives users were significantly lower than the control (PT: 15.70±1.52s, APTT: 34.44±5.02s) ($P<0.05$) while mean±SD of fibrinogen were not significantly different between the groups ($P>0.05$). Contraceptive users were divided into implant and injectable groups. The implant group showed shortened APTT (29.97±3.02s) and increased fibrinogen (243.62±53.21mg/dl) compared to 32.46±4.13s and 199.08±75.02mg/dl respectively for the injectable group ($p<0.05$). These values were confirmed with the route of administration. A mild, positive association exist between APTT and duration of implant use ($p<0.05$). Fibrinogen increased with BMI increase as 201.13±54.35mg/dl, 205.27±72.26mg/dl, 235.11±66.96mg/dl and 276.05±70.59mg/dl were observed for underweight, normal weight, over weight and obese respectively ($p<0.05$). BMI correlated moderately and positively with fibrinogen, all favouring a state of hypercoagulability. Monitoring of POC users for coagulation parameters and regular weight checks at each visit is recommended.

KEYWORDS: Progesterone, contraceptives, coagulation, women, Kaduna, Nigeria.

INTRODUCTION
Progestogen-only contraceptives are hormonal contraceptives that contain only progestogen without estrogen. They include the oral preparations (progestogen only pills) and the long acting reversible contraceptive (LARC) medications which include the levonorgestrel intra-uterine system (IUS), the subcutaneous contraceptive implants and the injectable progestogen-only contraceptives. Progestogen-Only Injectables and Implant contraceptives are highly effective, longer-acting contraceptive devices that are ideally offered as part of a wide range of contraceptive options and can be used by women in most situations. Globally, approximately 6% of women who use hormonal contraceptive use injectables and 1% use implants (Jacobstein & Polis, 2014). In Sub- Saharan Africa, injectables are predominant, accounting for 43% of modern contraceptive methods used". The three available progestin-only injectables are depot medroxyprogesterone acetate given intramuscularly (DMPA-IM), Sayana press, a subcutaneous formulation of DMPA (DMPA-SC) and Norethisterone enanthate (NET-EN). DMPA offers contraceptive protection for 3months while Norethisterone enanthate for 2months.

However, the subcutaneous hormonal contraceptive implants consist of one or two small, flexible, non-biodegradable rods, measuring 40 - 44 mm in length and" 2.0-2.5 mm in diameter (Sivin *et al*., 2002). These are made up of different progestogen preparations and dosages, with different intended durations of use (Meirik *et al*., 2013; Mommers *et al*., 2012). Three implants are

currently available. The first available implant was the Norplant, contained 216mg of levonorgestrel (LNG) in six rods, and intended for five years of use but was discontinued in 2008 (Jacobstein & Polis, 2014). This was followed by the two-rod methods (Jadelle and Sino-implant (II) which contain 150 mg of levonorgestrel (LNG), 75 mg in each rod and are supplied with a single-use disposable trocar (Brache *et al*., 2006). Jadelle offers contraceptive protection for five years". "The third implant is the Implanon, a single-rod contraceptive implant which contains 68 mg of etonogestrel (ENG), licensed for three years' use (Graesslin & Korver, 2008"). Implanon delivers ENG at a dose sufficient to suppress ovulation in every cycle throughout the 3 years of use (Makarainen *et al*., 1998; Croxatto, 2002).

The injectable and implant methods prevent pregnancy primarily through ovulation suppression and possibly by increasing the thickness of cervical mucus, which presents a barrier for sperm penetration. In addition, they change the quality of the endometrium, making it an unfavorable environment for fertilization and implantation (Hickey & Fraser, 2000; Bhathena, 2001).

The commonest reason for discontinuation of contraceptive implants and injectables is bleeding disturbances as irregular vaginal bleeding is the main side effect of these steroids (Abdel-Aleem *et al*., 2007; d' Arcangues, 2000; Mainwaring *et al*., 1995). This is also the observation in our setting. Hormonal contraceptives are often associated with side effects commonly, irregular menses, bleeding, amenorrhea, weight gain, wild headache and abdominal pain or discomfort (Davis, 1996). The most drastic but rare side effect has been predisposition to increased risk of thromboembolic phenomena. Researchers have studied the influence of estrogens and progestins on various coagulation parameters and have shown a consistent prothrombotic effect of oral estrogen. Although the increased risk of thrombosis with oral contraceptive pills was attributed to estrogen and its dose (Goldstein *et al*., 2007), subsequent studies suggested increased risk with oral progestins". Coagulation factors, used as a marker for the risk of VTE, have been shown to be adversely effected by progestins particularly of the third generation type (Lidegaard *et al*., 2002). These studies have raised concerns regarding the adverse effect of progestins on coagulation and VTE risk. Prasad *et al*., (1999) "documented the metabolic effect of hormonal contraceptives on haemostatic parameters. Rosendaal *et al*.,(2002) reported increases in coagulation factors VII, VIII, IX, X, XI, XIII and Von Willebrand factor (vWF), and reductions in the activities of natural coagulation inhibitors, i.e. protein C (PC), Protein S, antithrombin and thrombomodulin. These changes may lead to the formation of an obstructive clot in the face of an inadequate balance among procoagulant, anticoagulant and fibrinolytic factors. Reid *et al*., (2011) "noted that Progestin has both antiplasmin and antithrombin activity and that progestin use increases platelet count and aggregability, thereby predisposing to hypercoagulability.

