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Relationship between the Use of Hormonal Contraceptives and the Promotion of Changes in Hemodynamic Factors that Predispose to Cardiovascular Risk

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***Abstract*—**The use of hormonal contraceptive drugs is widely used in different age groups, mainly due to easy acquisition and due to a large number of prescriptions. Besides, several studies point to the high cardiovascular risk concerning the use of hormonal contraceptives. In this study, we evaluated 620 Brazilian women to demonstrate the correlation between the hormonal contraceptives uses with the increase of the predisposition of risk for cardiovascular diseases. Our data demonstrated that concomitant use of contraceptives showed a significant reduction activated partial thromboplastin time and prothrombin time similar to hypercoagulability clinical conditions. Besides, as a compensation mechanism, there was an increase in the Fibrinogen levels. We also verified a significant increase at the total cholesterol and platelet aggregation up to 10%. Therefore, it was evidenced through this study that the use of hormonal contraceptives may increase cardiovascular risk. Besides, our data represents an alert since, in Brazil, many third-generation contraceptives are still prescribed in public health units, which are the ones that most present associations with cardiovascular risk.

***Keywords*—**Cardiovascular Disease, Fibrinogen, Hormonal Contraceptive and Woman.

I. INTRODUCTION

HORMONAL contraceptives (HC) have been worldwide diffused since the year 1960 [1]. The main contraceptive action of estrogen progestin-associated drugs occurs due to the suppression of GnRH, LH, and FSH secretion, and follicular development [2]. HC promotes modifications of the physical-chemical characteristics of the endometrium and cervical mucus, reduction of the menstrual flow, relief of the effects of premenstrual tension, aid in the treatment of acne and dysmenorrhea [3,4].

HC are present in several forms of administration of this type of medication, such as oral, injectable, intradermal implant and intrauterine system, which may vary according to contraceptive generation, dose-organism ratio, type of method (combined or isolated), or if alteration of homeostatic factors and metabolism [5,6].

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In this context, according to Padovan and Freitas (2015), among the forms of hormonal contraception, oral contraceptives are classified into four generations based on the estrogen dose, with the first generation having the highest hormonal amount [7].

However, when it began to enter hormones as a contraceptive form, there was still no evidence that the use of these drugs could promote adverse effects such as thrombosis [8]. Besides, HC induce significant changes in the coagulation system, culminating in increased thrombin generation, increased coagulation factors (fibrinogen, VII, VIII, IX, X, XII and XIII) and reduction of natural coagulation inhibitors S and antithrombin), producing a mild procoagulant effect [9,10]

According to the European Society of Cardiology, women who use HC have a significant cardiovascular risk, presenting moderate risk in 8.6% of the cases and high risk in 5.2% [11]. Asare et al. (2014) showed that women using contraceptives for more than eight years had higher blood pressure levels adjusted for age than women using oral contraceptives for shorter periods. Besides, the use of HC has as a standard feature to promote an increase in the distal blood pressure [12].

Thromboembolic phenomena are evidenced precisely because the presence of estrogen and progesterone in the HC formulation promotes direct action on the receptors of these constituents in the blood vessel layers [13].

Thus, it was believed that the primary cause of deep vein thrombosis (DVT) was due to the high estrogen dosage (150 mcg) present in the drug [14]. However, in 1995, research has shown that third-generation oral contraceptives composed of progestogens increase twice-daily changes in hemostasis compared to levonorgestrel, which is second-generation [9].

Currently, some brands have low concentrations of these hormones, but even with this reduction in estrogen dosages, studies show that hormones still trigger significant changes in the hemostatic system due to their androgenic action, resulting in the formation of fibrils, triggering the formation of clots in the venous system [15].

The relation between the use of HC and coagulation factors, regarding the risk of developing thromboembolic phenomena, is a subject of scientific interest, since it generates alterations in human metabolic physiology and, consequently, influences the quality of life and health of the patients who use them. Thus, in the present study, we evaluated the incidence of risk factors for the development

of DVP and its relation to the use of HC.

