

Effect of Different Exercise Intensities on Blood Coagulation and Fibrinolysis in Oral Contraceptive Women

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ABSTRACT

Background: Oral contraceptives increase the thrombotic risk and also physical exercises changing the blood haemostasis. For exercise training it is recommended to apply the appropriate intensity of exercise to obtain its benefit and get away its hazards. **Purpose of the study:** So, this study investigated the effect of different intensities (mild, moderate, and severe) of exercises on blood coagulation factors including bleeding time, clotting time, prothrombin time as well as concentration, and platelet count. Also, fibrinolytic parameters including tissue plasminogen activity (t-PA) and plasminogen activator inhibitor-1 (PAI-1) activity. **Study design:** Forty five healthy multiparous women taking oral contraceptives participated in this study and randomly assigned into equal 3 groups. Each group exercised for 3 months (3 times/week) in different exercise intensity on treadmill, and each group had an exercise intensity determined according to the target heart rate. The previous parameters were measured pre and post training program. **Results:** Revealed that severe exercise showed a statistically highly significant decrease ($P < 0.02$) in bleeding time, increase ($P < 0.03$) & ($P < 0.04$) in clotting time and in platelet count. While, there were non significant differences in mild and moderate exercises in all coagulation parameters. In fibrinolytic parameters, moderate exercise showed a highly significant increase ($P < 0.03$) in t-PA and a highly significant decrease ($P < 0.02$) in PAI-1. On contrary, severe exercise had non significant change ($P < 0.07$) in t-PA and a significant increase ($P < 0.05$) in PAI-1. **In conclusion,** it is safe to design a program of exercises with moderate intensity especially to women who taking oral contraceptives as it shows no change in blood coagulation parameters and has a favorable improvement in fibrinolytic parameters.

Key Words: Exercise, coagulation, fibrinolysis, oral contraceptives.

INTRODUCTION

It has been reported that there is an increased risk of developing blood clots or deep vein thrombosis (DVT) in women who are taking oral

contraceptives⁸. It is estimated that 100 million women worldwide use oral contraceptives. With such a large number of individuals taking these medications, even the smallest increase in risk of side effects will have affects on many lives. Therefore, knowledge and

education regarding these risks and efforts to reduce the threats are of crucial importance¹.

Oral contraceptives are widely used by women for a variety of reasons, including contraception and relief of cyclic problems. However, oral contraceptive use has long been associated with hypercoagulability and data continue to support an increased risk for thromboembolic disorders, particularly venous thrombosis¹⁶. Both the estrogen and progestin components appear to play a role in the haemostatic changes that have been observed in oral contraceptive women⁸.

Oral contraceptives clearly activate both coagulation and fibrinolysis as demonstrated by changes in the molecular markers of these systems²¹. Increases in markers of coagulation as prothrombin fragment and thrombin-antithrombin complexes have been observed in oral contraceptive users¹⁶. Thus, oral contraceptives have the potential to alter haemostatic parameters that have been linked with what has been termed as hypercoagulable state. Although these changes may not lead to thrombus formation *per se*, they may increase the chance of experiencing an adverse event if a thrombotic stimulus occurs^{16,22}.

Coagulation and fibrinolysis constitute two important physiological opponents in the process of haemostasis and thrombus formation⁶. Activation of the coagulation system induces the formation of fibrin, whereas activation of the fibrinolytic mechanism results in the degradation of fibrin clots. Both systems are regulated by a balance between activators and inhibitors. Several acute stimuli, such as strenuous exercise and mental stress are known to enhance the activity levels of coagulation and fibrinolysis²².

The effects of maximal physical exercises on blood coagulation and fibrinolysis have been studied thoroughly^{4,11,18,24,25}. The

activation of blood coagulation is normally balanced by increased activity of the fibrinolytic system⁷. Nevertheless it is known that physical conditioning has an influence on blood coagulation and fibrinolysis¹⁸. The overall increase in fibrinolytic activity is produced by an increase in tissue plasminogen activator activity and a decrease in plasminogen activator inhibitor I activity, with the magnitude of these changes being dependent on exercise intensity and physical fitness status⁷.