However, hormonal contraceptives do not pose the same risk of thrombosis in different populations (Ferreira *et al*., 2001). Differences exist in the coagulation and haemostatic tests among women who use hormonal contraceptives from widely diverse geographical areas, the cause of which is not clearly understood (Isaac *et al*., 2014). Although, some authors suggested that it could be due to varying incidence of thrombosis, the picture still remains vague concerning the risks of taking such hormonal preparations in different populations (Afsar *et al*., 2005). Consequently, WHO recommended that studies should be conducted in different localities to bring about a better understanding (WHO, 1995). However, the use of progestogen-only injectable and implant contraceptives is on the increase among Nigerian women yet; there is paucity of data on their effect on coagulation variables of Nigerian women hence, this study.

MATERIALS AND METHODS

Study Design

This is a comparative cross-sectional study carried out among women attending family planning clinic of Yusuf Danstoho Memorial Hospital, Kaduna and Primary Health Center, Kaduna South, in Kaduna State who were on either progestogen-only injectables (DMPA or Noristerat or Sayana press) or subcutaneous implant (Implanon or Jadelle). The blood pressure and weight of these subjects were determined by the Nurses working in the family planning Clinic. Informations on age, duration of use, menstrual flow, parity, history of disease and reaction to the contraceptives were obtained from the patients using a structured questionnaire.

Study Area

The study was conducted in family planning clinic of Yusuf Dantsoho Memorial Hospital, Kaduna and in Primary health Center, Kaduna South, in Kaduna State of Nigeria. Kaduna state is located between latitude 90N and 120N of the equator and longitude 60E and 90E of the prime meridian. The state shares boundaries with Abuja and Niger at the South-West, Katsina, and Zamfara at the North-West, Kano and Bauchi at the North-East, Plateau and Nasarawa at the South-East.

Study Population

A total of two hundred and fifty (250) apparently healthy, non-pregnant, non- smoking women, between the age of 18 and 50years, who had no underlying disease condition that could affect their clotting system. One hundred and fifty (150) women on either injectable or implant progestogen-only contraceptives served as the study subjects while one "hundred (100) women who never used hormonal contraceptive method constituted the control participants".

Inclusion Criteria
The entire contraceptive users were subjects who were aged between 18 and 50years, sexually active, normotensive females using long acting contraceptives for a period of at least 2months and above, Women who were willing to participate in the study, non-pregnant and not smoking, women on progestogen-only implant and injectable contraceptives, without underlying disease condition that could affect their clotting system.

Exclusion Criteria
Women below 18years or more than 50years, combined oral contraceptives users or combined injectable contraceptives users non-hormonal contraceptive use and contraceptive use of < 2months, hypertensive, presence of underlying disease condition that could affect their clotting system and failure to give informed consent to participate in the study.

Ethical Consideration
The study was approved by the Research Ethical Committee of the Kaduna State ministry of Health and Primary Healthcare Centre, Kaduna. In addition each of the participants in this study gave informed consent to participate.

Sample Collection and Analysis
4.5mls of venous blood was collected from each participants using standard operating procedure into 0.5mls of 31.3g/L trisodium citrate solution in a test tube. "The blood samples in the citrated containers were thoroughly mixed and centrifuged at 2500g for 15minutes and the plasma was separated into plastic containers for manual determination of prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen concentration using KLabkit reagent (CHEMELEX KLabkit reagent, Barcelona, Spain). The investigations were performed with strict adherence to the manufacturer's instruction.

Data Analysis
All generated data were analyzed using R 3.03 (2016) software. Comparison between two factors was analyzed using T-test while comparisons among three or more factors were analyzed using Analysis of Variance. The Turkey procedure for mean comparison was used to rank the means after a significant effect was observed. Phenotypic correlations between variables were computed using Spearman correlation. Significance was established at $p < 0.05$.

RESULTS
Table 1 shows the demographic characteristics of the contraceptive users. Out of the 150 contraceptive users, 51(34%) were less than 20years while 62(41.33%) were between 20-39years and 37(24.7%) were 40years and above. 39(26%) were Christians while 111(74%) were Muslims. However, their educational status were as follows: primary school: 19(12.66%), secondary education: 86(57.33%), Tertiary education: 35(23.33%) and no formal education: 10(33.33%). None smoked. The menstrual status showed that 25(16.7%) had amenorrhea, 12(8%) had normal flow, 58(38.7%) had irregular menses, 2(1.33%) had uncontrolled bleeding and 53(35.3%) had spotting.

Table 1: Demographic Characteristics of Contraceptive Users.

Characteristics	Number	Percentage
AGE		
<20	51	34
20-39	62	41.33
40 and above	37	24.7
Total	**150**	**100**
Religion		
Christianity	39	26
Islam	111	74
Total	**150**	**100**
Educational Status		
Primary	19	12.66
Secondary	86	57.33
Tertiary	35	23.33
None	10	6.66
Total	**150**	**100**
Smoking Status		
Yes	Nil	
No	150	100
Total	**150**	**100**
Menstrual Status		
Amenorrhea	25	16.7
Normal	12	8
Irregular	58	38.7
Uncontrolled bleeding	2	1.33
Spotting	53	35.3
Total	**150**	**100**

Table 2 shows the comparison of Mean±SD of coagulation parameters of contraceptive users and non-contraceptive users. The mean values of PT and APTT among the contraceptive users (15.06±1.58seconds; 31.74±3.99seconds respectively) were significantly shorter than that of the non-contraceptive users (15.70±1.52seconds; 34.44±5.02seconds respectively) ($P<0.05$). The Mean±SD fibrinogen were not significantly different between the groups ($P>0.05$).

