Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

RESEARCH ARTICLE BIOSCIENCE RESEARCH, 2021 18(3):2211-2218. **OPEN ACCESS**

Measurement of Prothrombin time, Partial thromboplastin times and Fibrinogen level among women who using oral contraceptive pills and implanon in Khartoum – Sudan

AadilYousif[1*], Elharam Abdallah[2], Dalia Taj Alsir[2] and Anait Balal[3]

[1]Department of Medical laboratory technology faculty of Apply Medical Sciences, University of Tabuk, **Saudi Arabia**
[2]Department of Hematology and Immunohematology, Faculty of medical laboratory sciences, Alzaiem Alazhari University, **Sudan**
[3]Department of Hematology and Immunohematology, Faculty of medical laboratory sciences, Alzaiem Alazhari University, **Sudan**

***Correspondence:** aalmahi@ut.edu.sa **Received: 31-01-2020, Revised: 21-03-2021, Accepted: 15-08-2021 e-Published: 21-08-2021**

The combined oral contraceptive pill regarded as a safe and highly effective method of contraception, but has various side effects and serious complications. In recent years, the usage of IMPLANON (etonogestrel implant) being recommended to minimized the side effects. The present study aims to measure PT, APTT and fibrinogen level in women using of oral contraceptive pills and Implanon. The study was conducted in family planning in clinic of Khartoum and Bahri Hospitals. A total of hundred women were selected as volunteers and 50 women considered as cases group and other 50 women who didn't used any contraceptive were selected as control. PT, APTT and fibrinogen level measured by using coagulameter. (Colt). The result revealed that the mean of PT 12.46 second, PTT 29.82 second, fibrinogen 2.64g/dl in women using Implanon, were as the PT 12.44 second, PTT 30.97 second, fibrinogen 2.93g/dl in women using contraceptive pills. The result showed significant decrease of PTT in women using Implanon when compared with control group (*P* value < 0.05) and no significant different in in the PT, APTT and fibrinogen in women used contraceptive pill.

Keywords: Prothrombin, Thromboplastin, Fibrinogen, contraception and Implanon

INTRODUCTION

1.1 Contraceptive Pills:

Contraceptive is prevention of conception with many devices, sexual practices, chemical, drugs, or surgical procedure. The pills are the common name for oral contraception. It's one of the most safer, effective, and popular methods of birth control. There are two types of contraceptive pills; combined oral contraceptive pills and progestin –only pills. The pills must be taken daily to sustain the hormone levels needed to prevent ovulation (Egbunah, 2019).

Oral contraceptive related thrombosis has become an important field of study. Women taking oral contraceptive appear to have 3 to 4 fold increased risk of thrombosis (primary deep venous thrombosis) compared to women not taking oral contraceptives (S. Jadelle et al. 2002).Oral contraceptives can interact with inherited thrombophilia, particularly factor V Leiden. Women who are heterozygous for the mutation and take oral contraceptive have a 30 fold increase in risk of

contraceptives . Women who are homozygous for the mutation and take oral contraceptives have a hundred – fold increase in risk of thrombosis (Williams, 2016).

Hormonal contraceptives are often associated with side effects commonly, irregular menses, bleeding, amenorrhea, weight gain, wild headache and abdominal pain or discomfort (Davis, A.J. 1996, Polis et al. 2014).

The mechanism of the increased thrombotic risk is that the estrogens content in the pills have many effects on coagulation system that results in shifting of the hemostatic balance toward a prothrombotic state, these include the increased levels of the prothrombin, fibrinogen, factors VII, VIII, IX, X, XI, XII, and XIII and with reduced S and antithrombin, and acquired resistance to activated protein C that underlies the major COCPs' thrombogenic potential (Vandenbroucke et al. 2002,Helmerhorst et al, 2003, Laufer et al.2011).

1.2 Contraceptive Implants:

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 component, making it inconvenient environment for fertilization and implantation (Bhathena 2001, Schürmann et al. 2004, Peipert et al. 2012).

