



Investigation of the Possible Effects of Injectable and Skin Patch Contraceptives on Selected Haemostatic and Haematologic Parameters in Women Attending Primary Healthcare Centre in Eleme, Rivers State

**Evelyn Mgbeoma Eze^{1*}, Fiekumo Igbida Buseri², Serekara Gideon Christian¹,
Andrew Temide Olasebiomo¹, Baribefe Daniel Koate¹
and Ferdinand Chukwuma Ezeiruaku²**

¹Department of Medical Laboratory Science, Rivers State University, Nkpolu-Oroworukwo, Port-Harcourt, Nigeria.

²Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Authors EME and FIB designed the study, wrote the protocol and supervised the study. Author SGC performed the statistical analysis and wrote the first draft of the manuscript. Authors ATO and FCE managed the laboratory analyses of the study. Authors ATO, BDK and SGC managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The was a case control and comparative study aimed at investigating the possible effects of injectable and skin patch contraceptives on selected haematologic and haemostatic parameters in women attending primary healthcare centre at Eleme, Rivers State The study population consists of seventy-five (75) apparently healthy, non-pregnant, non- smoking women, aged between 25 and 45years; (31 women on DEPO-PROVERA contraceptive, 14 women on Implanon, and 30

*Corresponding author: E-mail: evelyn.eze@ust.edu.ng;

apparently healthy non-contraceptive users as control group). Fibrinogen, antithrombin, tissue plasminogen activator was analysed with reagents prepared by Elabscience, Wuhan, China, using an ELISA machine (STAT FAX-2100). Prothrombin time and activated partial thromboplastin time was done manually with reagents prepared by Quimica Clinica Aplicada S.A, Spain. Haematologic parameters were analysed using SYSMEX KX-21-N auto analyser. Graph-pad Prism 5.0 was used in analysing all data, $p < 0.05$ was considered statistically significant. For haemostatic parameters, results showed that there was statistically significant increase in mean values of antithrombin ($38.48 \pm 17.48/\text{ml}$ versus $21.02 \pm 15.54\text{ng/ml}$, $p=0.0011$) and tissue plasminogen activator ($1.34 \pm 1.35\text{ng/ml}$ versus $0.28 \pm 0.46\text{ng/ml}$, $p=0.0047$) in women using the two types of contraceptive, while activated partial thromboplastin time ($28.11 \pm 2.37\text{s}$ versus $29.87 \pm 2.77\text{s}$, $p=0.0205$) was statistically decreased in women on the investigated contraceptives, other haemostatic parameters were not statistically significant. For haematological parameters, the results showed that there was statistically significant increase in mean values of packed cell volume $38.13 \pm 2.28\%$ versus $36.21 \pm 3.07\%$ ($p=0.0126$), haemoglobin $12.35 \pm 0.79\text{g/dL}$ versus $11.56 \pm 0.99\text{g/dL}$ ($p=0.0028$), white blood cells $6.17 \pm 1.22 \times 10^9/\text{L}$ versus $5.26 \pm 1.18 \times 10^9/\text{L}$ ($p=0.0143$) in women using injectable (DEPO-PROVERA) and skin patch (IMPLANON) contraceptive, other parameters showed no statistically significance. Based on duration of use of contraceptive, there was no statistically significant difference ($p>0.05$) in women using skin patch; while for injectable, platelet count was high in those who had used it for more than a year. Comparing values obtained from using injectable and skin patch, there was no statistical significant difference in all the parameters. Using analysis of variance to compare values based on parity, there was no statistical significant difference. Conclusively, increase in antithrombin and tissue plasminogen activator, and a decrease in activated partial thromboplastin time in women using IMPLANON (skin patch) and DEPO-PROVERA (injectable) are the haemostatic changes that occurs while using contraceptives and these changes may likely predispose them to bleeding, therefore adequate monitoring of the blood haemostatic processes while taking these contraceptives is critical in order not to expose users to haemorrhage.