Table 2: Comparison of Mean±SD of Coagulation Parameters of Women on Contraceptives and the Control subjects.

		Group	
Parameters	**Contraceptive users (n=150)**	**Non-contraceptive users (n=100)**	**P-value**
PT (secs)	15.06±1.58[b]	15.70±1.52[a]	0.0212*
APTT (secs)	31.74±3.99[b]	34.44±5.02[a]	0.0004*
FIB (mg/dl)	212.05±72.10	205.26±63.15	0.5810

[abc]Means with different superscript differ significantly, *P<0.05. PT=Prothrombin Time; APTT=Activated Partial Thromboplastin Time; FIB=Fibrinogen

Table 3 shows the comparison of Mean±SD of coagulation parameters of Women on Implants and Injectable contraceptives. The mean values of APTT among the women on implant (29.97±3.02secs) contraceptives were significantly decreased compared to those on injectables (32.46±4.13secs) (P<0.05), while women on implant have higher fibrinogen concentration compared to those on injectable contraceptives group (P < 0.05). There is no significant difference in the mean values of PT between the two groups (P > 0.05).

Table 3: Comparison of Mean±SD of Coagulation Parameters of Women on Implants and Injectable Contraceptives.

	Group		
Parameters	**Implant (n=63)**	**Injectables (n=87)**	**P-value**
PT (secs)	15.36±1.50	14.94±1.60	0.1606
APTT (secs)	29.97±3.02[a]	32.46±4.13[b]	0.0009*
FIB (mg/dl)	243.62±53.21[a]	199.08±75.02[b]	0.0010*

[ab]Means with different superscript differ significantly, *P<0.05. PT=Prothrombin Time; APTT=Activated Partial Thromboplastin Time; FIB=Fibrinogen

Table 4. shows the Mean±SD values of coagulation parameter based on route of contraceptive administration There was no significant difference in the mean values of the PT of women on intramuscular and subcutaneous route of contraceptive administration (P > 0.05) whereas APTT of women in the subcutaneous route of administration group (30.61±3.61secs) was significantly shortened compared to the APTT of the intramuscular route of administration (32.27±4.09secs) (P < 0.05). The fibrinogen concentration of the subcutaneous group (237.40±56.59mg/dl) increased significantly compared to those of the intramuscular group (199.22±75.90mg/dl) (P < 0.05).

Table 4: Comparison of Mean±SD Values of Coagulation Parameters Based on Route of Contraceptive Administration.

	Route of administration		
Parameters	**Intramuscular (n=72)**	**Subcutaneous (n=78)**	**P-value**
PT (secs)	14.98±1.61	15.22±1.52	0.3989
APTT (secs)	32.27±4.09[a]	30.61±3.61[b]	0.0030*
FIB (mg/dl)	199.22±75.901[b]	237.40±56.59[a]	0.0034*

[abc]Means with different superscript differ significantly, *P<0.05. PT=Prothrombin Time; APTT=Activated Partial Thromboplastin Time; FIB=Fibrinogen.

Table 5 shows the Mean±SD values of coagulation parameters of contraceptive users based on BMI. The BMI of the contraceptive users were divided into four classes- underweight, normal weight, over weight and obese. The coagulation parameters revealed that the obese women had a greater fibrinogen concentration (276.05±70.59mg/dl) when compared to the underweight (201.13±54.35mg/dl), normal weight (205.27±72.26mg/dl) and overweight (235.11±66.96mg/dl) contraceptive users (P = 0.0367). There was no statistical difference in the mean values of PT and APTT among the women across the various BMI range (P > 0.05).

Table 5: Comparison of Mean±SD Values of Coagulation Parameters of Contraceptive Users Based on BMI.

	BMI range				
Parameters	**Underweight (n=22)**	**Normal (n=60)**	**Overweight (n=37)**	**Obese (n=31)**	**P-value**
PT (secs)	15.60±1.40	14.97±1.59	14.92±1.50	15.20±1.82	0.4940
APTT (secs)	33.27±3.88	31.56±4.01	31.22±3.27	32.10±5.08	0.3808
FIB (mg/dl)	201.13±54.35	205.27±72.26	235.11±66.96	276.05±70.59	0.0367*

Means with different superscript differ significantly, *P<0.05; SD-Standard deviation. PT=Prothrombin Time; APTT=Activated Partial Thromboplastin Time; FIB=Fibrinogen.

Table 6 shows Mean±SD values of coagulation parameters with regards to duration of contraceptive consumption. No significant difference was observed in the mean values of PT, APTT and fibrinogen between the contraceptive durations of ≤ 1year, 1 – 3 years and ≥ 4 years (P > 0.05).

Table 6: Comparison of Mean±SD values of Coagulation Parameters Based on Duration of Contraceptive Consumption.

