

THROMBO-EMBOLIC RISK IN HIGH ESTROGENIC PHASE OF NORMAL MENSTRUAL CYCLE IN HEALTHY WOMEN

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ABSTRACT

Objective: This study is conducted to compare the risk of thrombo-embolism during different phases of menstrual cycles.

Methodology: 105 healthy premenopausal unmarried females of 18 -21 years with a history of previous three normal menstrual cycles and 32 age matched male volunteers were recruited in the study. The phase of menstrual cycle of female volunteers was established by taking menstrual history. Bleeding time was determined by Duke's method.

Results: Bleeding time in 105 females was 73.03 ± 1.89 Seconds and in 32 males was 69.33 ± 4.94 Seconds which were not significantly different statistically ($p=0.063$). Among females, 69 volunteers were in follicular phase of their hormonal cycle. Bleeding time in 29 females in early follicular phase was 70.86 ± 3.38 Seconds and 40 females in late follicular phase was 68.25 ± 4.03 Seconds. Statistically significant difference was not seen ($p=0.095$) when the two phases were compared. Bleeding time is not found to be reduced in late follicular phase as compared to early follicular phase, even high concentration of estrogen is present in the body in this phase as per normal menstrual physiology.

Conclusion: High Estrogen in normal menstrual cycle does not increase thrombo-embolic risk in healthy women.

Key Words: Estrogen, Bleeding time, Thrombo-embolism.

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INTRODUCTION

Estrogen is one of the important female steroid sex hormones. Incidences of thromboembolism in women taking estrogen support the fact that there exists an increased risk of thromboembolism in such women¹. Many causes are associated with it like it increases pro-coagulants², neutralizes anti coagulants like anti-thrombin III³, increases clotting factor^{4,5} and decreases Nitric oxide⁶. However the protective role of estrogen against thrombogenesis has also been identified in many studies but without clear cascade^{7,8}. Our study is designed to assess the role of high endogenous estrogen during normal menstrual cycle for increasing the risk of thromboembolism. We compared the bleeding time in early and late follicular phases because estrogen levels are relatively very low and very high⁹ during these phases respectively. APPT and PTT were not considered because of limited role of these two parameters^{10,11} as compared to bleeding time in platelets adhesions, activation and aggregation at the sites of vascular disruption¹².

METHODOLOGY

150 male and female volunteers of an undergraduate class of Karachi Medical and Dental College were randomly recruited from Jan 01 till Jan 15, 2014. Study was explained properly to them. The plan was approved by ethical committee of the institute.

Criteria of inclusion was: absence of any chronic illness or bleeding disorder, no drug therapy in the last 15 days, abstinence from consumption of flavonoid rich foods or beverages since 24 hours and three consecutive previous normal menstrual cycles (28 ± 2 days) in case of females while any congenital anomaly, skin disease affecting the test site and any addiction was the criteria for exclusion. 137 volunteers were eligible after consent to find bleeding time by Duke's method¹³.

Stage of menstrual cycle of each female was determined by a structured interview. The early follicular phase was designated from day 1 after menstruation to day 7 while late follicular phase from day 8 to day 15. Only 69 out of 105 females were found to be in follicular

phase while the remaining were excluded from further stages of this study.

SPSS version 16.0 was used for statistical analysis.

RESULTS

A total of 137 unmarried volunteers took part in the study in whom 32 were males and 105 were females. The mean age was 20.12 years with an age range of 18 to 21 years. A total of 69 females were in follicular phase of their menstrual cycle Table 1.

Table 2 shows the comparison of bleeding times in early and the late follicular phases in 69 females. Mean bleeding time in 29 female in early follicular phase was 70.86±3.38 Seconds (Mean±SEM), while in 40 female in late follicular was 68.25±4.03 Seconds (Mean±SEM).No statistically significant difference (p>0.05)is found between them.

DISCUSSION

Conflicting data exists in literature regarding the effect of estrogen on cardiovascular system. At one side estrogen is found to be thrombogenic by cohorts of the patients using contraceptive pills or receiving hormonal replacement therapy^{1,2} which is also supported by the fact that a number of pathways are altered by estrogen that effect the cardiovascular system^{14,15} and many changes in factors influencing coagulation have been reported including increased circulating levels of factors II, VII, IX and X and decreased anti-thrombin III pathway due to hepatic effects¹⁶. At other side it proves to be non thrombogenic^{7,8} because premenopausal women have less chances of developing thromboembolism due to high estrogen than men of same age while post-menopausal females equalizes their risk with males of same age due to low estrogen¹⁷ which is also supported by the fact that estrogen has found to maintain vascular health by inducing prostacyclin and nitric oxide synthase through estrogen alpha receptors^{17,18}. Our study does not support thrombogenic nature of estrogen. An initial support comes from insignificant difference (p>0.05) in the bleeding time of male hav-

ing low estrogen and female having high estrogen. But the strong support comes by comparing the bleeding times in early having Low estrogen¹⁶ and late having high estrogen 16follicular phases of menstrual cycle of normal healthy females rejecting the hypothesis that risk of thromboembolism should be increased during the phase of menstrual cycle in which body has relatively high estrogen. However the thrombogenic nature cannot be easily overlooked simply by these results because it is supported by a number of studies mentioned earlier. The hypothesis that the endogenous estrogen act in equilibrium with other components of coagulation adjusted as per demand of the body created with high level of this hormone while exogenous estrogen does not exist in equilibrium with these components, can accommodate both thrombogenic and non thrombogenic nature of estrogen. One of the recent studies support this through the assessment of Activated Protein C resistance which is found to be one of the major factors that contributes in developing Deep Venous Thrombosis in both oral contraceptive and estrogen replacement therapy users¹⁹and concluded that normal physiological levels of estrogen during menstrual cycle don't alter the Activated Protein C sensitivity²⁰. Considering the receptor regulation of estrogen also support this hypothesis. It is well known that the increased levels of steroid hormones down regulate their own receptors²¹ therefore, it can be considered that estrogen receptors are down regulated by persistently increased level of estrogen in women using contraceptives. Estrogen α receptors are mainly present on vessels endothelial cells therefore when there are less α receptors there may be less NO and prostacyclin produced that may increase risks of thromboembolism in premenopausal women. Although the levels of serum NO and prostacyclin in oral contraceptive users are not directly measured but this fact is supported by a study in which estrogen present in contraceptives significantly decrease prostacyclin and NO levels than estrogen at physiological levels²². Similarly the methylation associated inactivation of estrogen α receptors seems to be the main cause of thromboembolism in post-menopausal aged women on HRT^{23,24}.

Table 1: Bleeding time in both genders (n= 137).

SEX	BLEEDING TIME(SEC.)	CV	P
Male	69.33(32)4.94*	39.07%	0.063
Female	73.03(105)1.89	24.60%	

Table 2: Bleeding time in females in Early and Late Follicular Phase (n=69).

PHASE	BLEEDING TIME(SEC.)	CV	P
Early follicular	70.86(29)3.38*	25.71%	0.095
Late follicular	68.25(40)4.03	23.83%	

CONCLUSION

It is concluded that endogenous estrogen does not increase the risk of thrombo-embolism in healthy women.

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CONTRIBUTORS

MTA conceived the idea, supervised the study and wrote the manuscript. SS and HT helped in data collection and intellectual input. All authors contributed significantly to the final manuscript.