Keywords: *Haematologic; haemostatic; injectable contraceptive; skin patch contraceptive; IMPLANON; DEPO-PROVERA.*

1. INTRODUCTION

The size of a family is of so much consideration currently as a result of so many factors among which include economic, child-maternal health and shelter which now makes married couple to plan and limit the number of children they want to have and can also carter for. Contraception is mostly used to achieve a desirable family size.

Contraception is the control of fertility to prevent pregnancy [1]. It involves methods that prevent ovulation in women, block sperm from getting to the ovum in the fallopian tube (prevention of fertilization) or prevent a fertilized ovum from implantation in the uterus. Contraception is broadly divided into two: hormonal and non-hormonal contraception. The technique or substance used in achieving contraception is known as a contraceptive [1]. Hormonal contraceptives have been available for more than 50years and currently millions of women worldwide use hormonal contraceptives. In the Western Europe and the United states, approximately 80% of women of reproductive ages relied upon hormonal contraceptive

methods to prevent unintended pregnancy. In Africa, women of child bearing age who use contraceptives, have accelerated. However, the Nigeria Demographic and Health Survey revealed that the frequency of hormonal contraception in Nigerian women of reproductive age, have stagnated, remaining about 9% between 2008 and 2013 [2,3].

The first available hormonal contraceptive was developed into oral contraceptive pills containing estrogen and progestogen as the active ingredients, and was approved in 1960 by the Federal Drug Administration. Today other available non-oral routes of administration of hormonal contraceptives which contain only progestogen have been developed: a patch, a vaginal ring, subcutaneous implants and injectables. It is important to state that Progestin-only contraceptive injectables and implants are known to be highly effective, and are longer-acting contraceptive methods mostly used by women. Globally, 6% of women using modern contraceptives use injectables and 1% use implants [4].

Injectable contraceptive is a hormonal method of contraception whereby long acting progestogen drugs are given by injection every 2-3 months and most women prefer this contraceptive method because they take the drug just once in 2 or 3 months as compared to oral. According to Lidegaard et al., [5], the use of hormonal contraceptives comes with side effects that includes; weight gain, irregular bleeding, nausea, headache, tenderness of the breast, and mood changes.

The brand DEPO-PROVERA® used in this study is a medroxyprogesterone acetate injectable suspension. DEPO-PROVERA contraceptive injection is normally given as an intramuscular injection (a shot) in the upper arm or buttock once every 13 weeks (3 months). Promptly at the end of the 3-month interval, users of this contraceptives are advised to return to their health-care provider for the next injection so as to continue the contraceptive protection. DEPO-PROVERA acts by preventing the ripening of the egg. If the egg is not released from the ovaries during the menstrual cycle, it cannot be fertilized by a sperm for pregnancy to occur. It also causes a change in the lining of the uterus making it difficult for pregnancy to occur. To ensure that DEPO-PROVERA Contraceptive Injection is not administered inadvertently to a pregnant woman, the first injection must be given only and during the first 5 days of a woman's normal menstrual period; also it should be administered only within the first 5-days postpartum if not breast-feeding, and if exclusively breast-feeding, it should be administered only at the sixth postpartum week. The use of DEPO-PROVERA may predispose a woman to blood clots or stroke and also there have been reported cases of irregular menstrual bleeding [6].

Skin patch is a kind of an implant in which long acting contraceptive drugs are inserted under the skin through an implanted small rod that steadily releases the progestogen drug into the bloodstream and quite a few numbers of women still prefer this method to using oral pills.

IMPLANON™ (etonogestrel implant), a skin patch contraceptive also used in this study is a non-biodegradable off-white etonogestrel that contain a single sterile rod implant for sub-dermal use. The implant is 4 cm long in length with a diameter of about 2 mm. The IMPLANON™ rod is composed of an ethylene vinylacetate (EVA) co-polymer core that contains 68 mg of synthetic progestin etonogestrel (ENG), which is surrounded by an EVA co-polymer skin [7]. The

rate at which it is released is 60-70 µg/day in week 56 and then decreases to about 35-45 µg/day at the conclusion of the first year, to about 30-40 µg/day at the conclusion of the second year, and then to about 25-30 µg/day at the conclusion of the third year. IMPLANON™ is a progestin-only contraceptive and it does not contain the hormone estrogen. IMPLANON™ does not also contain latex and it is not radio-opaque [8].