Exercise also, increases coagulation activation as evidenced by increases thrombin-antithrombin and prothrombin fragment 1+2. With exercise intensity and physical fitness status again influencing the magnitude of change^{23,24}. But few studies have investigated the combined effect of oral contraceptive use and exercise on homeostasis and results are conflicting^{8,16,21}.

Because oral contraceptives have the potential to increase the risk for hypercoagulability and because strenuous exercise may also increase coagulation potential, so the combination of exercise and oral contraceptive use may alter the balance between coagulation and fibrinolysis. Also, no previous study revealed the influence of different intensities of training program on blood coagulation and fibrinolysis in women taking low-dose oral contraceptives. Therefore, the purpose of this study was to investigate the effect of different intensities (mild, moderate and severe) of exercise training program on blood coagulation and fibrinolysis in women taking low dose oral contraceptives.

SUBJECTS, MATERIAL AND METHODS

Forty five healthy multiparous (1-2 times) women who are oral contraceptive users were participated in this study from the family planning department at El Sahel Teaching Hospital, their age ranged from 24 to 30 years old (26.7 ± 1.2 years), their body mass index $< 28 \text{ kg/m}^2$ ($26.4 \pm 1.6 \text{ kg/m}^2$).

All women used oral contraceptive containing 6 tablets each with 0.05 mg levonorgestral and 0.03 mg ethinylestreadol plus 5 tablets with 0.075 mg levonorgestrel and 0.04 mg ethinylestread and 10 tablets each with 0.125 mg levonorgestrel and 0.03 mg ethinylestread as well as, did not participate at any exercise training program for at least six months prior of starting the study. Oral contraceptives were taken for 21 consecutive days during one hormone induced cycle.

Exclusion criteria for all women included the following: use of any medications other than oral contraceptives for at least one month before the study, history of smoking in the previous year or current smoking; diabetes, current pregnancy or pregnancy within the previous six months, as well as liver, renal, thyroid, autoimmune, cardiovascular and bronchopulmonary diseases.

Women were assigned randomly into three equal groups in numbers:

Group (I): participated in a mild intensity (20-40% of target heart rate).

Group (II): participated in moderate intensity (40-60% of target heart rate).

Group (III): participated in severe intensity (60-85% of target heart rate).

All women in the three groups performed walking exercise training for three months, three times per week and each session was for 30 minutes.

Instruments

- 1- Electronic treadmill was used for performing the exercise training program in the three groups.
- 2- Weight and height scale to measure both weight and height and calculate body mass index (BMI).
- 3- Commercially available kits for measuring of blood coagulation and fibrinolytic parameters.

Procedures

I- Evaluative procedures

All women in the three groups (I, II, III) subjected to lab in a fasting state (for at least 6 hours before evaluation) and having abstained from caffeine for 24 hours before evaluation. Evaluation took place between 9 and 11 Am to control for diurnal variations. Because the menstrual cycle phase may affect fibrinolytic activity⁶, so, evaluation in all women was performed during the early follicular phase of the menstrual cycle (days 3-6) to control this potential confounding variable.

Hence, venous blood samples were collected before exercise training program and the post blood sample was taking the 24 hours from the end of the last exercise session of the exercise training program (3 months) for determining blood coagulation markers (bleeding time, clotting time, prothrombin time as well as its concentration and platelets count using sysmex SF-3000 automated blood cell counter) and fibrinolysis markers [tissue plasminogen activator activity (t-PA) and plasminogen activator inhibitor I activity (PAI-1)].

For t-PA and PAI-1 were determined by using commercially available kits. t-PA activity was determined after serum was separated, aliquotted and kept at -70 C till assay time, using Imubined t-PA and PAI-1

ELISA kits (American Diagnostica, Greenwich, CT, USA).

II- Exercise training program

Each woman in the three groups was participated at exercise training program for 3 months (3 times per week) each exercise session was hold for 30 minutes. Each woman should be instructed not to eat for 3 hours before the exercise session.