Contraceptive Implants (etonogestrel implant) is an off-white, non-biodegradable, etonogestrel-containing single sterile rod implant for subdermal use. The implant is 4 cm in length a diameter 0f 2cm. Implanon rod contain of an ethylene vinyl acetate copolymer core, which contain 68 mg ethylene vinyl acetatImplanon is a progestin – only contraceptive does not contain estrogen. Implanon does not contain latex and is not radio –opaque (Hiller, 2000).

Implanon single rod inserted into the upper arm after a woman is given a local anesthetic, insertion takes only a few minute. Implanon give off very small amounts of hormone much like progesterone a women 's body produce during the last two weeks of each monthly cycle and is highly effective for 3 years.

Impanon was first approved in Indonesia in 1998 ,then approved for use in over 60 countries in 2003, and approved for use in United State in 2006, implant are now used by 11 million women around the world (Hanretty , 2010).

1.3 The Role of Blood Coagulation:

The fibrin clot is the product of multiples of complex reactions of plasma proteins called coagulation or clotting factors. Most of the clotting factors are zymogens of serine proteases and are transform to active enzymes during the process of blood coagulation (Lillicrap D, 2009).The mechanism of coagulation process involves activation, adhesion, and aggregation of platelets then the coagulation factors activation along with deposition and maturation of fibrin. Disorders of coagulation pathways are disease conditions, which can result in bleeding (hemorrhage or bruising) or obstructive small clots (thrombosis) (Dacie and Lewis, 2006, Watson M, 2010).

1.4 Prothrombin time (PT):

The Prothrombin time (PT) and its derived measures of Prothrombin ratio (PR) and international normalized ratio (INR) are used to measure the extrinsic pathway of coagulation. This test is also called "ProTime INR" and "PT/INR". They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status. PT measures factors I (fibrinogen), II (Prothrombin), V, VII, and X. The test measures the clotting time of plasma in the presence of an optimal concentration of tissue extract (Thromboplastin) and indicates the overall efficiency of the extrinsic clotting system. although to measure Prothrombin ,the is now known to depend also on reaction with factors V,VII and X , and on the fibrinogen concentration of plasma (Higgs et al. 2016, Williams, 2016).

1.5 Activated partial thromboplastin time (APTT):

The partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT or APTT) is a medical test that characterizes blood coagulation. Apart from detecting abnormalities in blood clotting, it is also used to monitor the treatment effects with heparin, a major anticoagulant. PTT is a performance indicator of the efficacy of both the "intrinsic" (now referred to as the contact activation pathway) and the common coagulation pathways. In addition, is used in conjunction with the prothrombin time (PT) which measures the extrinsic pathway. Kaolin cephalin clotting time (KccT) is a historic name for the activated partial thromboplastin time (Higgs et al. 2016).

1.6 Fibrinogen:

Thus, fibrinogen plays a central role in the coagulation cascade and in platelet activation. Plasma fibrinogen is widely recognized as a major mediator of platelet aggregation and is vital for fibrin formation. Fibrinogen is composed of three, disulphide-linked chains in a symmetrical structure (Montes et al. 2001).

Numerous methods of determining fibrinogen concentration have been devised, including clotting , immunological , physical and nephelometric techniques, and all tend to give slightly different results, perhaps, partly because of the heterogenous nature of plasma fibrinogen . Many automated analyzers will now provide an estimate of fibrinogen concentration determined from the coagulation changes during the PT (PT-derived fibrinogen), (Higgs et al. 2016).

However, hormonal contraceptives do not show the same risk of thrombosis in different populations (Yakubu, A. et al. 2014).There are differences in the coagulation and hemostatic parameters among women who use hormonal contraceptives from different geographical areas, the cause of which is not clearly understood (Bartiromo, et al. 2020). Consequently, WHO recommended that studies should be conducted in different regions to accomplish a better understanding (Suleiman SA 2014).

However, the use of progestogen-only injectable and implant contraceptives is on the increase among Sudanese women yet; there is a lack of data concerning the coagulation variables of Sudanese women hence, this study.

MATERIALS AND METHODS

2.1 Study design:

This is a case control study conducted to measure coagulation parameter (PT/PTT/fibrinogen level) in women who using oral contraceptive pills and implanon in Khartoum state. The blood pressure and weight of these participants were determined by the Nurses working in the family planning Clinic. Information's 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.