The contraceptive effect of IMPLANON™ is achieved by mechanisms that include increased viscosity of the cervical mucus, suppression of ovulation, and alterations in the endometrium. The risk of getting pregnant is relatively low (1.24/100users/year) (95% CI 0.19-2.33) using skin patch [9]. The use of skin patch is not recommended for use in women weighing 90 kg and above [10].

Safe use of these hormonal contraceptives still remained quite controversial [11,12] Epidemiological research works have associated the use of the combination of hormonal contraceptives with an increased incidence of venous thromboembolism (deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism) [8].

This study examined some haemostatic parameters including activated partial thromboplastin time (APTT), fibrinogen concentration, prothrombin time test (PT), tissue plasminogen activator (tPA) and antithrombin (AT) in women who are using contraceptives to prevent pregnancy, in addition to some haematological parameters, to ascertain if as a result of the usage of contraceptive, such a woman would be prone to having abnormal bleeding or any haemostatic/haematological imbalance that may predisposes her to suffer ailments associated with such type of imbalance.

The need for child spacing and number of children in Nigeria is now of major consideration as a result of increasing population and considerable rate of poverty. Just like any other drugs, the use of contraceptives comes with side effects of which haemostatic and haematological parameters have been implicated. This makes it imperative to synthesize scientific research findings in an attempt to decipher the extent of haemostatic or haematological changes that are associated with the use of contraceptives. Also despite the wide spread use of these contraceptives and the several studies carried out all over the world today, there are still limited

studies on the effect of injectable and skin patch contraceptives on the haemostatic and haematological parameters in Southern Nigerian women, hence this study.

2. MATERIALS AND METHODS

2.1 Study Design

This study was a case-control and comparative study carried out among women attending family planning clinic of Primary Healthcare Center, Akpajo, Eleme, in Rivers State who were on either progestogen-only injectable (DEPO-PROVERA) or skin patch (IMPLANON) for at least the past one year. The blood pressure and weight of these subjects were determined by the Nurses working in the family planning Clinic. Information on age, duration of use, menstrual flow, parity, history of disease and reaction to the contraceptives were obtained from the patient's medical folders while a structured questionnaire was used to obtain the bio data of the control group. All subjects were recruited within the month of February, 2016.

2.2 Study Population

The total study population consists of Seventy-five (75) apparently healthy, non-pregnant, non-smoking women, aged between 25 and 45 years. Forty-five (45) women on either DEPO-PROVERA (31) or Implanon (14) served as the test subjects while thirty (30) apparently healthy non-pregnant women of the same age bracket who never used hormonal contraceptive or any other family planning method, constituted the control group.

2.3 Eligibility Criteria

Women who were apparently healthy and were under controlled contraceptive medication constituted the test group and their bio-data and medical history were obtained from their respective folders in the Healthcare Centre. Individuals who were not on any contraceptives or any other medication for the past one month and have not smoked cigarette and taken alcohol for a period of one month were recruited as control and their demographic information obtained through a structured questionnaire.

2.4 Sample Collection and Processing

A total of 8 ml of venous blood was collected with vacutainers, 4 ml added into a vacutainer

containing 0.5 ml of 32.0 g/l trisodium citrate solution, properly mixed and processed for the determination of prothrombin time and activated partial thromboplastin time. Two milliliters (2 ml) collected into a vacutainer containing 0.5 ml of 1.2 mg/ml dipotassium ethylene diamine tetra-acetic acid (EDTA) for full blood count including platelet count and 2 ml collected into a non-anticoagulated plain vacutainer for determination of fibrinogen, antithrombin and tissue plasminogen concentration.