The exercise training program was in the form of walking on treadmill, and asking each woman not to tightly grasp the rails because this action reduces the workload at any stage of exercise. To overcome this problem each woman was asked to remove their hands from rails, close their fists, and place one finger on the rails to maintain balance after they accustomed to walking on the treadmill.

The exercise session was started by five minutes warm up which involved walking with no resistance and no inclination at the walk way of the treadmill followed by twenty minutes of walking with 15 degrees inclination at the walk way of the treadmill and adjusted resistance to reach (20-40% THR) in group (I),

(40-60% THR) in group (II), and (60-85% THR) in group (III).

The THR = [(maximal heart rate - resting heart rate)] + resting heart rate⁵. Maximum heart rate was detected according to Borg scale for rating perceived exertion. Then the session is ended by 5 minutes of cool down in which the intensity of the exercise was reduced to the level of the warm up.

III- Data analysis

For all the statistical testes done, the threshold of significance was fixed at the 5% level (P-value). P-value > 0.05 indicated non significant results. P-value < 0.05 indicated highly significant results. Using student t-test to compare intrasubjects while, one way ANOVA to compare between subjects in the three groups¹⁹.

RESULTS

Age, weight, height, & BMI, parity, & oral contraceptive (O.C) usage period showed statistically non significant differences (P > 0.05) between the three groups, table (1).

Table (1): Physical characteristics of the three groups.

Variables	Group I	Group II	Group III
Age (yrs)	27.06±1.64	26.91±1.89	26.66±1.49
Weight (kgs)	69.91±1.72	70.41±1.88	71.06±1.97
Height (cm)	1.61±1.82	1.60±1.91	1.62±1.79
BMI (kg\cm ²)	26.69±0.92	27.34±0.95	27.09±0.91
Parity (times)	1.42±0.62	1.67±0.70	1.48±0.82
O.C usage period (months)	8.72 ±0.05	7.91±0.07	8.01±0.06

Table (2): Changes in the blood coagulation and fibrinolytic variables in the three groups (pre & post training).

	Group I		Group II		Group III	
	Pre	Post	Pre	Post	Pre	Post
Bleeding time (sec)	97.71 ±18.9	96.32 ±24.8	95.3 ±16.4	87.3 ±26.9	96.3 ±24.8	74.3 ±21.6
	P<0.9		P<0.09		P<0.02	
Clotting time (sec)	407.8 ±51	393.7 ±53	392.7 ±53.1	359.3 ±61.1	405 ±54.5	419.2 ±54.3
	P<0.4		P<0.06		P<0.03	
Prothrombin time (sec)	13.1 ±0.7	13.3 ±0.6	13.2 ±0.4	13.1 ±0.3	13.1 ±0.4	13.0 ±0.5
	P<0.6		P<0.61		P<0.94	
Prothrombin concentration %	95.7% ±6.8	96.0% ±6.9	96.7% ±6.2	97.7% ±5.3	97% ±6.2	96% ±6.9
	P<0.91		P<0.69		P<0.68	
Platelets count	254066.7 ±56683.9	246333.3 ±54689.6	268666.7 ±61369.5	250666.7 ±4736.8	269666.7 ±53867.1	285333.3 ±5846.5
	P<0.7		P<0.39		P<0.04	
Tissue plasminogen activity (t-PA) ng.ml ⁻¹	5.9 ±0.9	6.6 ±2.1	5.7 ±0.8	7.6 ±1.1	6.0 ±1.9	6.3 ±3.2
	P<0.05		P<0.03		P<0.07	
Plasminogen activity inhibitor (PAI-1) ng.ml ⁻¹	14.4 ±1.9	16.6 ±2.1	13.1 ±5.5	9.1 ±3.8	13.5 ±3.6	19.1 ±10.6
	P<0.06		P<0.02		P<0.05	

Table (3): Haemostatic parameters between subjects in the three groups.

