TPT Trends in Pharmacology and Toxicology

OPEN ACCESS

Coagulation Alterations in Single Women using Oral and Injectables Contraceptives in Calabar: Implications for Thromboembolic Risk and Policy Regulation

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ABSTRACT

Background and Objective: Hormonal contraceptives have been reported to influence haemostatic parameters, potentially increasing the risk of thrombotic events. This study assesses PT, APTT, TT, and FIB of single women using some form of contraceptives in Calabar, Cross River State, Nigeria. **Materials and Methods:** A cross-sectional descriptive study and a well-filled questionnaire were used. A citrated sample was obtained from 198 females, grouped into 98 single women on contraceptives and 100 single women not on contraceptives, of age range 15-30 years in Calabar, Cross River State, Nigeria. The single women were on oral 42 (42.9%) progestogen-only pills (POPs) 22 (52.4%), combined oral contraceptives (COCs) 20 (47.6%), POIs = Progestogen-only injectibles (POIs) 56 (57.1%) [Depo-Provera 36 (64.3%) and Noristerat 20 (35.7%)]. Quick's one-stage was used for PT, APTT, and TT (Helena Bioscience), while Clauss's Method was used to assess Fibrinogen levels. Ethical Clearance was obtained. Data were analysed using SPSS v20 with significance set at $p<0.05$. **Results:** The Mean±SD of PT, FIB, and TT (12.8 sec, 2.7 g/L, and 12.61 sec) was shown to be significantly higher and reduced in single women on contraceptive when compared to single women not on contraceptive (12.3 sec, 2.5 g/L, and 14.41 sec), $p<0.05$, respectively. Meanwhile, there was a statistically significant progressive increase in PT and FIB levels, while APTT and TT decrease ($p<0.05$) in single women on contraceptive when age (15-20, 21-25 and 26-30 years), duration (<1 year, 1-3 years and >4 years) of intake and types of contraceptives (FIB) was considered. Women on progestogen-only injectables recorded the highest fibrinogen levels. Fibrinogen showed significant moderate positive correlations with PT, APTT, and TT ($p<0.05$). **Conclusion:** Abuse of long-term use of contraceptives raises the risk for blood clots or incessant bleeding as it causes changes in the PT, FIB, APTT, and TT levels of single women in Calabar. These changes are more pronounced with injectable formulations. Policies should be made that regulate who sells contraceptive devices to avoid their nonprescription it in our society.

KEYWORDS

Contraceptive, single women, fibrinogen, thrombin time, progestogen-only injectables, Calabar

https://doi.org/10.21124/tpt.2025.120.126

Received: 28 Jul. 2025
Accepted: 10 Oct. 2025
Published: 31 Dec. 2025

INTRODUCTION

Hormonal contraceptives are widely used among women of reproductive age for effective birth control, with oral contraceptive pills (OCPs) and injectable hormonal contraceptives among the most commonly used methods. These agents contain estrogen, progestin, or a combination of both, and their systemic effects extend beyond reproduction. One of the significant non-contraceptive effects is their influence on haemostasis, particularly on coagulation and fibrinolysis pathways. Estrogen-containing contraceptives, especially, have been implicated in modifying liver synthesis of clotting factors, predisposing users to a prothrombotic state[1,2].

Several studies have reported variations in coagulation parameters such as prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), thrombin time (TT), and plasma fibrinogen (FIB) among users of hormonal contraceptives. These changes may include shortened APTT, elevated fibrinogen, and alterations in thrombin generation, which collectively may increase the risk of Venous Thromboembolism (VTE). The risk varies depending on the type, dose, and route of administration of the contraceptive[3] with injectable progestin-only formulations like Depot Medroxyprogesterone Acetate (DMPA) considered to have a different impact on coagulation than combined oral contraceptives[4,5].

Despite widespread contraceptive use in many developing countries, including Nigeria, data on their impact on coagulation profiles among apparently healthy women remain limited. Understanding these effects is critical, particularly in settings with limited access to thrombophilia screening, as many users may unknowingly be predisposed to thrombotic events[6]. This study, therefore, aims to assess selected coagulation parameters (PT, APTT, TT, and FIB) among single women using oral and injectable contraceptives to evaluate potential haemostatic alterations and inform safer contraceptive practices.