The samples in sodium citrate vacutainers were centrifuged at 2,500 g for 15 minutes, plasma was separated into washed, dry and clean plastic containers for PT and APTT. The samples in EDTA were analysed within 2 hours of collection for full blood count. Samples in plain vacutainers clotted for 2 hours, the serum was separated into a sterile clean container and stored overnight in a refrigerator, centrifuged at 2,500 g for 15 minutes to obtain a clear serum for the estimation of fibrinogen, antithrombin and tissue plasminogen activator.

2.5 Sample Analysis

Samples for full blood count were analyzed using an automated machine (SYSMEX manufactured by KOBE, Japan, model no: KX-21N). Platelet count (PC) and calculation of platelet indices {mean platelet volume (MPV), plateletcrit (PLCR), and platelet distribution width, (PDW)} were determined using SYSMEX KX-21-N Haematology Auto-analyzer. SYSMEX KX-21-N uses impedance flow cytometry for calculating different haematological parameters including platelet count and platelet indices.

Fibrinogen (FBG), antithrombin (AT) and tissue plasminogen activator (t-PA) assays were carried out using ELISA machine (STAT FAX-2100, Awareness Technology Inc) using Human Fibrinogen Elisa Kit, Elabscience Biotech Co., Ltd, China. Lot No. AK0015OCT20019, Human Antithrombin Elisa Kit, Elabscience Biotech Co., Ltd, China; Lot No. AK0015OCT20017 and Human Plasminogen Activator, Tissue Elisa Kit, Elabscience Biotech Co., Ltd, China. Lot No. AK0015OCT20018, in the same order. All the ELISA kits utilized sandwich-ELISA methodology; with standard operating procedures as described by the Kit manufacturer.

Determinations of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) tests were performed manually using QCA

(Quimica Clinica Aplicada), S.A. Plasmascan Reagent Kit (Spain), Lot No. 130020. With each batch of coagulation screening tests and assays, a repeatability control was simultaneously processed. Standard operating procedures as described by the Kit manufacturer was employed during the analysis.

2.6 Statistical Analysis

Data were analyzed using Graph-Pad Prism 5.0 version to get the mean and standard deviation of subjects using injectable and skin patch contraceptives and control subjects that were apparently healthy. The analysis also gave the p-value between the study group and the control group from two tail sample t-test and p-values of < 0.05 were considered to be statistically significant. Results were presented in Tables.

3. RESULTS

3.1 Demographic Details of Participants

A total of 75 individuals were recruited for the study. A total of 45 female subjects using contraceptive, (31 females using injectable contraceptive and 14 females using skin patch contraceptive) of age between 24 and 45 were recruited as test subjects. Also, 30 female subjects that were apparently healthy, of age between 25 and 45, enrolled as control. Table 1 shows the demographic details of those recruited in the study.

3.2 Haemostatic Parameters in Women Using Contraceptive

Table 2 shows the comparison of the haemostatic parameters between the women on injectable and skin patch contraceptives, and those apparently healthy control subjects. There was no statistically significant difference between the test and control groups in the mean values of prothrombin time (PT), and fibrinogen, $p>0.05$ respectively. Whereas there was statistically significant increase in mean values of antithrombin and tissue plasminogen activator in stroke patients, $p<0.05$ respectively.

3.3 Haematologic Parameters in Women Using Contraceptive

Table 3 shows the comparison of the haematological parameters of women using contraceptives and those apparently healthy

control subjects. There was no statistically significant difference between the test and control groups in the mean values of platelets, mean cell volume, mean cell haemoglobin, mean cell haemoglobin concentration $p>0.05$ respectively. Whereas there was statistically significant increase in the mean values of packed cell volume, haemoglobin concentration and white blood cell counts in test group, indicating a statistical significant difference of $p<0.05$ respectively.