	Duration			
Parameters	**≤1 year (n=63)**	**1 – 3years (n=46)**	**≥4(n=41)**	**P-value**
PT (secs)	15.00±1.41	15.11±1.63	14.78±1.31	0.7177
APTT (secs)	34.50±6.36	31.71±3.92	31.61±4.41	0.6161
FIB (mg/dl)	227.00±67.88	212.96±74.31	204.61±60.09	0.8644

Means with different superscript differ significantly, *P<0.05; SD-Standard deviation. PT=Prothrombin Time; APTT=Activated Partial Thromboplastin Time; FIB=Fibrinogen

Figure 1a shows the scatterplot matrix of correlation of duration of contraceptive use with coagulation parameters among subjects on implants. Duration of contraceptive use have mild correlation with APTT (P<0.05) and no significant effect on the PT and Fibrinogen (FIB) (P>0.05). PT is strongly and positively correlated with APTT (r=0.8086) and negatively correlated with fibrinogen (r=-0.7642) while APTT is strongly and negatively associated with fibrinogen (r=-0.9543) (p<0.05).

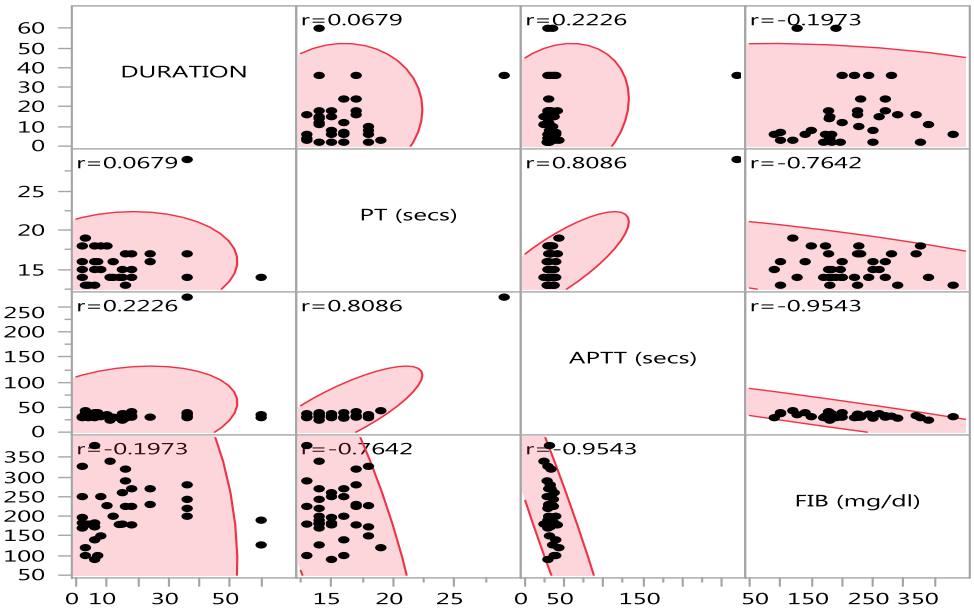

Figure 1a: The Scatterplot Matrix of Correlation of Duration of Contraceptive Use With Coagulation Parameters among Subjects on Implants.

Figure 1b: the scatterplot matrix of correlation of duration of contraceptive use with coagulation parameters of subjects on injectables. There is no significant relationship between the duration of contraceptive use and PT, APTT and Fibrinogen (p>0.05).

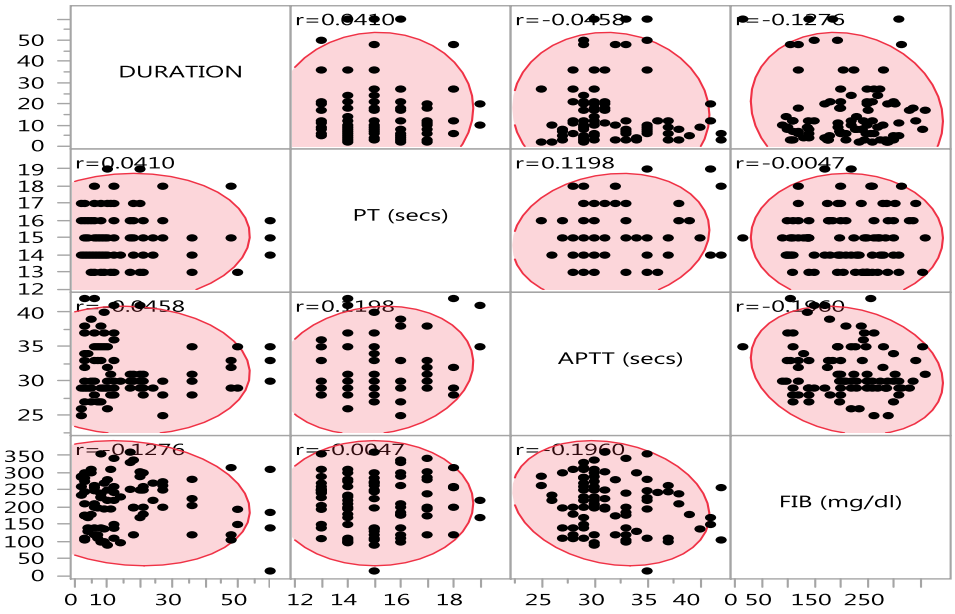

Figure 1b: The Scatterplot Matrix of Correlation of Duration of Contraceptive Use With Coagulation Parameters of Subjects on Injectables.