MATERIALS AND METHODS

This was a cross-sectional, observational study conducted among single women aged 18-40 years, students attending the University of Calabar, and residing in Calabar Metropolis, Nigeria. Single women on contraceptives as test participants were grouped into three categories as follows: Those on Progestogen-only pills (POPs), Combined Oral Contraceptives (COCs), Progestogen-only injectables (POIs), and non-contraceptive users who served as the control group. Individuals with known bleeding disorders, chronic illness, pregnancy, or recent surgery were excluded.

Ethical clearance/informed consent: A well-structured questionnaire was issued to each participant, and it was well-filled along with an informed consent which was obtained from participants. A certificate of Full Ethical approval was obtained from the Cross River State Health Research Ethics Committee (CRS-HREC) with REC No: CPSMOH/RP/REC/2022/299, and the research work (pre-analytical and analytical) was carried out between the periods of December, 2022-June, 2023.

Sample collection and laboratory analysis: Venous blood (4.5 mL) was collected from each participant into a tri-sodium citrate anticoagulant tube in a 9:1 blood-to-anticoagulant ratio. The samples were centrifuged at 4000 rpm for 10 min to obtain platelet-poor plasma (PPP), which was used to perform coagulation assays. The PT, APTT, and TT were measured using standard clot-based methods (e.g., Quick One-Stage) with a semi-automated coagulometer. Fibrinogen levels were determined using the Clauss method. All reagents were used according to manufacturer specifications, and internal quality control was maintained throughout the procedures.

Statistical analysis: Data were analyzed using SPSS version 20. Descriptive statistics were used to summarize demographic characteristics using proportions/percentages. Mean values of coagulation parameters were compared across groups using Student's t-test, Analysis of Variance (ANOVA), and Pearson correlation as appropriate. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 98 single women using contraceptives were enrolled in the study. The majority (53.1%) were within the age range of 21-25 years, while 20 (20.4%) and 26 (26.5%) were aged 15-20 and 26-30 years, respectively. All participants were undergraduate students, and 51% had used contraceptives for less than a year.

Table 1 shows the comparison of prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), thrombin time (TT), and fibrinogen (FIB) levels between contraceptive users (test group) and non-users (control group). The mean PT, APTT, TT, and FIB for the test group were 12.80±1.74 sec, 32.54±5.65 sec, 12.61±2.81 sec, and 2.76±1.45 g/L, respectively, while control subjects had mean values of 12.30±1.59 sec, 32.52±6.52 sec, 14.41±2.13 sec, and 2.57±0.25 g/L. The PT and FIB were significantly prolonged and elevated ($p<0.05$) in contraceptive users, while TT was significantly shortened ($p<0.05$).

There was a significant difference among the mean values of APTT, TT, and FIB ($p<0.05$) of single women using contraceptives. Further analysis based on age (Table 1) revealed a progressive decrease in APTT and TT values from the youngest to the oldest age group, with a corresponding increase in fibrinogen concentration ($p<0.05$). The group aged 15-20 years had APTT and TT values of 36.05±4.08 and 14.49±2.75 sec, respectively, while the 26-30 years group had reduced values of 28.65±4.99 and 10.86±2.25 sec, but elevated FIB at 2.96±0.52 g/L.

Duration of contraceptive use (Table 2) also influenced the parameters significantly ($p<0.05$). All four parameters (PT, APTT, TT, and FIB) were significantly different among the groups ($p<0.05$). Those using contraceptives for less than a year had the highest APTT and TT values (35.70±4.40 and 14.18±2.56 sec), while those using them for four or more years showed the lowest (28.27±4.13 and 10.07±1.79 sec) and the highest FIB level (3.10±0.53 g/L). A progressive increase in fibrinogen concentration and a decrease in clotting times with duration of use were observed.

Table 1: PT, APTT, TT, and FIB of single women on contraceptives, single women not on contraceptives, and parameters based on their age

Variables	Single women on contraceptives (n = 98)	Single women not on contraceptive (n = 100)	T	p-value
PT (sec)	12.80±1.74	12.30±1.59	2.092	0.038*
APTT (sec)	32.54±5.65	32.52±6.52	0.023	0.981
TT (sec)	12.61±2.81	14.41±2.13	-5.076	0.001*
FIB (g/L)	2.76±1.45	2.57±0.25	6.876	0.001*
Age (years)	15-20	21-25	26-30	
Variables	(n = 20)	(n = 52)	(n = 26)	f	p-value
PT (sec)	12.05±1.23	12.90±2.04	13.15±1.22*	2.566	0.082
APTT (sec)	36.05±4.08	33.13±5.42*	28.65±4.99*[a]	12.825	0.001*
TT (sec)	14.49±2.75	12.77±2.59*	10.86±2.25*[a]	11.730	0.001*
FIB (g/L)	2.59±0.22	2.69±0.38	2.96±0.52*[a]	17.654	0.005*