II. PATIENTS AND METHODS

III. Patients

Six hundred twenty women users of hormonal contraceptives were included in this study. These volunteers were recruited at a Brazilian higher education institution, located at Barreiras, Bahia State, Northeastern Region of Brazil. The participants were divided by age, time of use of the hormonal contraceptive, hormonal contraceptive generation, if there was a need for contraceptive change, presence of medical indication and previous request for exams, family history of thromboembolic diseases, the existence of vascular disease. This study was approved by the institutional Ethics Committee (permit number: 2.666.433), and all the participants signed written informed consent.

IV. Anthropometric Measurements

Participants weights and heights were measured with a stadiometer (Cardiomed, Curitiba, Brazil). Body mass index (BMI), as well as abdominal circumference, were classified according to the criteria established by Rech 2016 [16]. The women were classified as having a high risk of metabolic complications when the abdominal circumference measure was higher than 80 cm and very high risk when more significant than 88 cm. BMI < 25 kg/m² healthy, BMI 25 - 30 kg/m² overweight, BMI ≥ 30 e < 35 kg/m², class one obesity, BMI ≥ 35 ≤ 39,9 kg/m² class two obesity and BMI ≥ 40 kg/m2 class three obesity.

V.Laboratory Methods

The laboratory data were analyzed according to the criteria determined by the manufacturers of the kits used, which are of the Bioclin model. The fibrinogen, TP, and APTT assays were performed using the CloTimer equipment, while the tests for the determination of total cholesterol, HDL, LDL, and triglycerides, used the BioSystems semi-automatic biochemical analyzer (BTS-350). The determination of platelet count was performed using the ABX Micros ES 60 Hematology Analyzer. Thus, all exams were performed with blood samples.

VI. Blood pressure (BP)

The blood pressure levels, by the Brazilian Hypertension Directive was defined as normal when BP (120/80 mmHg), prehypertension (BP between 121/81 mmHg - 139/89 mmHg), hypertension in stage one (BP between 140/90 mmHg - 159/99 mmHg), stage two hypertension (BP between 160/100 mmHg - 179/109 mmHg) and stage three hypertension (BP ≥ 180/110 mmHg). These levels were evaluated in two moments with an interval of 5 minutes and were considered the average between the values collected.

VII. Lifestyle

It was evaluated using a questionnaire if the sample used alcoholic beverage, tobacco and if they practiced physical activity.

VIII. RESULTS

The observation of the age in the women showed that the population between 19 and 24 years constitutes 41.92% of the studied sample, being the average age of 30.647. Regarding the time of use of the hormonal contraceptive, it was noted that: 217 women used it for less than or equal to 1 year; 179 in use from 2 to 5 years; 26 in the range of 6 to 9 years and 98 in a time-space greater than or equal to 10 years. Besides, 98.46% of the studied population had received the prescription of a medical professional; the others used the contraceptive as self-medication. In this context, 100% of the sample received the contraceptive empirically, without previous examinations, showing negligence to correct dose adjustments. Cardiovascular diseases were reported in 92 women (Table I).

Table I: Type of cardiovascular diseases

CARDIOVASCULAR DISEASES	RESULTS
Yes	92 (17.69%)
No	149 (28.65%)
Unknow	279 (53.65%)
***Types**	
hypertension	31 (33.70%)
Varicose veins	23 (25%)
Dyslipidemia	29 (31.52%)
Deep vein thrombosis	2 (2.17%)
Cardiopathies	7 (7.61%)

Table II: Hormonal contraceptive

Generation	Composition	RESULTS
FIRST GENERATION	Linestrenol 0,5 mg	28
	Noretisterona 0,35 mg	87
	Linestrenol 1 mg Etinilestradiol 0,05 mg	2
	Total	**107 (20.5%)**
SECOND GENERATION	Levonorgestrel 0,15 mg Etinilestradiol 0,003 mg	235
	Norgestrel 0,5 mg Etinilestradiol 0,05 mg	2
	Levonorgestrel 0,050 / 0,075 / 0,125 mg Etinilestradiol 0,03 / 0,04 / 0,03 mg	31
	Levonorgestrel 0,25 mg Etinilestradiol 0,05 mg	67
	Total	**335 (65.6%)**
THIRD GENERATION	Desogestrel 0,15 mg Etinilestradiol 0,02 mg	8
	Gestodene 0,075 mg Etinilestradiol 0,02 mg	4
	Desogestrel 0,15 mg Etinilestradiol 0,03 mg	21
	Gestodene 0,075 mg Etinilestradiol 0,03 mg	10
	Desogestrel 0,025 / 0,125 mg Etinilestradiol 0,04 / 0,03 mg	5
	Gestodene 0,075 mg Etinilestradiol 0,03 mg	10
	Total	**58 (11.1%)**
FOURTH GENERATION	Etinilestradiol 0,035 mg Acetato de ciproterona 2mg	20
	Total	**20 (3.8%)**