2.2 Study Area:

The study was conducted in family planning in clinic of Khartoum and Bahri Hospitals. Women were using oral conceptive pills or implanon in Khartoum state.

2.3 Study population:

Women, between the age of 18 and 45 years, who had no underlying disease condition that could affect the clotting system. 50 women were using oral contraceptive pills 50 women were using Implanon and 50 who weren't using oral contraceptive or Implanon (Control subjects in same ages).

2.4 Inclusion Criteria:

All participants subjects who were aged between 18 and 45 years, sexually active, normotensive females using long acting contraceptives for a period of at least two months, non-pregnant and not smoking, on progestogen-only implanon injectable contraceptives, without underlying disease condition.

Exclusion Criteria:

Women below 18years or more than 45 years. Women who were not using contraceptive pills, implanon, or presence of diseases.

2.5 Ethical Consideration:

The ethical approval has been taken from ethical committee of Ministry of Health (Sudan). In addition each of the participants in this study gave informed consent to participate.

2.6 Sample Collection and Analysis:

4.5 mls of venous blood was collected from each participants using standard procedure into 0.5mls of 31.3g/L tri-sodium citrate solution in a test tube and well 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.

2.7 Methodology:

The coagulometer:

Hospitex Diagnostics - Calenzano (Florence) – Italy

The blood coagulometer is an analyzer used to test the coagulation efficiency of blood so as to diagnosis and asses the bleeding disorders, or monitor patients who are taking anticoagulant medicines .

Principle

The coagulometer has an optical measurement system which detect sudden difference in optical density when a clot is formed . The initiation of the time measurement when the sample is added to the reagent and stop the measurement time at the moment that the clot is formed.

2.8 Statistical Analysis

Statistical Package for Social Sciences (version 13) was used for analysis and to perform Pearson Chi-square test for statistical significance and one way an ova for numerical data.

RESULTS

This is analytical case control study was conducted in Khartoum state during the period from March to May 2018, to measurement of coagulation parameters (PT, PTT, and fibrinogen level) in women who using oral contraceptive pills and implanon . Hundred women were selected as volunteers and considered as case and other fifty women not used the contraceptive pills or not used implanon were selected as control group. The comparison of Mean±SD of coagulation parameters of implanon users and controls, the mean values of PT and among the women were used implanon (12.46 seconds) were slightly insignificantly increased than that of the control group (12.34 seconds) with P = 0.116, also there was insignificant shorter in the mean of fibrinogen level results among the implanon users (2.64g/L) and control group (2.84g/L) with P = 0.84. However, there was significantly reduction in the mean of PTT result among implanon users (29.82 seconds) and control group (31.50 seconds) with P = 0.002 (Table1). It was observed that the comparison of Mean±SD of coagulation parameters of contraceptive users and controls, the PT results among cases and control were (12.44 seconds and 12.34 seconds respectively) were insignificant with P = 0.367. In addition, there was insignificant difference in the mean of fibrinogen level result among case were used contraceptive pills (2.93 g/L) and control (2.84 g/L) with P = 0.519. However, there was significant difference in the mean of PTT result among case were used contraceptive pills (30.97seconds) and control (31.50seconds) with P = 0.026 (Table 2). The comparison of Mean±SD of coagulation parameters of implanon users and contraceptive users. The mean values of all parameters among them were insignificant. The PT values among the women on implant (12.46 seconds) and among the oral contraceptive users (12.44 seconds) with P = 0.871. The PTT values among the women on implant(30.82seconds) and among the contraceptive users (30.82 seconds) with P = 0.489. The fibrinogen level values among the women on implant (2.94 g/L) and among the contraceptive users(2.93 g/L) with P = 0.987 (Table 3). The study reveal that the comparison of Mean±SD of coagulation parameters PT,PTT and fibrinogen level of only implanon users based on the age 30 years old and less than 30 years. There was no significant difference in the mean values of the all coagulation parameters, the PT result among women at 30 years and less than 30 years (12.45 second and 12.46 respectively) with P = 0.909 (Table 4). Further the result shows significant difference in the mean of PT result among cases used implanon for (5-12) months (12.15Sec.) and (13-24) months(12.59Sec.)and (25-36) months (12.48Sec.) P = 0.035 and also the result shows that there was insignificant difference in the mean of PTT result among cases used implanon for (5-12) month (30.76), and (13-24) month (30.96), and (25-36) month(30.73) with P value 0.720 and also insignificant difference in the mean of fibrinogen level result among cases used implanon for (5-12) month (3.09), (13-24)months (2.92)and (25-36) month (2.89) P = 0.772 (Table 5).