Variables	Before training	After training
Bleeding time (sec)	F= 2.25 & P<0.16	F= 4.16 & P<0.01
Clotting time (sec)	F= 1.85 & P<0.73	F= 4.01 & P<0.05
Prothrombin time(sec)	F= 2.71 & P<0.12	F= 3.57 & P<0.08
Prothrombin concentration %	F= 2.36 & P<0.10	F= 3.38 & P<0.09
Platelets count	F= 0.32 & P<0.72	F= 4.92 & P<0.01
Tissue plasminogen activity (t-PA) ng.ml ⁻¹	F= 1.95 & P<0.39	F= 3.97 & P<0.05
Plasminogen activity inhibitor (PAI-1) ng.ml ⁻¹	F= 1.19 & P<0.31	F= 8.13 & P<0.001

In respect to the coagulation parameters table (2) & (3) and figure (1), firstly, showed that bleeding time in group III who participated in the severe intensity of exercise had a highly significant decrease post training ($P < 0.02$). While, there were a statistically non significant differences in the other groups (I & II) who participated in mild and moderate intensities ($P < 0.9$ & $P < 0.09$) respectively. Whereas comparing between the three groups revealed a statistically significant increase ($F =$

4.16 & $P < 0.01$). For the clotting time, group III who trained on the severe intensity of exercise had a statistically highly significant increase post training ($P < 0.03$). While, there were non significant differences in mild and moderate intensities of exercises ($P < 0.4$ & $P < 0.06$) respectively. But when comparing three groups showed a statistically significant increase ($F = 4.01$ & $P < 0.05$). Prothrombin time and its concentration showed a statistically non significant differences among

the three groups in both intra and between subjects ($F = 3.57$ & $P < 0.08$) & ($F = 3.38$ & $P < 0.09$) respectively. In platelet count showed a statistically highly significant increase ($P < 0.04$) in the severe exercise

group), while, there were non significant differences in mild and moderate intensities ($P < 0.7$ & $P < 0.39$) respectively. At comparing between the three groups showed a statistically significant increase ($F = 4.92$ & $P < 0.01$).

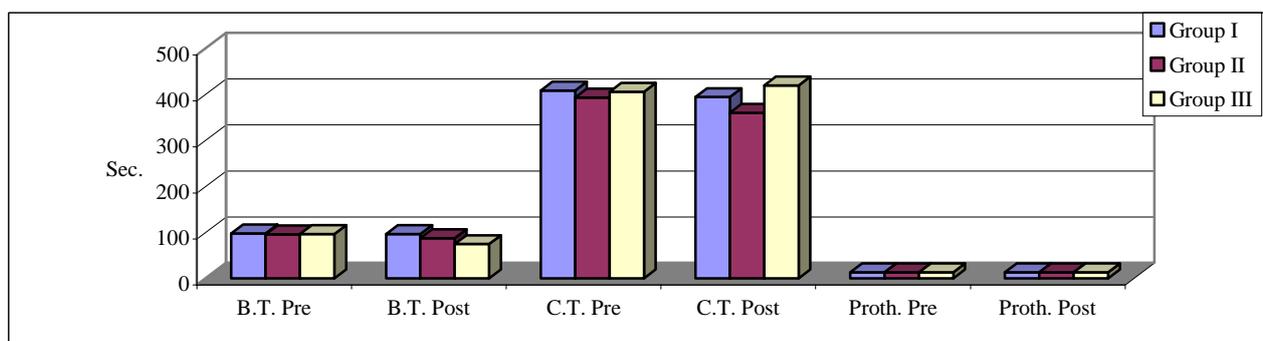


Fig. (1): Shows the Bleeding Time, Clotting Time and Prothrombin Time pre and post training in the three groups.

