

Effect of low dose combined oral contraceptives on prothrombin time

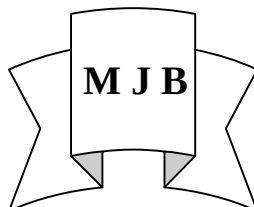
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Abstract

A 35 females used low dose combination oral contraceptives were enrolled in addition to 20 age matched healthy females included as a healthy control group . PT was estimated in plasma of all subjects . It was found significantly prolonged PT in users when compared with nonusers , and the results indicated prolong PT in the first 2 years of drug used and the alteration of PT disappear with continuous used . The results demonstrated the effect of low dose combination oral contraceptives on PT.

الخلاصة

تضمنت الدراسة 35 من النساء المستخدمات للأقراص إضافة إلى 20 من النساء غير المستخدمات لهذه الأقراص استعملت بوصفها مجموعة سيطرة و بأعمار مقاربة إلى المستخدمات 0 تم تقدير زمن التخثر في جميع النساء ، ولوحظت زيادة معنوية في زمن التخثر في النساء المستخدمات عند مقارنتها مع مثيلاتها لدى مجموعة السيطرة 0 ولوحظ أيضا زيادة زمن التخثر في الستين الأولى من استخدام الأقراص وعدم تأثر زمن التخثر عند استمرار الاستخدام لمدة أربع سنوات تشير النتائج إلى تأثير أقراص منع الحمل المركبة واضحة الجرعة على زمن التخثر

Oral contraceptives are medications taken by mouth for the purpose of birth control [1]. Most oral contraceptives used are combination of an estrogen and a progestin[2], these preparation suppress of gonadotropin release , then inhibit follicular development and prevent ovulation [3-4] . Oral contraceptives are usually taken for 21 days during the menstrual cycle followed by 7 days of placebo pills [5]. Contraceptives steroids are metabolized by the liver and effect the metabolism of carbohydrates, lipids, amino acids, vitamins, and clotting factors .The use of oral contraceptive is associated with

several clinical problems such as liver cancer, blood clots, and stroke [6]. While common side effects include depression, mastalgia of breast enlargement, some times amenorrhea, and weight gain [7]. Liver is responsible for synthesis of most coagulating factors, assessment of these factors is made by measuring prothrombin time (PT)[8]. PT measures the clotting time from the activation of factor VII through the formation of fibrin clot[9], another blood clotting test called partial thromboplastin time (PTT), measures other clotting factors (X,V, II) . PT and PTT are often done at the same time to check bleeding problems and how well the

liver is working [10]. PT commonly prolonged in liver disease because the liver is unable to manufacture adequate amount of clotting factors [11].

Patients and Method

A 35 healthy women used low dose combined oral contraceptives (Microgynon) each tablets consist 30 µg ethinyl estradiol and 150 mg levonorgestrel, attended to family planning clinic in maternity and pediatric hospital in Najaf, and 20 healthy age matched female who had not used steroidal preparation (control group).

The female users were categorized in to 2 groups according to the duration of use. Blood sample collected by clean vein puncture preferably 0.9 /0.1 ml trisodium citrate, then blood centrifuged at (300 xg), place plasma at room temperature (20 -25 °C) until time of test . The test performed within 4 hours after blood collection. Determine of PT done by special kits imported from bioMerieux Sa . The results were expressed as mean $\pm$ SD. The differences between the results groups determined by using *t*-test. Significant variation was considered when the P value was less than (0.05). In addition to that the influences of duration of the use on PT was evaluated by linear regression.

Results

The results of PT (table1), demonstrated significantly prolong ($p < 0.05$) in users when compared with the control group , (table 2) show increase PT significantly in group 1 of users in comparing with those of control group , while PT in group 2 remained to those of control group.

Discussion

Liver is the principle organ for drug metabolism and its responsible for the synthesis of most coagulating factors[12]. In this study we observed prolong PT among healthy users of low dose combined oral contraceptives, the reason of this finding may be attributed mainly to the steroid preparation on protein synthesis and release from the liver.

Use of oral contraceptives causes changes in procoagulant, anticoagulant, and fibrinolytic parameters, resulting in a net prothrombotic effect [13]. A large number of these changes have been attributed to estrogen.

Ethinyl estradiols have pronounced action on hepatic protein synthesis, estrogen dominant formulation such as ethinyl estradiol with gestodene and TRI-gestodene cause elevation in serum levels of various coagulation and fibrinolytic factors, but levonorgestrel antagonize the ethinyl estradiol effects on hepatic synthesis of coagulation factors[14]. In addition to that epidemiological observations indicated, users of oral contraceptives containing desogestrel or gestodene more resistant to the anticoagulant action of activated protein C than users of oral contraceptives containing levonorgestrel [15,16]. Moreover the use of low estrogen oral contraceptives containing of levonorgestrel decrease the risk of venous thromboembolism more than low estrogen containing other formulations[17,18]. On the other hand the pills use today contain much lower dose of estrogen and this reduced the serious of side effect. Thus we can suppose that used low dose of estrogen with levonorgestrel decrease hepatic synthesis of coagulation factors.

when comparing the current result with those mentioned in previous reports, some of them are in agreements and others are different from our results [19], have shown prolong PT after 3 months in females used combined oral contraceptives. While [20] shown that PT shorted in females used ethinyl estradiol with gestodene and TRI-gestodene formulations.

However, the remarkable differences of the obtained results and these mentioned by others may be due to the variation of the administration routs, types, and the dose of formulations.

Our finding seemed that the effects of contraceptive steroids on coagulation

factors were approximately comparable depending to the type, and dose of them.

Our result also indicated prolong PT in the first 2 years of use oral contraceptive , while PT not alter with continuous used. This result may reflect the continuous changes in hepatic synthesis with the progress of the administration , such changes may remove when liver being well adapt for oral contraceptives [21].

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Table (1): Prothrombin time in females used low dose combination oral contraceptives and the control group .

	subjects	No.	Mean $\pm$ SD	P value
Prothrmbin time (second)	users	35	14.6 $\pm$ 3.80	P<0.05
	control	20	13.5 $\pm$ 1.19	-

Table (2): Effect of duration use on Prothrmbin time of females used low dose combination oral contraceptives and control group.

	subjects	No.	Mean $\pm$ SD	P value
Prothrmbin time (second)	Up to 2 y	25	15.24 $\pm$ 4.05	P<0.05
	>2 -4 y	10	13 $\pm$ 2.61	N.S
	control	20	13.5 $\pm$ 1.19	—