Figure 2a shows the correlation of BMI with coagulation markers among subjects on implants. BMI shows a positive, mild association with fibrinogen (r=0.3829). PT had a positive, mild relationship with APTT (r=0.3358) while APTT had a moderate, negative association with fibrinogen (r=-0.4541) ($p<0.05$).

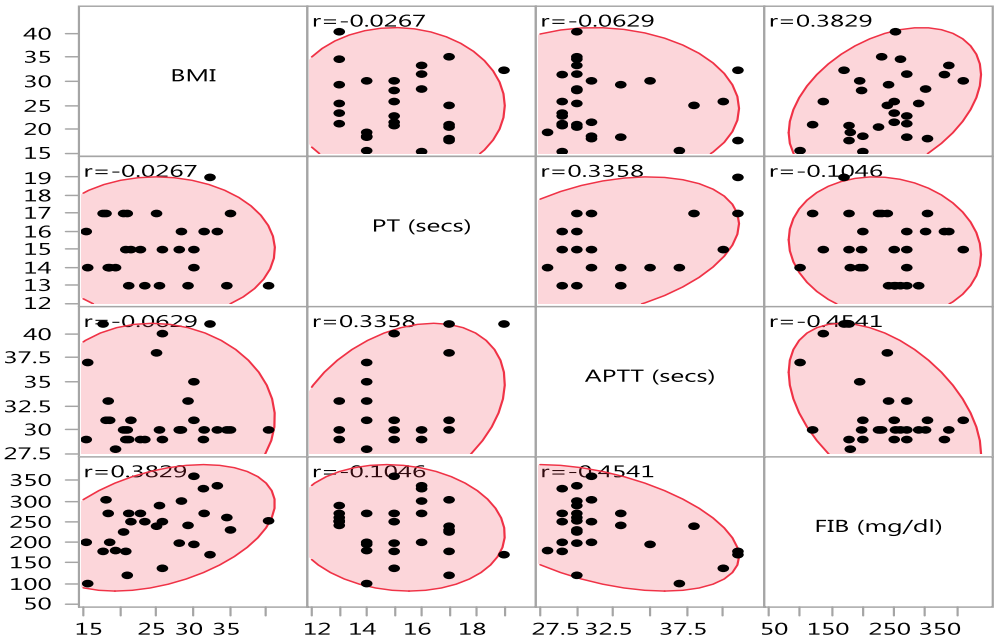

Figure 2a: The correlation of BMI with coagulation markers among women on implants.

Figure 2b shows the correlation of BMI with coagulation markers among subjects on injectables. BMI had a negative, low and insignificant relationship with PT and APTT; and low and insignificant association with fibrinogen concentration ($p>0.05$). PT had a positive and strong correlation with APTT (r=0.6636) and a negative, moderate association with fibrinogen (r=-0.4845) ($p<0.05$). APTT had strong negative correlation with fibrinogen (r=-0.7478) ($p<0.05$).

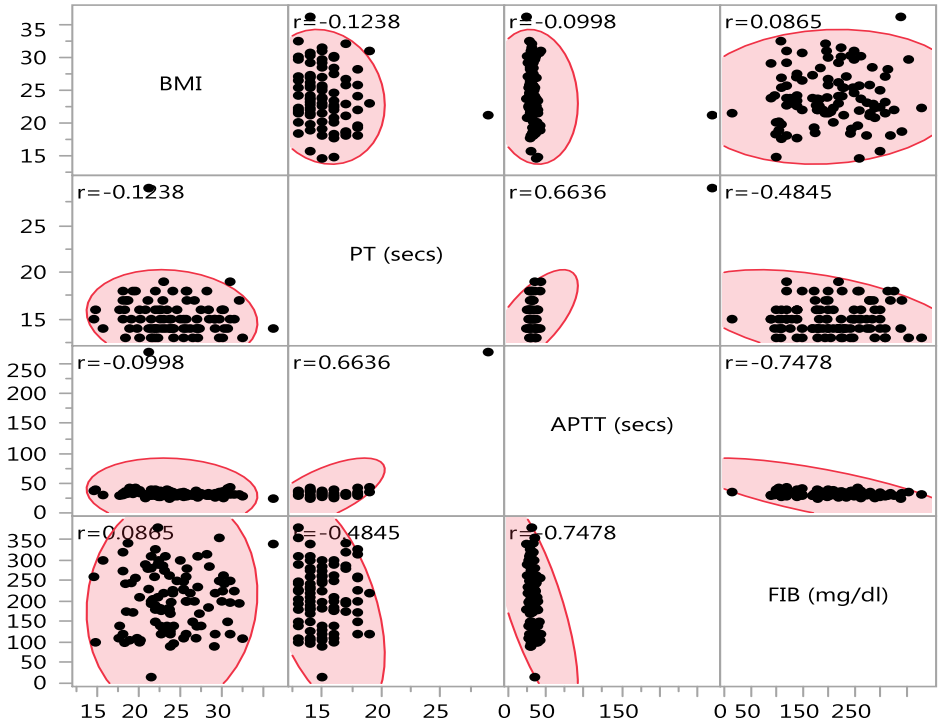

Figure 2b: the correlation of BMI with coagulation markers among subjects on injectables.

