The Effects of Different Forms of Contraceptives on the Coagulation Profile

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Abstract

Background: The association between combined oral contraceptive pills and increased risk of venous thromboembolism has been extensively researched but little has been reported on its effects on all haematological parameters and coagulation factors. This study aimed to evaluate the effects of different forms of oral contraceptives on the coagulation profile of female subjects in Enugu metropolis. This case-control study was conducted among women attending the Family planning unit of University of Nigera Teaching Hospital, Ituku Ozalla, Enugu State.

Methods: The subjects were 36 women undergoing oral contraceptive medication and the control were 36 healthy women not taking this medication. ABO blood grouping and Full blood count (FBC) were carried out while prothrombin time (PT) and activated partial thromboplastin time (APTT) of test subjects were determined using test kits from Technoclone Austria. Most of the test subjects were found to be of the O^+ blood group. The haematological profile of test subjects showed a statistically significant increase in Red blood cell (RBC), packed cell volume (PCV), neutrophil, eosinophil, mean platelet volume (MPV) and plateletcrit while showing statistically significant reductions in mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), lymphocyte, basophil, platelet volume distribution width (PDW) and red cell distribution widths in comparison to the control group. There was a significant decrease in the PT of test subjects (16.06±1.35 secs) in comparison to the control group (19.63±1.28 secs) while the slight increase in their APTT values was not significant.

Conclusion: Thrombotic markers such as increased Red cell markers; RBC, haematocrit and platelet indices; MPV, PCT were increased along with decreased PT levels and prolonged APTT values though not significant can link oral contraceptives medication use to a hypercoagulable state in subjects thereby increasing their risk to venous thromboembolism.

Keywords: venous thromboembolism, oral contraceptives, coagulation, birth control, thrombosis risk.

Introduction

Background

Worldwide, more than 100 million women use hormonal contraceptives while about 93 million of them make use of combination oral contraceptives-COCs[1]Numerous metabolic effects on lipids, carbohydrates, and hemostatic parameters are caused by these hormonal contraceptive they use. On the other hand, when procoagulant, anticoagulant, and fibrinolytic factors are not balanced appropriately, these alterations may result in the production of an obstructive clot[2]

The equilibrium between pro- and anti-thrombotic

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forces is known as hemostasis. Hypercoagulability and endothelial damage are factors that promote thrombosis as well as stasis. Standard laboratory tests to assess haemostasis usually include Prothrombin time (PT), Activated partial thromboplastin time (Aptt) and Thrombin time(TT) assays. They also assess thrombotic risk[3].

Contraception is a generic term referring to the intentional avoidance of pregnancy through the use of various devices, agents, drugs, sexual practices or surgical procedure; all of which is otherwise referred to as birth control[4].

Oral contraceptives (birth control pills) are medications that prevent pregnancy. They are one method of birth control. Oral contraceptives are hormonal preparations that may contain combinations of the hormones estrogen and progestin or progestin alone[5]. Combinations of estrogen and progestin prevent pregnancy by inhibiting the release of the hormones; luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland in the brain, which is the basic principle of contraception. This is achieved because the LH and FSH play key roles in the development of the ovum and preparation of the lining of the uterus for implantation of the embryo[4,5]. In the same vein, progestin makes the uterine mucus that surrounds the egg more difficult for sperm to penetrate, therefore, for fertilization to take place. In some women, progestin inhibits ovulation (release of the egg). The anti-gonadotropic action of progestin causes an estrogenic shortage, which is compensated for by the estrogenic component, which controls endometrial proliferation[5].

Oral contraceptive pills are currently available in three different forms:

- Progesterone-only
- Mixed estrogen-progesterone
- Continuous or extended-use pills.

In the United States, the most often prescribed method of birth control is the pill. Of the women who presently use contraception, over 25% of those between the ages of 15 and 44 said they prefer the pill[6]. A report have also shown that in Lagos , Nigeria, only 17% of women use the pills and as an emergency means of contraception while 21.7% were observed to use it in Calabar, Nigeria [22] [23]

Moreso, these pills have been shown to have several adverse effects on the users with the most common side effects including nausea, headache, breast tenderness, weight gain, irregular bleeding, and mood changes. However, these side effects often subside after a few months' use[7]. Uncommonly, at extreme cases, oral contraceptives may contribute to increased blood pressure, blood clots, heart attack, and stroke. Beyond that, women who smoke, especially those over 35, and others with unique medical conditions, such as a history of blood clots or breast or endometrial cancer are strongly advised against taking these pills as their condition can be worsened through the consumption of these contraceptive pills[5].

JUSTIFICATION

Women and men have long tried many methods to prevent pregnancy. Prior to modern methods of birth control, women relied on withdrawal or periodic abstinence. These methods often failed but with the advent of oral contraceptives in the 1950's, the rate of success in preventing pregnancy increased while focus shifted to its adverse effects and its wide range of side effects[8].