3.4 Comparison of Haemostatic and Haematologic Parameters in Women Based on Type of Contraceptive in Use

Table 4 shows the comparison of haemostatic and haematologic parameters in women based on the type of contraceptive in use (Injectable and Skin Patch). Using student t-test, there was no statistically significant increase in mean values of all the parameters analyzed at $p<0.05$ respectively.

3.5 Comparison of Haemostatic and Haematologic Parameters in Women Using Injectable Contraceptive Based on Duration of Usage

On comparing the duration of the years, the subjects have been using injectable contraceptive (Table 5), there was statistically significant increase ($p<0.05$) in platelet count, for women who have been using the injectable contraceptive for more than one year. Other analysed parameters showed no statistically significant difference ($p>0.05$) in mean values of less than or equal to one-year duration when compared to mean values of above one-year duration.

3.6 Comparison of Haemostatic and Haematologic Parameters in Women Using Skin Patch Contraceptive Based on Duration of Usage

On comparing the duration of the years the subjects have been using skin patch contraceptive (Table 6), none of the parameters analyzed showed statistically significant difference ($p>0.05$) in mean values of less than or equal to one-year duration when compared to mean values of above one-year duration.

3.7 Comparison of Haemostatic and Haematologic Parameters in Women Using Contraceptive Based on Parity

On comparing the number of children the subjects have as seen in Table 7, none of the parameters analyzed showed statistically significant difference ($p>0.05$).

4. DISCUSSION

From this study, activated partial thromboplastin time, tissue plasminogen activator, and antithrombin showed statistically significant differences in contraceptive users when compared to non-contraceptive users. Activated partial thromboplastin time was lower ($p=0.0205$) in test group than the control group.

Tissue plasminogen activator activates inactive plasmin in clearing up fibrin deposited after the formation of a clot. Lower than normal levels of tissue plasminogen activator may accentuate the occurrence of thrombosis which may lead to stroke while higher than normal values can trigger bleeding. In this study, tissue plasminogen activator was higher in contraceptive users than in the control group ($p=0.0047$) and as such contraceptive users should be properly monitored to avoid bleeding.

Antithrombin is an important protein necessary for prevention of intravascular coagulation and as such higher concentration predisposes an individual to bleeding. Antithrombin was higher ($p=0.0011$) in test (contraceptive) group than in the control group from this study. This finding

implies that the women using injectable and skin patch contraceptives were not prone to thrombosis but may be prone to bleeding. This suggests that contraceptives users should be properly monitored. The findings in this study disagrees with the findings of Mohamed et al., [13], who observed that there was no statistically significant difference in prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen and antithrombin, between users of injectable contraceptives and non-users of contraceptives. Also, there was no agreement with the study carried out by Whigham et al., [14], where they observed no statistically significant differences in antithrombin and fibrinogen. Additionally, the findings in this study is at variance with that of Joseph et al., [15], where they reported no statistically significant difference in platelet counts, prothrombin time and activated partial thromboplastin time between contraceptives users and non-users.

Based on the type of contraceptives used, there was no statistical significant difference in all the measured haemostatic and haematological parameters ($p>0.05$). Based on the duration of use of different type of contraceptives, and it was observed that there was no statistically significant difference in all the measured parameters except an observable difference ($P=0.0139$) in platelet counts for those using injectable contraceptive, where those who were just using it for a period of time that is not more than a year had platelet counts that were lower than those that have been using it for more than one year. Comparing the findings in this research based on duration with that of

Table 1. Demographic details of the study population

Parameters	Contraceptive (n=45)	Control Group (n=30)
Number of Subjects	31 (Injectable); 14 (Skin Patch)	30
Age range (years)	24-45	25-45

Table 2. Comparison of mean \pm standard deviation of haemostatic parameters of the study population