Table1: Statistics of PT, PTT and fibrinogen level among implanon and control groups.

		No.	Mean/Sec.	Std. Deviation	Minimum	Maximum	*P* value
Pt (secs)	Implanon	50	12.4680	.42783	11.50	13.10	
	Control	50	12.3400	.37850	11.70	13.00	0.116
Ptt (secs)	Implanon	50	29.8260	.92732	29.00	33.40	
	Control	50	31.5080	1.17332	29.00	33.40	**0.002**
Fibrinogen level (g/dl)	Implanon	50	2.6416	.71937	1.71	4.20	0.486
	Control	50	2.8428	.69440	1.62	4.80	

P value ≤ 0.05 considered as significant

Table 2: Statistics of PT, PTT and fibrinogen level among oral contraceptive pills and control groups.

		No.	Mean/Sec.	Std. Deviation	Minimum	Maximum	*P* value
Pt (secs)	Contraceptive pills	50	12.44	.75248	11.00	13.90	0.367
	Control	50	12.3400	.37850	11.70	13.00	
Ptt (secs)	Contraceptive pills	50	30.9740	1.18577	29.00	33.40	**0.026**
	Control	50	31.5080	1.17332	29.00	33.40	
Fibrinogen level (g/dl)	Contraceptive pills	50	2.9392	.79067	1.42	4.34	0.519
	Control	50	2.8428	.69440	1.62	4.80	

P value ≤ 0.05 considered as significant

Table 3: Statistic of PT, PTT and fibrinogen level among implanon and oral contraceptive pills groups.

		No.	Mean	Std. Deviation	Minimum	Maximum	*P* value
Pt (secs)	Implanon	50	12.4680	.42783	11.50	13.10	0.371
	Contraceptive pills	50	12.44	.75248	11.00	13.90	
Ptt (secs)	Implanon	50	29.8260	.92732	29.00	33.40	0.489
	Contraceptive pills	50	30.9740	1.18577	29.00	33.40	
Fibrinogen level (g/dl)	Implanon	50	2.6416	.71937	1.71	4.20	0.987
	Contraceptive pills	50	2.9392	.79067	1.42	4.34	

P value ≤ 0.05 considered as significant

Table 4: Statistic of PT, PTT and fibrinogen level in difference age groups among women used implanon:

		No.	Mean	Std. Deviation	Minimum	Maximum	P value
Pt (secs)	30 years and less	56	12.4518	.61170	11.20	13.90	0.909
	more than 30 year	44	12.4659	.61264	11.00	13.40	
Ptt (secs)	30 years and less	56	30.8089	1.05422	29.10	33.20	0.366
	more than 30 year	44	31.0159	1.07183	29.00	33.40	
Fibrinogen level (g/dl)	30 years and less	56	3.0127	.76490	1.42	4.34	0.280
	more than 30 year	44	2.8484	.73367	1.70	4.34	

P value ≤ 0.05 considered as significant

Table 5: shows the comparison of Mean±SD of coagulation parameters PT, PTT and fibrinogen level in different duration groups among women used implanon

	Duration			
Parameters	5-12 months	13-24 months	25-36 months	P - value
PT (secs)	12.15±0.37	12.59±0.42	12.48±0.22	0.453
APTT (secs)	33.50±6.36	30.71±3.92	29.61±4.41	0.006
Fibrinogen(g/L)	3.01±0.71	2.84±0.74	2.74±0.69	0.746

- ANOVA test was used to calculate P value

P value less than 0.05 considered significant.