Based on the evaluation of the use of hormonal contraceptives, it was found that 335 women, or 65.6% of the users, reported using third generation contraceptives (Table II). Besides, 186 women reported having to change their contraceptives due to some adverse effects, of which 44% had a headache; 11.82% reported nausea, vomiting, and gastric discomfort; 18.27% appearance of varicose veins; 13.97% attended with weight gain; 6.98% reported anemia and 4.8% had a dyslipidemic condition. Regarding lifestyle habits, alcohol consumption was present in 60% of the sample, with 77 women having mild dependence, 19 with moderate dependence and 21 with severe dependency (Table III).

Table III: Alcohol consumption

CONSUPTION	RESULT
USE	312 (60%)
DON'T USE	208 (40%)

The dependence of cigarettes was found to a lesser degree than the alcoholic in the studied population, being active in 22% of the women (Table 4).

Table IV: Cigarette consumption

CONSUPTION	RESULT
USE	117 (22.5%)
DON'T USE	403 (77.5%)

Regarding the sedentary lifestyle, 55.96% were sedentary, 19.61% reported a high degree of activity, 15.96% were considered active, and 8.46% were irregularly active. This shows a high cardiovascular risk in the sample since more than half demonstrates completely inactive. The anthropometric data correlating BMI and abdominal circumference (AC) are detailed in Table 5, showing that 76 women are considered obese, and 170 are at risk for metabolic complications due to the increased abdominal circumference.

Table V: BMI and abdominal circumference (AC)

BMI	RESULT (%)
< 25 healthy	337 (64.9)
25 a < 30 overweight	107 (20.6)
30 a < 35 class one obesity	50 (9.6)
35 a < 40 class two obesity	19 (3.6)
≥ 40 class three obesity	7 (1.3)
Metabolic Complications	**RESULT (%)**
Without risk < 80 cm	350 (67.3)
Elevate risk between 80 - 88 cm	162 (31.1)
Increased risk > 88 cm	8 (1.6)

Blood pressure levels were obtained as normal in 359 constituents of the sample, and among the altered levels 45 constitute prehypertension; 82, stage 1 hypertension; 19, in stage 2 hypertension and 15 women had stage 3 hypertension. Laboratory analyzes showed that 74,8% of the population studied of users had high total cholesterol, while 2,5% had increased triglycerides. As for HDL levels, 19.61 presented a risk (HDL≤ 40 mg / dL), while LDL showed intermediate risk in 2.3% of the sample and 21.73% in high risk (≤ 6). In contrast, glycemic levels showed pre-diabetes in 6.3% of women in the study and diabetes in 2.3%.

Table VI: Lipid profile of sample

	Hormonal Contraceptive				*p*
	Yes		No		
	n	**%**	**n**	**%**	
Total Cholesterol					0,004
< 190mg/dL	131		91		
≥ 190mg/dL	389		9		
Triglyceride					0,0189
< 150mg/dL	507		89		
≥ 150mg/dL	13		11		
HDL					0,0231
≥40mg/dL	512		94		
< 40mg/dL	8		6		
LDL					
≤ 70 mg/dl	506		91		0,0175
≤ 100 mg/dl	12		8		
≥ 130 mg/dl	2		1		
Glycemia					
≤ 90mg/dL	497		94		0,0137
100 e 125 mg/dl	21		6		
≥ 126 mg/dl	2		0		

The coagulogram explained the following result: 10.96% had a prothrombin time (PT) ≤ 9 s; 8.2% with aPTT less than 26 seconds, demonstrating a high risk of hypercoagulation; 5.38% with hyperfibrinogenemia and 5% with plaquetocytosis, and 9.23% of the sample had a platelet aggregation greater than 10% (Table 7).