Parameters/Units	Contraceptive group N 45	Control group N = 30	p-value
Prothrombin Time (Seconds)	12.09 \pm 1.09	12.33 \pm 0.82	0.4363 (NS)
Activated Partial Thromboplastin Time (Seconds)	28.11 \pm 2.37	29.87 \pm 2.77	0.0205 (S)
Fibrinogen (ng/ml)	24.20 \pm 11.12	21.09 \pm 9.19	0.3326 (NS)
Antithrombin (ng/ml)	38.48 \pm 17.48	21.02 \pm 15.54	0.0011 (S)
Tissue Plasminogen Activator (ng/ml)	1.34 \pm 1.35	0.28 \pm 0.46	0.0047 (S)

KEY: NS = Non Significant, S = Significant; HS = Highly Significant (N/B: Applicable to all Tables)

Table 3. Comparison of mean \pm standard deviation of haematologic parameters of the study population

Parameters/Unit	Contraceptive Group N = 45	Control Group N = 30	p-value
White Blood Cell ($\times 10^9$)	6.17 \pm 1.22	5.25 \pm 1.17	0.0143 (S)
Haemoglobin Concentration (g/dl)	12.35 \pm 0.79	11.56 \pm 0.99	0.0028 (S)
Packed Cell Volume (%)	38.13 \pm 2.28	36.21 \pm 3.07	0.0126 (S)
Mean Cell Volume (fl)	82.87 \pm 6.98	84.27 \pm 5.16	0.4791 (NS)
Mean Cell Haemoglobin (pg)	26.62 \pm 2.41	27.55 \pm 3.12	0.2322 (NS)
Mean Cell Haemoglobin Concentration (g/dl)	31.66 \pm 1.61	31.94 \pm 0.66	0.5237 (NS)
Platelet ($\times 10^9$)	221.70 \pm 36.00	228.60 \pm 42.41	0.5405 (NS)

Table 4. Comparison of mean \pm standard deviation of haemostatic and haematologic parameters in women based on type of contraceptive in use

Parameters/Units	Injectable N = 31	Skin Patch N = 14	p-value
Haemoglobin (g/dl)	12.38 \pm 0.78	12.28 \pm 0.85	0.6948 (NS)
Packed Cell Volume (%)	38.19 \pm 2.38	37.99 \pm 2.12	0.7830 (NS)
Mean Cell Volume (fl)	83.65 \pm 5.98	81.14 \pm 8.83	0.2708 (NS)
Mean Cell Haemoglobin (pg)	26.86 \pm 1.92	31.97 \pm 0.37	0.3248 (NS)
Mean Cell Haemoglobin Concentration (g/dl)	31.53 \pm 2.14	31. \pm 0.57	0.3968 (NS)
White Blood Cell ($\times 10^9$)	6.12 \pm 1.12	6.28 \pm 1.47	0.7084 (NS)
Platelets ($\times 10^9$)	224.9 \pm 39.51	214.50 \pm 26.54	0.3741 (NS)
Prothrombin Time (Seconds)	12.10 \pm 1.24	12.07 \pm 0.73	0.9369 (NS)
Activated Partial Thromboplastin Time (Seconds)	28.16 \pm 2.33	28.00 \pm 2.54	0.8352 (NS)
Fibrinogen (ng/ml)	24.58 \pm 10.57	23.36 \pm 12.63	0.7363 (NS)
Antithrombin (ng/ml)	41.82 \pm 15.71	31.08 \pm 19.47	0.0552 (NS)
Tissue Plasminogen Activator (ng/ml)	1.36 \pm 1.32	1.30 \pm 1.45	0.8801 (NS)

Table 5. Comparison of mean \pm standard deviation of haemostatic and haematologic parameters in women using injectable contraceptive based on duration of usage