DISCUSSION

A case control study was conducted in Khartoum state during the period from August 2018 to May to measure coagulation parameter (Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and fibrinogen level) in women using oral contraceptive pills and implanon. A 100 samples were collected from women according to inclusion criteria and considered as case, and 50 samples from healthy women not used pills and not used implanon, and considered as control. The main findings of the current study, the mean of PT was slightly shorter of the study group who used the oral contraceptive pills than control group (p 0.36) which agreed with the study of Babatunde et. al (2004) which conducted in healthy Nigerian women and also similar to study reported by Abbas (2010) which conducted in women on oral contraceptives pill in Sudan with insignificant reduced (p = 0.29), also agree with study done by Egbunah et al. (2019) in Kaduna State, Nigeria. But disagree with Abdalla et al. (2008) also reported reduction in PT in women taking oral contraceptive. Our finding is however, agreed with the study of Elsayid et al. (2016) who a slightly raised PT among the study group to the control. Although the increasing in the mean value of the PT was not statistically significant, but it possibly an indication of some degree of enhanced coagulation process in the subject due to exogenous estrogens in the pill accumulated in the liver and stimulate the synthesis of the clotting factors more especially factors II, VII, and X (J Bonnar. 1987). The mean PT of study group who used the implanon was slightly increased than control group, but without significant difference (P = 0.116) and also slightly increased than mean of contraceptive pills but without significant difference (p= 0.871) it possible due to absents of estrogen in implanon (Kevin,2010). The mean APTT of study group who used the pills was shorter than control group with significant difference (P=0.026), which agreed with the study of Tsakok and et. al. (1980) which conducted in Non- Caucasian women taking oral contraceptive containing 50 mg estrogen, Egbunah M et al. (2019) also reported significant reduction APTT in women taking oral contraceptive. Mean APTT result of study group who used the implanon was slightly shorter than of control group but with significant difference (p=0.002). The shortened PT and APTT may be explained by the procoagulant effect of the used progestogen-only contraceptives which includes the increased plasma levels of several coagulation factors such as fibrinogen, prothrombin, FVII and FX. Decreased PT & APTT may predisposes patients to an increased risk of thrombotic complications (Korte et al., 2000). The mean fibrinogen level of study who used the pill was slightly increased than that of control group but without significant difference (p= 0.515) which agreed with the study the study Elsayid et al. (2016) which conducted in women on oral contraceptive pill in Sudan with slightly increased when compared with his control but without significant increased (P = 0.18) it also agree with study of Babatunde et. al (2004) which conducted in healthy Nigerian women. But the mean fibrinogen level result of study group who used the implanon was slightly decreased than of control group without significant difference (P = 0.468). Mean PT result of study group who in age less than 30 year and used the implanon was slightly reduced than that of age more than 30 years but without significant difference (P = 0.909). The mean APTT result of study group who in age less than 30 years used the implanon was slightly reduced than of age more than 30 years but without significant (P = 0.336). The mean fibrinogen level result of study group who in age less than 30 year and used implanon was slightly increased than that of age more than 30 years (P = 0.280). Duration of implant use had no effect on the PT and fibrinogen, but there was a mild association between APTT and duration of implant use. This finding is agreed with the study of Egbunah et al. (2019).

CONCLUSION

This study showed that there were insignificant increased in the PT and significant shortening in the PTT when compared with control groups on the both of implanon and the contraceptive users. The mean of fibrinogen level was slightly increased on the contraceptive users and slightly reduced on the implanon users without significant differences. No significant change of PT, PTT, and fibrinogen among different age group used implanon and over all the mean of these parameters were in normal ranges. Moreover, a further study is needed to bring about a clearer picture.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEGEMENT

We are thankful to the colleagues at the

Department of Hematology, Faculty of medical laboratory sciences, Alzaiem Alazhari University their cooperation and to all the staff of Khartoum and Bahri Hospitals. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

Dr. Aadil responsible for reviewing all work and preparing manuscripts and presenting abstracts in national and international conferences.
DA designed and performleed the PT experiments and a part fibrinogen level. AB designed and performed PTT experiments and the rest of fibrinogen level. EA followed them during the performing experiments and done data analysis. All authors read and approved the final version.