Table VII: Coagulation tests

	Hormonal Contraceptive				*p*
	Users		**No users**		
	n	%	n	%	
TP					<0,002
10 - 14s	31	6%	97	97%	
≤ 9s	489	94%	4	4%	
APTT					<0,001
27 – 38s	19	4%	91	91%	
< 26s	501	96%	9	9%	
Fibrinogen					<0,001
150 - 350mg/dL	28	5%	88	88%	
> 350mg/dL	492	95%	12	12%	
Platelet Aggregation					<0,003
Ristocetina 0,5 mg/ml: maximum aggregation up to 10%	53	12%	93	93%	
A**ggregation** > 10%	467	88%	7	7%	
Platelets					<0,462
150.000 - 400.000 mm³	473	89%	98	98%	
> 400.000 mm³	43	11%	2	2%	

IX. DISCUSSION

Cardiovascular risk factors are related to lifestyle and make an influence on the development of some comorbidities. BARBARESKO et al. demonstrated in a meta-analysis study that of 22 studies performed, only three

did not show a relation of healthy habits with the reduction of cardiovascular risks [17]. This study detailed that people who have a healthy lifestyle including physical activity, average weight, low or moderate alcohol consumption, and non-smoker were statistically significantly associated with reduced risk of: overall CVD in 66%, stroke in 60% 69% CI and 70% CHD (coronary heart disease) [17].

In their studies, Domnan and Domnan (2018) affirm that HDL and LDL are associated with sudden death [18]. Beller and MacCartney showed that the use of contraceptives is not risk-free, indicating that combined oral contraceptives were associated with increased risks of venous thromboembolism and lipid abnormalities [19]. Besides, it is emphasized that low doses (i.e., ethinylestradiol dose <50 g) may increase the risk of myocardial infarction and ischemic stroke by approximately twice the general population of combined oral contraceptive (COC) users. Moreover, according to Vos et al. (2018), the use of contraceptives was related as a risk factor for cerebral ischemia in ischemic stroke [19,20]. Corroborating with these facts, the data reached in the study demonstrate that the risk ratio between hormonal contraceptives and increase in total cholesterol was statistically significant. In contrast, triglycerides associated with hormonal use did not show any significance.

In these parameters, as well as Machado, et al. (2010) found a reduction in activated partial thromboplastin time (APTT) and contraceptive use; this finding was present in this study [10]. Besides, high levels of fibrinogen correlate with obesity and contribute to a procoagulant state [21]. Our studies have demonstrated a significant statistic that relates to the use of hormonal contraceptives and the increase of fibrinogen.

According to Horton, Simmons, and Curtis (2016), both the use of COC and the increase in BMI increase the risk of TVE, and a higher risk is found for those with both factors present [22]. In this context, Romero et al. (2005) detailed that oral contraceptive users are four to six times more likely to have deep venous thrombosis when compared to women who do not use them, although the absolute risk is low (between one and two cases per 10,000 women-year), 10% of these events are fatal [22,23]. Based on this, 35.20% of the studied sample has a high BMI, which may represent a high-risk factor in conjunction with the CH.

Besides, hormonal contraceptives have different generations of use. Thus, studies by Konkle and Suman show that women who use the third-generation compared to non-users have a triple risk of TVE, while second generation increase the risk of TVE by approximately twofold. Thus, it is known that ethinylestradiol modifies several hemostatic factors, resulting in a procoagulant state and a slight fibrinolytic imbalance, favoring thrombosis [24,25]. Third-generation contraceptives are distributed in public health in Brazil, being, therefore, used a lot in the population and, consequently, in the studied sample, corroborating, according to these studies, an increase in the risk of DVT.

The fact that 92 women in the sample had vascular comorbidity, and 100% of them did not perform prior exams to the use of hormonal contraceptives, attracts attention to the current negligence of the professionals regarding the risks of thromboembolic complications. In this context, SHUFELT and MERZ (2009) evidenced that the current guidelines address the definition of the individual risk-benefit of each patient to the use of contraceptives, and women with 35 years or more with atherosclerosis, cardiovascular events, smoking, hypertension, migraine, and other risk factors, should be rigorously evaluated [26].

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