Values are represented as; Mean±Standard Deviation, PT: Prothrombin time test, APTT: Activated Partial Thromboplastin Time test, TT: Thrombin time test, FIB: Fibrinogen, n: Number of subjects, *Statistically significant, *Significantly different from 15-20 years and [a]Significantly different from 21-25 years

Table 2: PT, APTT, TT, and FIB among single women using contraceptives based on duration of intake

	Duration				
Variables	<1 year (n = 50)	1-3 years (n = 26)	>4 years (n = 22)	f	p-value
PT (sec)	12.30±1.45	13.54±2.72*	13.05±1.56	5.002	0.009*
APTT (sec)	35.70±4.40	30.92±4.93*	28.27±4.13*	29.214	0.001*
TT (sec)	14.18±2.56	11.74±1.93*	10.07±1.79*[a]	28.205	0.001*
FIB (g/L)	2.55±0.19	2.87±0.45*	3.10±0.53*[a]	27.756	0.001*

Values are represented as; Mean±Standard Deviation, PT: Prothrombin time test, APTT: Activated Partial Thromboplastin Time test, TT: Thrombin time test, FIB: Fibrinogen, n: Number of subjects, *Statistically significant, *Significantly different from <1 year and [a]Significantly different from 1-3 years

Table 3: PT, APTT, TT, and FIB among single women using contraceptives based on the type of contraceptive used

	Types of contraceptives				
Variables	POPs (n = 22)	COCs (n = 20)	POIs (n = 56)	f	p-value
PT (sec)	12.25±1.45	12.17±1.74	12.29±1.86	2.052	1.786
APTT (sec)	33.50±4.40	31.92±4.53	32.43±4.71	2.232	1.927
TT (sec)	14.23±1.75	13.45±1.62	14.38±1.61	1.995	2.001
FIB (g/L)	2.45±0.39	2.66±0.85*	3.19±0.58*[a]	21.256	0.001*

Values are represented as; Mean±Standard Deviation, PT: Prothrombin time test, APTT: Activated Partial Thromboplastin Time test, TT: Thrombin time test, FIB: Fibrinogen, POPs: Progestogen-only pills, COCs: Combined Oral Contraceptives, POIs: Progestogen-only injectables, n: Number of subjects, *Statistically significant, *Significantly different from POPs and [a]Significantly different from COCs

Table 4: Correlation of studied coagulation parameters of 98 single women using contraceptives

Variables	PT (r)	APTT (r)	TT (r)
TT (sec)	-0.235	0.431	-
APTT (sec)	-0.172	-	0.431
FIB (g/L)	0.385	0.452	0.426

TT: Thrombin time, PT: Prothrombin time, APTT: Activated partial thromboplastin time, FIB: Fibrinogen and *Significant at $p \leq 0.05$

Table 3 assessed the type of contraceptives used. Those on progestogen-only injectables (POIs) had the highest fibrinogen concentration (3.19±0.58 g/L), compared to those on progestogen-only pills (POPs) (2.45±0.39 g/L) and combined oral contraceptives (COCs) (2.66±0.85 g/L). While PT, APTT, and TT showed no significant differences across types, fibrinogen was significantly different ($p<0.05$).

Finally, Table 4 revealed a mild negative correlation between TT and PT ($r = -0.235$) and APTT and PT ($r = -0.172$), while TT and APTT had a moderate positive correlation ($r = 0.431$; $p<0.05$). Fibrinogen showed moderate positive correlations with PT ($r = 0.385$), APTT ($r = 0.452$), and TT ($r = 0.426$), all statistically significant ($p<0.05$).

DISCUSSION

The present study demonstrates significant alterations in coagulation parameters (prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), thrombin time (TT), and fibrinogen (FIB)), among single women using hormonal contraceptives in Calabar. The observed elevation in PT and fibrinogen, and shortening of TT, suggest a shift toward a prothrombotic state. These findings align with recent studies that associate hormonal contraceptive use with changes in haemostatic balance, leading to increased thrombin generation and reduced fibrinolytic activity[7-11]. Elevated fibrinogen is a known marker of increased clotting potential and cardiovascular risk[12]. Such changes may heighten the risk of thromboembolic complications even in young, ostensibly healthy women.