REFERENCES

A. Victor Hoffbrand , Douglas R. Higgs. et al. Postgraduate Haematology. Seventh edition. Wiley Blackwell; 2016. 508 -511

Abbas, Waad Mohammed. Estimation of Haemostatic Parameters among Sudanese Women On Combined Oral Contraceptives Pills in AL-Ahfaad Family Center. SUST. 2013.

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.

Babatunde, A. S. and Olatunji, P.O. Short-term effect of oral contraceptive pills on some haemostatic parameters in healthy Nigerian women. The Nigerian Postgraduate Medical Journal. 2004;11(4):246-250

Brooke Winner, M.D., Jeffrey F. Peipert. et al. Effectiveness of Long-Acting Reversible Contraception. N Engl J Med 2012; 366 (21):1998-2007.

Dacie and Lewis Practical Haematology, 10th ed., Copyright © 2006 Churchill Livingstone.

Davis, A.J. Use of Depot Medioxyprogesterone acetate Contraception in adolescents. Journal of Reproductive Medicine, 1996; 41: 407 – 413.

Egbunah M. O., Eze E. M. Isolated effect of progestogen-only contraceptives on some coagulation parameters of women attending family planning clinics in kaduna state, Nigeria. ejbps, 2019, Volume 6, Issue 1, 01-10

Egbunah M. O., Eze E. M., et al. Isolated Effect Of Progestogen-Only Contraceptives On Some Coagulation Parameters Of Women Attending Family Planning Clinics In Kaduna State, Nigeria. ejbps, 2019, Volume 6, Issue 1, 01-10.

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.

Erhabor, Isaac IZ, Kaoje AU , John RT and Suleiman SA. Assessment of Some Coagulation Parameters among Clients on Hormonal Contraceptive in a Tertiary Health Facility in Sokoto, North Western, Nigeria. J Hematol Thrombo Dis 2014, 2:3

Ferreira, A.C.P., Montes, M.B.A., et al.. 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

H.B. Croxatto, R. Schürmann et al. New Mechanisms for Tissue-Selective Estrogen-Free Contraception. *Springer Science & Business Media.2004.*

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.

J.Bonnar. Coagulation Effects of Oral Contraception. Am J Obstet Gynecol . 1987 Oct;157(4 Pt 2):1042-8.

Jacobstein, R. & Polis, C.B. Progestin-only contraception: Injectables and Implants. Best Practice & Research Clinical Obstetrics and Gynaecology, 2014; 28: 795-806

Keven P. Hanretty , 2010:Obstetrics IIlustrated 7th edition British (18): 404-419

Key N, Makris M, O'Shaughnessy D, Lillicrap D.

Practical hemostasis and thrombosis: Wiley Online Library; 2009.

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.

Massimo Candiani, Stefano Ferrari, Ludovica Bartiromo, et al. Fertility Outcome after CO2 Laser Vaporization versus Cystectomy in Women with Ovarian Endometrioma: A Comparative Study. jmig. 2020.07.014

Pallister C, Watson M. Haematology second edition, October 31, 2010. Scion Publishing.

Reinhold Munker, Erhard Hiller, Ronald Paquette. Modern Hematology: Biology and Clinical Management. Springer Science + Business. 2000. pp 247-265.

RK Bhathena. The long-acting progestogen-only contraceptive injections: an update. BJOG. 2001 Jan;108(1):3-8.

RosendaalFR,Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. ArteriosclerThrombVasc *Biol. 2002; 22: 201-210.*

Rosendal FR, Van Hylckma VA, Tanis BC, Helmerhorst FM. Estrogens, progestogens and thrombosis. J ThrombHaemost *2003; 1(7): 1371-1380.*

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.

Taskok FHM. KohS.Ratnam SS, 1980. Effect of oral contraceptive containing 50mg estrogen on blood coagulation in non – Caucasion women contraception 21(5): 505 – 527

Trenor CC, Chung RJ, Michelson AD, Neufeld EJ, Gordon CM, Laufer MR, Laufer MR et al. Hormonal contraception and thrombotic risk: a multidisciplinary approach*. Pediatrics 2011; 127(2): 347-357*

Williams Hematology, 9th edition Copyright © 2016, by McGraw-Hill Education.