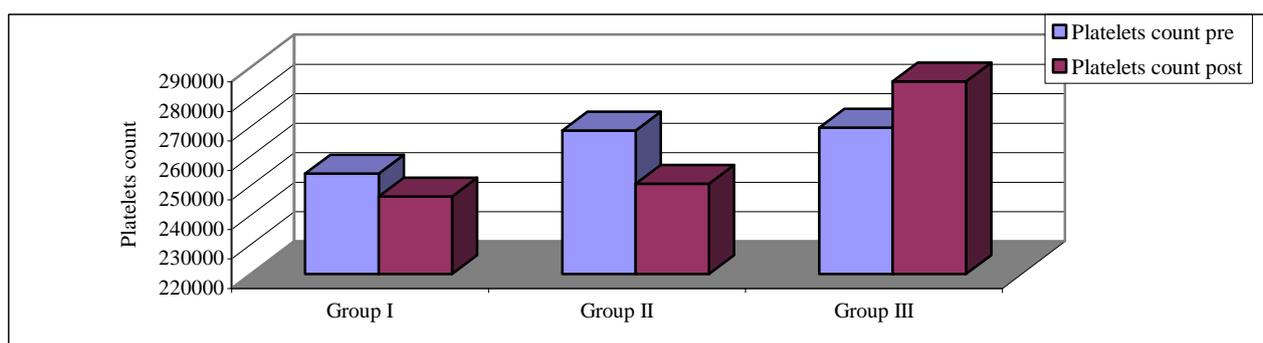


Fig. (2): Shows the platelet count pre and post training in the three groups.

For the fibrinolytic parameters as in figure (3), tissue plasminogen activity (t-PA) showed intrasubjects a highly significant increase ($P < 0.03$) in the moderate intensity and a significant increase ($P < 0.05$) in mild intensity of exercise, but there was non significant change ($P < 0.07$) in severe intensity. Between subjects, also moderate exercise showed a significant increase in t-PA

($F = 3.97$ & $P < 0.05$). For the plasminogen activity inhibitor (PAI-1) there was a highly significant decrease in moderate exercise in both intrasubjects ($P < 0.02$) and between subjects ($F = 8.13$ & $P < 0.001$). On the contrary, there was a significant increase ($P < 0.05$) in severe exercise and in addition, there was non significant difference ($P < 0.06$) in mild intensity of exercise.

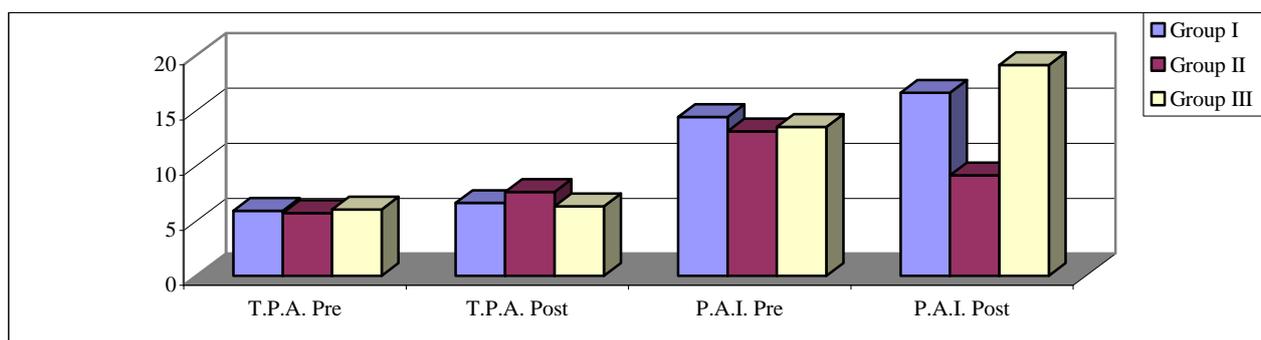


Fig. (3): Shows the tissue plasminogen activity (TPA) and plasminogen activity inhibitor (PAI) pre and post training in the three groups.

DISCUSSION

It is apparent that physical activity is essential in the prevention of chronic diseases and premature death. However, doubts remain over the optimal volume (frequency, duration, & intensity) of exercises and the minimum volume for health benefits in particularly about intensity (e.g. moderate versus vigorous) on health status¹³.

Exercises have a well known effect on coagulation and fibrinolysis and so do low dose O.C. Many studies investigated the effect of strenuous exercises with O.C on blood coagulation and fibrinolysis^{9,14,16}, but no previous studies investigated the effect of different intensities and that is the aim of this study.