Age revealed a progressive reduction in APTT and TT and a corresponding increase in fibrinogen levels from the youngest (15-20 years) to the oldest age group (26-30 years). These trends may reflect cumulative hormonal exposure effects, especially in the liver, where clotting factors are synthesized. According to Yong and Toh[13], estrogen and progestogen derivatives increase the synthesis of fibrinogen and factor VII, contributing to hypercoagulability in women of reproductive age. This may reflect cumulative hormonal effects, as estrogen-containing contraceptives have been shown to increase levels of coagulation factors such as fibrinogen and factor VII[14]. Similar trends have been reported in cohort studies from Europe and Africa[15,16]. These age-related haemostatic shifts warrant consideration in contraceptive counseling and surveillance programs, especially for women approaching their third decade of life.

A similar pattern was noted with the duration of contraceptive use. Users of more than four years exhibited the most pronounced changes, with elevated fibrinogen and reduced clotting times, indicating a chronic effect of hormonal exposure. This is consistent with the previous findings of Tekle *et al.*[17], who

reported significant haemostatic alterations among long-term contraceptive users in Sub-Saharan Africa. The progressive increase in fibrinogen may serve as an early marker of systemic inflammation and vascular risk, as supported by evidence from longitudinal studies on oral contraceptives[18].

The type of contraceptive used also influenced haemostatic markers, particularly fibrinogen. Women on progestogen-only injectables exhibited the highest fibrinogen levels, suggesting that injectable formulations may exert a stronger hepatic stimulatory effect compared to oral formulations. This is in line with the findings of Özcan *et al*.[19] and Fahmy *et al*.[20], who noted greater impact on clotting factors among users of Depot Medroxyprogesterone Acetate (DMPA) than users of combined oral contraceptives. While PT, APTT, and TT showed no significant differences across contraceptive types in this study, the elevated fibrinogen level in injectable users underscores the importance of individualized contraceptive choice, especially for women with underlying thrombotic predispositions. Also, although PT, APTT, and TT were not significantly affected by contraceptive type, the increase in fibrinogen remains a concern due to its association with thrombo-inflammation[21,22].

Finally, the correlation analysis in this study demonstrated moderate positive relationships between fibrinogen and the major clotting parameters (PT, APTT, TT), suggesting that fibrinogen may be central in modulating the observed haemostatic changes. Conversely, a mild inverse relationship between TT and PT, and between APTT and PT, may reflect complex feedback mechanisms in the clotting cascade, influenced by contraceptive-mediated hormonal modulation. These interactions highlight the complex but significant role of hormonal contraceptives in coagulation pathway modulation, as previously demonstrated in a high-resolution thrombin generation assay[23,24]. Ongoing screening and education on contraceptive-related haemostatic risks remain essential in preventive healthcare for women.

CONCLUSION

The findings of this study demonstrate that the use of hormonal contraceptives among single women in Calabar significantly alters key coagulation parameters, particularly by increasing fibrinogen levels and shortening thrombin time, with age and duration of use being important modifiers. These changes suggest a shift toward a prothrombotic state, raising concerns about long-term cardiovascular and thromboembolic risks, especially in women using contraceptives for extended periods or opting for progestogen-only injectable methods. These results add to growing global evidence that supports routine haemostatic surveillance in reproductive health planning and contraceptive administration. The correlations observed among fibrinogen, PT, APTT, and TT also underscore the utility of these markers in monitoring women at risk of haemostatic imbalance due to hormonal contraceptive use. Regulatory bodies in Nigeria should ensure that contraceptive agents, particularly injectable types, are prescribed with appropriate clinical evaluation and not sold indiscriminately over the counter. Awareness should be created in communities and tertiary institutions on the safe use of hormonal contraceptives, including potential side effects and the importance of regular medical follow-up.

SIGNIFICANCE STATEMENT

This study discovered the significant haemostatic alterations associated with hormonal contraceptive use among single women in Calabar, particularly changes in prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen levels, that can be beneficial for clinicians, public health policymakers, and reproductive health educators in tailoring contraceptive choices and counseling. The findings highlight that age, duration of use, and contraceptive type, especially progestogen-only injectables, influence thromboembolic risk, emphasizing the need for routine coagulation monitoring. This study will help researchers to uncover the critical areas of contraceptive-related coagulation changes in African populations that many researchers were not able to explore. Thus, a new theory on personalized contraceptive risk assessment and vascular health protection may be arrived at.

ACKNOWLEDGMENT

The authors wish to acknowledge the single women on contraceptives, especially our students and single women living in some part of Calabar Metroplis who willingly consent to partake in the study.

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