DISCUSSION

In the present study, the mean prothrombin time and activated partial thromboplastin times were shortened in the contraceptive group compared to the control group ($P < 0.05$). This finding is in agreement with previous reports by Kluft *et al*., (2006) who observed a decrease in the mean values of PT and APTT in the groups evaluated in their study. A similar study by Ahmed *et al*., (2007) and Afsar *et al*., (2008) reported a significant reduction in APTT and PT of women taking hormonal contraceptives. Abdalla *et al*., (2008) also reported significant reduction in PT and APTT in women taking COC whereas Claus *et al*., (2006) in their study observed shorter APTT in addition to higher levels of fibrinogen in women using hormonal contraceptive compared to the non-users. Our finding is however, at variance with the works of Elsayid *et al*., (2016) who reported significant increase in APTT and a slightly raised PT among the subjects compared to the control although the difference in the mean value of the PT was not statistically significant. Aldright *et al*., (2006) in a trial study also reported a significant increase in APTT result while Osaro *et al*., (2014) reported no statistical significant association between PT and APTT of hormonal contraceptive users and that of the control. The significant shortened PT and APTT observed in this study may be explained by the procoagulant effect of the used progestogen-only contraceptives which includes the increased plasma levels of several coagulation factors including fibrinogen, prothrombin, FVII and FX that are known to affect the extrinsic pathway of the coagulation and hence the shortening of the PT. while there may be accelerated activity in intrinsic pathway of haemostasis thereby giving rise to decreased APTT. Decreased PT & APTT predisposes patients to an increased risk of thrombotic complications (Korte *et al*., 2000).

Elevated plasma fibrinogen levels exert adverse effects on plasma viscosity, platelet activity, coagulation, inflammation and consequently, cardiovascular events (Kakafika *et al*., 2007). In this study, plasma fibrinogen level in women of progestogen-only contraceptive users was higher than that of nonusers. But the result was not statistically significant. This finding was in agreement with the study of different researchers of different countries (Elsayid *et al*., 2016 and Samsunnahar *et al*., 2014) who reported slightly increased fibrinogen concentration in the test subjects compared to the control but without statistical significance. On the contrary, similar types of studies by other workers found higher plasma fibrinogen level in contraceptive users than nonusers, which was statistically significant (AL-Husaynee & Kashmoola, 2007; Abdalla *et al*., 2008). The non-significant increase in plasma fibrinogen levels in progestogen-only contraceptive users than nonusers are most likely due to higher level of blood clotting factors caused by the different progestogen content of the contraceptives and different durations of contraceptive use. In the quantification of the plasma fibrinogen concentration, the implant group presented a significantly increased mean value compared to the injectable group. The result in this study is in consonance with the study of Stocco *et al*., (2015) who observed significant increase in fibrinogen concentration in their comparative study of the effect of COC in haemostatic variables. The effect of the route/mode of administration of POCs produced a statistically significant increase in the plasma fibrinogen levels of contraceptive users on

subcutaneous mode of adminstration compared to contraceptive users on intramuscular mode of administration. This result is in agreement with the report of Claus *et al*., (2006) and Stocco *et al*., (2015) and disagrees with the work of Kasem *et al*., (2017) who reported no significant difference in the plasma fibrinogen levels of their subjects. Duration of contraceptive use had no effect on the PT, APTT and fibrinogen. Our work also showed no correlation between PT and duration of contraceptive use and a mild association between APTT and duration of implant use. This finding is at variance with the work of Osaro *et al*. (2014) who reported a negative association between PT and duration of contraceptive use.

According to World Health Organization, Obesity is defined as abnormal or excessive fat accumulation which may impair health (WHO, 2015). Body mass index (BMI) is the simple index of weight-for-height and is commonly used to classify overweight and obesity. Obesity is an independent risk factor for VTE and increases the risk of thrombosis two-fold (Israa *et al.*, 2015). The BMI correlated positively and moderately with plasma fibrinogen concentration in this study. This report concurs with the work of Harsoor *et al*. (2014) who reported positive correlation between BMI and plasma fibrinogen. The finding in this study is not in consonance with the work of Aigbe (2015) who reported a negative association between BMI and fibrinogen and the work of Halla *et al*. (2017) who reported insignificant association between BMI and fibrinogen in obese subjects. The effect of BMI on progestogen-only users in this study revealed a progressive statistical significant increased plasma fibrinogen level in overweight and obese progestogen-only users compared to the underweight and normal weight contraceptive users. The finding in this study is consistent with the report of Rosendaal *et al*. (2003); Murthy, (2010) who reported that obese individuals have higher levels of the procoagulant factors VII, VIII, XII and fibrinogen. On the contrary, other researchers reported decreased plasma fibrinogen levels in obese individuals (Abdullahi *et al.*, 2003). Elevated plasma fibrinogen level has been documented to be associated with increased risk of cardiovascular events which includes ischemic heart disease, peripheral arterial disease and stroke. Moreover, raised level of plasma fibrinogen promotes a hypercoagulable state and this partly explains the risk of thrombosis.

CONCLUSION

This study showed that there were significant differences between the mean values of some coagulation variables of progestogen-only users and non-users and that the mode of contraceptive administration and BMI affect some of these variables. Monitoring of Progestogen-only contraceptive users for coagulation parameters and regular weight checks at each visit is recommended. Moreover, a follow up study is needed to bring about a clearer picture.