Parameters/Units	≤ 1 year duration N = 16	> 1 year duration N = 15	p-value
Haemoglobin (g/dl)	12.08 \pm 0.83	12.63 \pm 0.69	0.0546 (NS)
Packed Cell Volume (%)	37.66 \pm 2.03	38.59 \pm 2.78	0.2916 (NS)
Mean Cell Volume (fl)	82.69 \pm 6.98	85.07 \pm 4.45	0.2708 (NS)
Mean Cell Haemoglobin (pg)	26.68 \pm 2.51	27.13 \pm 1.69	0.5633 (NS)
Mean Cell Haemoglobin Concentration (g/dl)	31.29 \pm 2.58	31.75 \pm 0.79	0.5142 (NS)
White Blood Cell ($\times 10^9$)	5.92 \pm 1.26	6.20 \pm 1.18	0.5234 (NS)
Platelets ($\times 10^9$)	208.80 \pm 37.37	242.6 \pm 34.23	0.0139 (S)
Prothrombin Time (Seconds)	12.31 \pm 1.49	12.00 \pm 1.04	0.5172 (NS)
Activated Partial Thromboplastin Time (Seconds)	27.69 \pm 2.96	28.73 \pm 1.16	0.2114 (NS)
Fibrinogen (ng/ml)	24.01 \pm 10.55	25.98 \pm 11.79	0.6264 (NS)
Antithrombin (ng/ml)	42.80 \pm 18.28	41.57 \pm 12.72	0.8301 (NS)
Tissue Plasminogen Activator (ng/ml)	1.073 \pm 1.28	1.68 \pm 1.27	0.2054 (NS)

Mohamed et al., [13], where they observed that there was no statistically significant difference as a result of duration, there was agreement in the findings of this study with that of theirs on prothrombin time, activated partial

thromboplastin time, antithrombin and fibrinogen; except for platelet count. From this study, parity did not affect any of the measured haemostatic and haematological parameters among the contraceptive users.

Table 6. Comparison of mean \pm standard deviation of haemostatic and haematologic parameters in women using skin patch contraceptive based on duration of usage

Parameters/Units	≤ 1 year Duration N = 7	> 1 year Duration N = 7	p-value
Haemoglobin (g/dl)	12.09 \pm 1.06	12.08 \pm 0.67	0.9814 (NS)
Packed Cell Volume (%)	37.33 \pm 2.59	37.77 \pm 1.93	0.7102 (NS)
Mean Cell Volume (fl)	81.43 \pm 8.54	79.38 \pm 10.97	0.6957 (NS)
Mean Cell Haemoglobin (pg)	25.94 \pm 2.69	25.44 \pm 3.60	0.7662 (NS)
Mean Cell Haemoglobin Concentration (g/dl)	31.99 \pm 0.33	31.96 \pm 0.36	0.8992 (NS)
White Blood Cell ($\times 10^9$)	6.20 \pm 1.21	6.16 \pm 1.72	0.9660 (NS)
Platelets ($\times 10^9$)	229.0 \pm 70.00	210.3 \pm 27.72	0.1729 (NS)
Prothrombin Time (Seconds)	12.14 \pm 0.69	12.00 \pm 0.76	0.7100 (NS)
Activated Partial Thromboplastin Time (Seconds)	28.71 \pm 2.50	27.63 \pm 2.56	0.4207 (NS)
Fibrinogen (ng/ml)	22.81 \pm 12.49	21.21 \pm 12.01	0.8048 (NS)
Antithrombin (ng/ml)	33.96 \pm 19.28	27.06 \pm 19.78	0.5077 (NS)
Tissue Plasminogen Activator (ng/ml)	1.517 \pm 0.94	0.94 \pm 1.52	0.4589 (NS)

Table 7. Comparison of mean \pm standard deviation of haemostatic and haematologic parameters in women using skin patch contraceptive based on parity