Hormonal contraception provides effective, tolerable, and reversible prevention of pregnancy. The most commonly reported adverse effects are weight gain and somatic symptoms[9]. Some others include: nausea, breast changes such as tenderness, discomfort, or swelling, depression or mood disturbances, decreased sexual desire or response and acne[6]. Rare but serious potential effects include cardiovascular diseases, such as stroke, and an increased risk for breast cancer, liver tumors, and gallbladder disease. Hormonal contraceptive use should be avoided in women at risk for blood clots, by heavy smokers, and in women with breast or other cancers[10].

However, it is important to note that more than half of the people that use contraceptive pills in Nigeria do so through proprietary patent medicine vendors whom are mostly poorly trained with very limited knowledge on the usage/dosage as well as the effects of these pills on the human body[24].

Consequently, these users are bereft of the knowledge on what these pills can do them as the patent vendors have little or nothing to tell them. This is worrisome when considering the fact that the relative risk of death from contraceptive pills have been shown to be around 2% - 5% across multiple studies[25] [26].

Moreso, reports from some research showed that medication containing estrogen has been linked to alterations in the hemostatic balance and raises the risk of developing problems from venous thromboembolism (VTE) in all women. Moreso, women who have an inherited or acquired propensity to thrombosis (hypercoagulable condition, thrombophilia) have been shown to be more susceptible to this impact than those without these underlying conditions [11].

While these studies have linked the effect of contraceptive pills on coagulation albeit, being quite few, none at all have been carried out locally. Consequently, the effects of these contraceptives are still largely unknown to the current population in Eastern Nigeria. Therefore, this current study is very important in order to note the precise effects oral contraceptives have on haematological and haemostatic parameters, predisposing factors to serious medical conditions such as venous thromboembolism and other benefits and consequence of its use.

AIM

The aim of this study is to find out the effects of different forms of oral contraceptives on the coagulation profile of female subjects under such medication.

SPECIFIC OBJECTIVES

1. To carry out full blood count (FBC) and ABO blood grouping for the study population.
2. To carry out activated partial thromboplastin time (APTT) and prothrombin time (PT) tests.
3. To determine the relative risk of thrombosis associated with different contraceptives compared to a control group.

Materials and Methods

STUDY AREA: The study area is located at University of Nigeria Teaching Hospital ItukuOzalla, Enugu in Enugu State. It is about 21km from Enugu capital city which is located in Eastern Nigeria which has a population of 3.27 million in 2006 and has an area of 7, 161km^2.

STUDY DESIGN: A case-control study design was employed for this study.

SAMPLE SIZE: 30 age matched female subjects undergoing contraceptives medication was recruited for the research. 30 female subjects not under such medication was used as control.

- Power analysis for sample size was calculated using GraphpadStatmate version 2.00(www.graphpad.com). With a sample, size of 30 in each group the study has a 90% power to detect a difference between means of 0.05 with a significant level (alpha) of 0.05(two-tailed)

ETHICAL CONSIDERATION

An ethical clearance certificate was obtained from the University of Nigeria Teaching Hospital Health Research Ethics Committee with the Ref no: UNTH/CSA/329/VOL.5. Duly informed and consenting individuals were registered for this research. Confidentiality of involved participants was assured by anonymous recording and coding of blood samples and results.

SAMPLE COLLECTION: A total of seven mililitres (7ml) of venous blood was collected with great care and precision avoiding traumatic venepunctures by a qualified phlebotomist at University of Nigeria Teaching Hospital into anti coagulated test tubes containing EDTA and sodium tri citrate as anticoagulant.

For EDTA; two and a half (2.5ml) of blood was transferred into an Ethylenediaminetetracetic acid (EDTA) bottle with an EDTA concentration of 3.75mg (3.75µl) and used to carry out FBC and ABO blood grouping.

For Tri-sodium Citrate; an exact ratio of nine parts blood to one part 3.2% citrate (4.5mls of blood + 500µl of tri-sodium citrate) was mixed properly to yield

about 2ml of plasma which was separated immediately into cryovalves and stored at -80°c (dry ice)

On thawing, the plasma was then spun again to obtain platelet poor plasma.

LABORATORY TESTS:

Activated Partial Thromboplastin Time (APTT): A commercial test kit: Technozyme, by Technoclone Austria was used for this assay.

PRINCIPLE: DAPTIN TC (LOT: 6V02CB0) containing kaolin, a surface activator and phospholipid is incubated with citrated plasma at 37°c. Calcium chloride is then added and time taken for clot to form is taken.