In this study, moderate and mild intensities of exercises resulted in non significant changes and on the contrary the severe exercises showed a highly significant increase in bleeding and clotting times ($P < 0.02$ & $P < 0.03$) respectively in coagulation parameters. While, in fibrinolytic parameters moderate exercises showed a highly significant increase ($P < 0.03$) in t-PA and a highly significant decrease ($P < 0.02$) in PAI-1 and mild exercises showed a significant increase ($P < 0.05$) in t-PA and non significant

change ($P < 0.06$) in PAI-1. severe intensity of exercises showed non significant differences ($P < 0.07$) in t-PA and a significant increase ($P < 0.05$) in PAI-1.

The results of this study were in agreement with Huisveld et al. (1984)⁹, who concluded that strenuous exercises resulted in a significant decrease in fibrinolytic activities and it is still observed even after correction of haemoconcentration. In addition, strenuous exercises increase XII dependant and urokinase dependant fibrinolytic potential. The effects of exercises are superimposed on the O.C. induced changes.

Furthermore, Paffenbarger et al. (1993)¹⁷, revealed that physical activity (expending > 2000 Kcal \week) was associated with increase in life expectancy. But, subsequent studies had shown that an average of energy expenditure of about 1000 Kcal\week is associated with a 20-30 % of reduction in all causes of mortality.

In addition, endurance exercises with an intensity below 90% of individual anaerobic threshold (resembling to mild and moderate intensities of exercises in this study) and duration 2 hours generates a more favorable condition for fibrinolysis than for blood coagulation in healthy young subjects⁷.

Strenuous exercise induces activation in both the coagulation cascade and in the fibrinolytic system, which counterbalance each other. Nevertheless, a period occurs after exercise during which this balance seems to shift slightly toward the coagulation because of the short half-lives of components in the fibrinolytic system. It seems, however, that this prothrombotic tendency that prevails after exertion leads to thrombotic complications mainly in individuals with preexisting significant atherosclerosis¹⁵.

Also, Hilberg and Colleagues (2000)⁸, concluded that maximal exercises are associated with an increase in blood coagulation and fibrinolysis in women taking oral contraceptives. After physical conditioning programme there was significant increase in fibrinolysis at rest in the training group (60 min\twice a week for 12 weeks) in comparing with the control group (non training group).

Currently, most health and fitness organization advocated a minimum volume of exercises that expending 1000 Kcal\week or may be half of that is sufficient especially who are extremely deconditioned or are frail and elderly. Also, acknowledge the added benefits of higher energy expenditure²³.

Furthermore, in healthy young individual, exercises induced activation of coagulation is well balanced by activation of the fibrinolytic system. Since moderate exercises result in increased plasmin formation only, while, at very heavy exercises generation of plasmin seems to exceed that of thrombin and fibrin²⁵.

In contrast, no epidemiological studies reported a greater cardio-protective benefit from moderate versus vigorous aerobic exercises. When energy expenditure was controlled, the vigorous exercises were more beneficial in altering one or more risk factors

to coronary heart disease. However, the reason behind this is presently unknown. But, it is well documented that vigorous exercises resulted in improved aerobic capacity²⁰.

Administration of oral conjugated equine estrogen or 17-B estradiol was revealed that PAI-1, t-PA and fibrinogen are lowered. PAI-1 is the major regulator of the fibrinolytic system, and its disturbances in the plasma level implicated in the pathogenesis of coronary heart disease (CHD). PAI-1 increased significantly in follicular phase than luteal phase in the menstrual cycle. On contrary, there is inverse relation between concentration of estradiol and PAI-1^{6,12}.

Estrogen therapy affects the coagulation system by production of procoagulation factors (VII, XII& XIII) in the liver and decrease production of anti coagulation factors such as antithrombin and antifibrinolytic protein (PAI-1)¹¹. In addition, estrogen therapy changes the coagulation protein produced in platelet which is the initiator of intra vascular formation of fibrin clots²¹.