REFERENCES

1. Jacobstein, R. & Polis, C.B. Progestin-only contraception: Injectables and Implants. *Best Practice & Research Clinical Obstetrics and Gynaecology*, 2014; 28: 795-806.
2. Sivin, I., Nash, H. & Waldman, S. Jadelle® Levonorgestrel rod implants: a summary of scientific data and lessons learned from programmatic experience. New York, NY: Population Council, 2002.
3. Meirik, O., Brache, V., Orawan, K. & Ali, M. A multicenter randomized clinical trial of one-rod etonogestrel and two-rod levonorgestrel contraceptive implants with non-randomised copper – IUD controls: methodology and insertion data. *Contraception*, 2013; 87: 113 – 120.
4. Mommers, E. Blum, G.F., Gent, T.G. & Marintchava-Petrova, M. Nexplanon, a radiopaque etonogestrel implant in combination with a next generation applicator: 3 years results of a non-comparative multicenter trial. *American Journal of Obstetrics and Gynaecology*, 2012; 207(5), 388.
5. Brache, V., Faundes, A., Alvarez, F. & Garcia, A. G. Transition from Norplant to Jadelle in a clinic with extensive experience providing contraceptive implants. *Contraception*, 2006; 73: 364–367.
6. Graesslin, O. & Korver, T. The contraceptive efficacy of implanon: a review of clinical trials and marketing experience. *European Journal of contraception and Reproduction Healthcare*, 2008; 13(1): 4 – 12.
7. Makarainen, L., Van Beek, A., Tuomivaara, L., Asplund, B. & Coelingh-Bennink, H. Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. *Fertility & Sterility*, 1998; 69: 714–721.
8. Croxatto, H.B. (2002). Progestin Implants for Female Contraception. *Contraception*, 65, 15 – 19.
9. Hickey, M. & Fraser, 1.S. The Structure of endometrial microvessels. *Human Reproduction*, 2000; 3: 57 – 66.
10. Bhathena, R. K. The long-acting progestogen only contraceptive injections: an update. *British Journal of Gynaecology*, 2001; 108: 3-8.
11. Abdel-Aleem, H., D'Arcangues, C., Vogelsong, K.M. & Gulmezoglu, A.M. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. *Cochrane Database Systematic Review*, CD003449, 2007.
12. Arcangues, C., Management of vaginal bleeding irregularities induced by progestin-only contraceptives. *Human Reproduction*, 2000; 15(3): 24–29.
13. Mainwaring, R., Hales, H.A., Stevenson, K., Hatasaka, H.H., Poulson, A.M., Jones, K.P. & Peterson, C.M. Metabolic parameter, bleeding, and weight changes in U.S. women using progestin only contraceptives. *Contraception*, 1995; 51: 149–153.