Procedure:

- The Calcium chloride and Daptin TC were preheated to 37°c.
- 0.10ml of the plasma sample was added to two tubes.
- 0.10ml of Daptin TC was also added respectively.
- The mixture was shaken briefly and incubated for 2mins at 37°c.
- 0.10ml of calcium chloride solution was added at 37°c and timing started.
- Clotting end point was determined

Reference range: 29-42 seconds

Prothrombin Time (PT): A commercial test kit: Technozyme, by Technoclone Austria was used for this assay.

PRINCIPLE: TECHNOPLASTIN His (LOT: 6T03CB0) containing brain thromboplastin and calcium chloride is added to citrated plasma at 37°c and the clotting end point determined.

Procedure:

- 0.1ml of plasma was pipetted into two different tubes and incubated for 1min at 37°c.
- 0.2ml of Technoplastin His was then added at 37°c and timing started.
- Clotting end time was determined.

Reference range: 13-17 seconds

ABO Blood Grouping: was carried out using commercially prepared anti-sera to ascertain the blood groups of involved subjects.

Procedure:

- A drop of each anti serum was dropped respectively on the opal tile.
- A drop of 20% patient's red blood cells was dropped and mixed together.
- Agglutination was checked within two minutes.

Full Blood Count (FBC): This test was performed using a Hematology Auto analyzer BC 5300 to determine the number of red cells, white cells, platelets amongst other parameters in a subject's sample.

DATA ANALYSIS

Before analysis, the gathered data was prepared by checking for missing data or outliers (values outside the calculated range), this also lead to rechecking the patient's information to see if a particular condition could be the reason behind this odd values. The data was then analyzed using the statistical software-SPSS version 23. Descriptive statistics and t-tests were performed were appropriate.

Results

TABLE 1: Method of contraception: intra-uterine contraceptive devices (IUCD)

Demographic and clinical characteristics of the study population

Variable (n=31)	Mean±SD
Age	34.55±5.58
Duration of menstrual cycle	28.20±0.56
Duration of menstrual flow	4.38±1.15
%(n) of subjects with regular flow	68.42%
Blood pressure	115.93±17.38 79.63±11.92
Body weight	79.38±14.23

Table 2: ABO BLOOD GROUPING OF STUDY POPULATION

Method of contraception: combined oral contraceptives

BLOOD GROUP	FREQUENCY
A^+	22%
B^+	22%
O^+	50%
O^-	6%

Table 3: Method of contraception: combined oral contraceptives

Comparison (Mean±SD) of hematological variables between subjects on contraceptives and control Subjects

Variable	Subjects on Contraceptives (n=36)	Control Subjects (n=36)	p-value
Hb (g/dl)	12.38±2.25	11.68±0.79	0.088
RBC (×10^12/L)	4.70±0.74	4.06±0.41	<0.001*
PCV (%)	36.75±6.17	34.18±2.29	0.023*
MCV (fl)	78.13±5.49	84.69±7.23	<0.001*
MCH (pg)	26.28±2.07	28.97±2.64	<0.001*
MCHC (g/dl)	33.66±0.95	34.19±0.61	0.007*
TWBC (×10^9/L)	5.38±1.47	4.97±1.30	0.219
Lymphocyte (%)	42.11±11.88	50.13±7.91	0.001*
Neutrophil (%)	48.44±13.65	39.90±9.19	0.003*
Monocyte (%)	5.78±1.87	6.74±2.73	0.085
Eosinophil (%)	3.67±1.31	2.89±1.95	0.050*
Basophil (%)	0.00±0.00	0.34±0.28	<0.001*
RDW-CV (%)	14.11±0.83	14.72±0.98	0.006*
RDW-SD (fl)	38.89±9.40	43.03±3.08	0.016*
Platelet Count (×10^9/L)	232.61±55.73	210.78±89.9	0.219
MPV (fl)	10.03±0.63	8.72±0.61	<0.001*
PCT (%)	0.228±0.050	0.181±0.071	0.002*
PDW	14.70±0.29	17.17±5.31	0.009*

*- Significant mean difference at p≤0.05, SD – Standard Deviation, Hb – Haemoglobin, RBC – Red Blood Cell, PCV – Packed Cell Volume, MCV – Mean Cell Volume, MCH – Mean Cell Haemoglobin, MCHC – Mean Cell Haemoglobin, TWBC – Total White Blood Cell, RDW-CV – Red Cell Distribution Width–Coefficient of Variation, RDW-SD – Red Cell Distribution Width–Standard Deviation, MPV – Mean Platelet Volume, PCT – Plateletcrit, PDW – Platelet Volume Distribution Width

Tabnd Activated Partial Thromboplastin Time between subjects on contraceptives and control Subjects

Table 4: Comparison (Mean±SD) of Prothrombin Time and Activated Partial Thromboplastin Time between subjects on contraceptives and control Subjects

Variable	Subjects on Contraceptives (n=36)	Control Subjects (n=36)	p-value
PT (seconds)	16.06±1.35	19.63±1.28	<0.001*
APTT (seconds)	35.94±4.40	34.39±4.01	0.121

* - Mean difference significant at p≤0.05, SD – Standard deviation, PT - Prothrombin Time, APTT - Activated Partial Thromboplastin Time

Discussion

Table 1 shows that most of the study population are normal and healthy women of premenopausal age, experiencing regular menstrual cycles and flows with a normal blood pressure range. A study had already noted a lack of casual association between combined oral contraceptives and weight gain[12]. Most had also not reached menopause and with an absence of medical history, this study could not adequately monitor the effects of oral contraceptives but a study already assured patients and providers of an absence of any meaningful correlations between combined oral contraceptives use and alterations in blood pressure or BMI in teenagers[12 13].