The changes in fibrinolytic system after acute maximal exercises between users and non users of oral contraceptives were non significant, there were significant increase in t-PA antigen, t-PA\PAI-1 complexes and antithrombin III. While, PAI-1 activity was reduced in both groups. So, fibrinolytic system changes induced by physical exercises are not affected by oral contraceptives³.

In this study, severe exercises showed a highly significant increase in platelet count in both intrasubjects ($P < 0.04$) and between subjects ($F = 4.92$ & $P < 0.01$). This in agreement with El Sayed et al. (2000)⁴, who concluded that strenuous exercises elicits a transient increase in platelet count. Also, moderate exercises appear to enhance blood fibrinolytic activity without concomitant activation of blood coagulation. While, on

contrary strenuous exercises induced simultaneous activation in blood coagulation and fibrinolysis.

Furthermore, Ikarugi et al. (1999)¹⁰, investigated the effect of aerobic exercises (60% of VO₂ max.) for 20 minutes in healthy subjects, this resulted in significant increase in platelet reactivity and coagulation. They attributed this increase to elevation of the circulating nor epinephrine during exercises. This is more supported by Bartsch (1999)², who explained the mechanism by which exercise activates haemostasis to the release of catecholamine and the considerable increase in shear stress might be relevant in particular for the activation of platelets with exercise.

In conclusion, after mild & moderate exercise, there is an activation of blood coagulation and fibrinolysis in women taking low dose oral contraceptives. But, strenuous exercise increase blood coagulation above normal levels which may lead to adverse effect for women taking oral contraceptives. So, planning of exercise training program for such women should be in the moderate level of exercise intensity to gain the benefits of exercise and without causing any harm to those women. Also, further studies of the same parameters are recommended to study the effect of exercise in obese OC women.

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الملخص العربي

تأثير التمرينات مختلفة الشدة علي عوامل تجلط الدم و انحلال الفيبرين لدي السيدات اللاتي يستعملن حبوب منع الحمل

من المعروف أن حبوب منع الحمل تزيد من أخطار تكون الجلطات كذلك التمرينات الرياضية تعمل علي تغيير في توازنات الدم لذلك من المفضل اختيار الشدة المناسبة للتمرين للحصول علي الفائدة المرجوة منه و البعد عن مخاطره . والهدف من هذه الدراسة هو تقييم المستويات المختلفة من الشدة للتمرينات (منخفضة- متوسطة- مرتفعة) علي معدل تجلط الدم متضمنة زمن النزف- زمن التجلط- زمن و تركيز البروثرومبين كذلك عدد الصفائح الدموية . أيضا قياس عوامل انحلال الفيبرين . اشتركت في تلك الدراسة و التي امتدت إلى ثلاثة شهور 45 سيدة يستخدمن حبوب منع الحمل و قسمن عشوائيا إلى ثلاث مجموعات متساوية كل مجموعة تؤدي التمرين بشدة مختلفة علي جهاز الجري . وأظهرت النتائج أن التمرينات مرتفعة الشدة أدت إلى زيادة ذو دلالة إحصائية عالية في عوامل تجلط الدم و لم يكن هناك أي تغييرات ذو دلالة إحصائية في المجموعات التي تعرضت إلى تمرينات منخفضة و متوسطة الشدة. و بالنسبة لعوامل انحلال الفيبرين فقد أظهرت التمرينات متوسطة الشدة زيادة ذو دلالة إحصائية عالية على عكس التمرينات مرتفعة الشدة و التي أظهرت انخفاض ذو دلالة إحصائية عالية . وفي النهاية من الأمان استخدام التمرينات متوسطة الشدة مع السيدات اللاتي يستخدمن حبوب منع الحمل حيث أنها لا تسبب تغيير في معدل تجلط الدم و أيضا أظهرت تأثير ايجابي في زيادة معدل انحلال الفيبرين .

الكلمات الدالة : التمرينات- تجلط الدم- انحلال الفيبرين- حبوب منع الحمل .