14. Davis, A.J. Use of Depot Medioxyprogesterone acetate Contraception in adolescents. *Journal of Reproductive Medicine*, 1996; 41: 407 – 413.
15. Goldstein, J. Cushman, M., Badger, G.J. & Johnson, J. V. Effect of depomedroxyprogesterone acetate on coagulation parameter: a pilot study. *Fertility and sterility*, 2007; 87: 1267 – 1270.
16. Lidegard O., Edstron, B. & Kreiner, S. Oral Contraceptive and Venous Thromboembolisms: A five year national case-control study. *Contraception*, 2002; 65; 187 – 196.
17. Prasad, R. N., Koh, S. C. & Viegas, O. A. Effects of hemostasis after two-year use of low dose combined oral contraceptives with gestodene or levonorgestrel. *Clinical Application of Thrombosis & Hemostasis*, 1999; 5: 60–70.
18. Rosendaal, F.R., Helmerhorst, F.M. & Vandenbroucke, J.P. Female hormones and thrombosis. *Arteriosclerosis, Thrombosis and Vascular Biology*, 2002; 22: 201–210.
19. Reid, R., Leyland, N., Wolfman, W., Allaire, C., Awadalla, A. & Senikas, V. SOGC clinical practice guidelines: Oral contraceptives and the risk of venous thromboembolism: an update. *International Journal of Gynaecology & Obstetrics*, 2011; 112: 252-256.
20. Ferreira, A.C.P., Montes, M.B.A., Franceschini, S.A. & Maria, R.T.T. Effect of two oral contraceptives containing 30µg or 20µg of ethinylestradiol in combination with gestodene on blood coagulation and fibrinolysis in Brazilian women. *International Journal of Fertility and Women's Medicine*, 2001; 46(5): 265-270.
21. Isaac, I.Z., John, R.T., Suleiman, A.S., Erhabor, O. & Yakubu, A. The effect of hormonal contraceptives on platelet count of women in Sokoto State North Western Nigeria. Merit Research Journal of Medicine and Medical Sciences, 2014; 2(1): 007-011.
22. Afsar, N. A., Barakzai, Q. & Adil, S. N. Effect of a Progestin only` contraceptive on platelet aggregation in a Pakistani set of population; *Journal of Ayub Medical College Abottabad*., 2005; 17(3): 21-25.
23. World Health Organization. Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet*, 346(8990): 1575-1582.
24. Kluft, C., Endrikat, J.and Mulder, M.S., Gerlinger, C. & Heithecker, R. A prospective study on the effects on hemostasis of two oral contraceptives containing drospirenone in combination with either 30 or 20(g ethinylestradiol and a reference containing desogestrel and 30(g ethinylestradiol. *Contraception*, 2006; 73: 336–340.
25. Ahmed, J., Al-Husaynee, A.J. & Kashmona, M.A. Effect of combined oral contraceptive pills on some haemostatic parameters. *Annals of the College of Medicine Mosul*, 2007; *33*(1 & 2): 66-69.
26. Afsar, N.A., Barakzai, Q. & Adil, S.N. Effects of low dose oral pill on haemostatic parameters in a set of Pakistani population. *Journal of Pakistan Medical Association*, 2008; 58: 229- 233.
27. Abdalla, T.M., Kordofani, A.A.Y. & Nimir, A.A.H. Haemostatic studies in Sudanese women on oral contraceptive pills. *Khartoum Medical Journal*, 2008; 3: 116-118.
28. Claus, W., Birgit, W., Micha, F. D. & Peter, B. Fibrinolytic response to exercise in women using third-generation oral contraceptives. *Blood Coagulation and Fibrinolysis*, 2006; 17: 563–568.
29. Elsayid, M., Elbasheer, M.A.M., Elgari, M.M. & Elfaki, T.E.M. The Effect of Contraceptive Pills on Coagulation Tests among Sudanese Women in Khartoum State- Sudan. *International Journal of Science and Research*, 2015; 5(10): 773-777.
30. Aldrighi, J.M., De Campos, L.S., Eluf Gebara, O.C., Petta, C.A. & Bahamondes, L. Effect of a combined oral contraceptive containing 20 microg ethinyl estradiol and 75 microg gestodene on hemostatic parameters. *Gynecology & Endocrinol*ogy, 2006; 22(1): 1-4.
31. Osaro, E., Isaac, I.Z., Kaoje, A.U., John, R.T. & Suleiman, S.A. Assessment of Some Coagulation Parameters among Clients on Hormonal Contraceptive in a Tertiary Health Facility in Sokoto, North Western, Nigeria. *Journal of Hematology and Thromboembolic Diseases*, 2014; 2: 139.
32. Korte, W., Clarke, S. & Lefkowitz, J.B. Short activated partial thromboplastin times are related to increased thrombin generation and an increased risk for thromboembolism". *American Journal of Clinical Pathology*, 2000; 113: 123–127.
33. Kakafika, A.I., Liberopoulos, E.N. & Mikhailidis, D.P. Fibrinogen: A Predictor of Vascular Disease. *Current Pharmaceutical Design*, 2007; *13:* 1647-1659.
34. Samsunnahar, Qazi, S. A., Atiquzzaman and Najneen, A., Umme, S.N.B. & Farhana, R. Assessment of Coagulation Disorder in Women Taking Oral Contraceptives. *Journal of Bangladesh Society of Physiology*, 2014; 9(1): 1-5.
35. AL-Husaynee, A.J. & Kashmoola, M.A. Effects of combined oral contraceptive pills on some haemostatic parameters. *Annals of the College of Medicine Mosul*, 2007; 33 (1& 2): 66-69.
36. Stocco, B., Fumagalli, H.F., Franceschini, S.A., Martinez, E.Z., Marzocchi-Machado, C.M. & Toloi, M.R.T. Comparative study of the effects of combined oral contraceptives in hemostatic variables. *Medicine*, 2015; 94(4): e385.
37. Kasem, S.B., Choudhury, T.A., Razzaque, S.A., Begum, F., Adiba, R. & Anika, S. Effect of Low Dose Oral Contraceptive Pill on Coagulation Status in Women with Normal and Low Body Mass Index. *Journal of Bangladesh College of Physicians and Surgeons*, 2017; 35(1): 3-8.

38. Israa, S. A., Haithem, A. Al-Rubaie, H.A. & Jaffar, N. J. A. The Effect of Combined Oral Contraceptive Pills on Factor VII Activity and D-dimer Level in Healthy and Obese Women. *Journal of Faculty of Medicine Baghdad*, 2015; 58, 63-70.
39. Harsoor, S., Kinagi, A. & Ananta, A. Correlation of plasma fibrinogen with blood pressure, BMI, lipid profile and glycemic status in type II diabetes mellitus. *Journal of Evolution of Medical and Dental Sciences*, 2014; 3(68): 14615 – 14627.
40. Aigbe, A. Any correlation between BMI, plasma fibrinogen concentration and euglobulin lysis time in obese Africans? Journal of obesity and weight loss, 2005; 5(6): 76.
41. Halla, A.J., Jaffar, N.A. & Haithem, A.A. Relationship between obesity and plasma level of factor V and fibrinogen. Journal of Fac Medicine Baghdad, 2017; 59(1): 53-59.
42. Rosendaal, F.R., Van Hylckama, V. A., Tanis, B.C. & Helmerhorst, F.M. Estrogens, progestogens and thrombosis. *Journal of Thrombosis & Haemostasis*, 2003; 1(7): 1371-80.
43. Murthy, A.S. Obesity and contraception: emerging issues. Seminar in Reproductive Medicine, 2010; 28: 156.
44. Abdullahi, M., Cushman, M. & Rosendaal, F.R. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thrombosis & Haemostasis, 2003; 89(3): 493-498.