A research by [19], proposed that stopping combined oral contraceptives (COC) may help women with hypertension better control their blood pressure and that women who had their blood pressure checked before using COCs had a 2-to 2.5-fold lower incidence of ischemic stroke and myocardial infarction. Consideration should be given to the use of progestogen-only contraceptives (POCs) in women who have several cardiovascular risk factors. Compared to COCs, POC treatment is significantly related with a lower risk of cardiovascular events[14].

Table 2 show the blood grouping of the study population where blood group O has the highest frequency and is most probably because of the prevalence of blood group O in the society. No other significant associations were noted in relation to the risk of developing haemostatic complications though a study established that two of the primary environmental factors associated with Venous thromboembolism (VTE) were smoking and a body mass index greater than 35 kg/m^2. Furthermore, non-O blood types and severe hereditary thrombophilia were significant genetic risk factors for VTE.[15]

From Table 3, the parameters in the haematological profile of test subjects which show a statistically significant increase in RBC, PCV, neutrophil, eosinophil, MPV and plateletcrit while showing statistically significant reductions in MCV, MCH, MCHC, lymphocyte, basophil, RDW-CV, RDW-SD and PDW giving approximately a 78% change in all haematological parameters. These findings were consistent with the work of Elede[16], who investigated the effects of oral contraceptives on haematological indices and can be attributed to the decreased menstrual flow and androgenic effects caused by using pills. It also agrees with a research which established the diverse effects of RBCs on blood viscosity, cellular function, and thrombus formation, structure, and stability, concluding that RBCs most likely contribute to arterial thrombosis and VTE in unique ways[17]. There is also a correlation with the findings of [18] that show how through erratic intravaginal bleeding, the use of intrauterine non-hormonal contraceptives carries the risk of well-defined anemia. On the other hand, because of the few instances of blood loss, hormonal contraceptives are linked to good hemoglobin profiles[18].

The increase in platelet count though not significant, agreed with the findings of [19] who by using thromboelastography (TEG), light microscopy, and scanning electron microscopy noted increased rouleaux formation, erythrocyte aggregation, and spontaneous fibrin formation in whole blood of subjects taking oral contraceptives which may explain the increased risk of VT associated with combined oral contraceptive use[19].

The significant increase in platelet indices may be indicative of a prothrombotic state though the role platelet indices play in diagnosis of platelet disorders is still under study as seen in a finding indicates that plateletcrit (PCT) can be used instead of platelet counts alone to determine if the patient needs platelet transfusions and is a useful screening tool for detection of platelet quantitative disorders. PCT is a measure of the total platelet mass and may come across to be more clinically useful than being just an additional value to the laboratory[20].

In Table 4, there was a significant decrease in the PT of test subjects in comparison to the control group while the increase in their APTT values is not significant. These are consistent with recent findings which proves that these combined oral contraceptives all favor a state of hyper coagulation[1].

Any discrepancies may arise from the fact that most test subjects recruited for this research were on medication with second generation pills containing levonorgestrel.

The results of a study indicated that women who take oral contraceptive pills are more likely to have hypercoagulability, which increases their risk of thromboembolic consequences[21].

Conclusion

Thrombotic markers such as increased Red cell markers; RBC, haematocrit and platelet indices; MPV, PCT were increased along with decreased PT levels and prolonged APTT values though not significant can link oral contraceptives medication use to a hypercoagulable state in subjects thereby increasing their risk to venous thromboembolism.

Recommendation

An author already reported in the year 2000 that global tests such as PT and APTT present inconclusive results about the clinical relevance of a drug, since different factors such as differences of handling of samples, use of tetracycline and antihistamines drugs, and lipemic samples may influence these tests and the only way to obtain conclusive evidence would be to evaluate coagulation factors in isolation.

Due to cost constraints, this research was limited to only factors used in screening for thrombotic states, therefore it is imperative that further research with more specific coagulation factors and a larger sample size that indicate thrombosis such as assays for fibrinogen, protein C, thrombin time, D-dimer and anti-phospolipid antibodies be carried out before these results can be validated.

Conflict of Interest: There is no recorded conflict of interest

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