Parameters/Units	3 Children N=11	4 Children N=22	5 Children N=12	P-value
Haemoglobin (g/dl)	12.66 \pm 0.97	12.14 \pm 0.17	12.45 \pm 0.16	0.2076(NS)
Packed Cell Volume (%)	12.66 \pm 3.05	37.49 \pm 2.02	38.49 \pm 1.68	0.1973(NS)
Mean Cell Volume (fl)	84.18 \pm 4.75	81.82 \pm 8.12	83.58 \pm 6.65	0.7748(NS)
Mean Cell Haemoglobin (pg)	27.02 \pm 1.93	26.18 \pm 2.76	27.06 \pm 2.12	0.5395(NS)
Mean Cell Haemoglobin Concentration (g/dl)	31.78 \pm 0.88	31.33 \pm 2.18	32.18 \pm 0.35	0.1799(NS)
White Blood Cell ($\times 10^9$)	6.37 \pm 1.12	6.11 \pm 1.36	16.10 \pm 1.13	0.8038(NS)
Platelets ($\times 10^9$)	223.5 \pm 22.30	229.0 \pm 42.18	206.6 \pm 31.27	0.2945(NS)
Prothrombin Time (Seconds)	12.27 \pm 0.90	12.05 \pm 1.02	12.00 \pm 1.41	0.4540(NS)
Activated Partial Thromboplastin Time (Seconds)	28.45 \pm 2.25	28.77 \pm 1.77	26.58 \pm 2.88	0.0682(NS)
Fibrinogen (ng/ml)	20.50 \pm 13.60	26.95 \pm 10.95	22.55 \pm 8.23	0.2927(NS)
Antithrombin (ng/ml)	41.09 \pm 18.07	38.89 \pm 17.03	35.34 \pm 18.82	0.7293(NS)
Tissue Plasminogen Activator (ng/ml)	2.01 \pm 1.65	1.22 \pm 1.17	0.95 \pm 1.28	0.1465(NS)

Platelets plays important role in coagulation or clot formation and enumeration of platelets is critical in understanding platelet function; and accentuated platelet function may be implicated in the occurrence of thrombosis. It was observed that women on injectable contraceptives for less than or up to a year have lower platelet count than those who have been taking the injection for more than one year. This implies that with increase in number of years their platelet count will increase and if not well monitored as regarding the effect of the injections, they may be prone to having thrombosis.

It was also observed from this study that packed cell volume, haemoglobin concentration and

white blood cell count showed statistically significant difference between women using contraceptives and the control. The values in contraceptive group were higher than the ones in the control group. The findings on packed cell volume and haemoglobin was not in agreement with that of Egbuna et al., [16] who reported no statistically significant difference between contraceptives users and non-users. Our finding on increase in haemoglobin level in users of contraceptives was in agreement with a study finding by World Health Organisation [17]. The increase in packed cell volume and haemoglobin level may be as a result of the high socio-economic status of our subjects; as most of them are of the rich class and they are capable of

affording diets that are beneficial to their body physiological and haemopoetic capacity to produce haemoglobin molecule and red blood cells. The increase of total white blood cell count in this study may be a reflection of the fact that progestogen-only contraceptives could cause some type of infection among the users. The findings in this study is at variance with the report of Stanford et al., [18], who reported lower total white blood cell count and with that of Di Napoli and Papa, [19] who reported no change.

5. CONCLUSION

The high concentration of antithrombin and tissue plasminogen activator may be the reason why these women are not prone to thrombotic accidents, as these two proteins are needed to maintain blood in fluid form but this advantage of not being thrombotic as a result of using these contraceptives, can however predispose these women to bleeding if not properly monitored. Low levels of activated partial thromboplastin time in contraceptive users also justify reasons why their blood physiology is somewhat normal. This correlates with the values obtained in other parameters. Conclusively, increase in antithrombin and tissue plasminogen activator, and a decrease in activated partial thromboplastin time in women using IMPLANON and DEPO-PROVERA are the haemostatic changes that occurs while using contraceptives; and these changes may likely predispose them to bleeding, therefore adequate monitoring of the blood haemostatic processes while taking these contraceptives is critical in order not to expose users to haemorrhage.

CONSENT AND ETHICAL APPROVAL

Ethical approval to conduct the research was granted by the Ethical and Medical Committee of Rivers State Primary Health Care Management Board, Port Harcourt, Nigeria and written consent were obtained from each participant.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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