ejpmr, 2021,8(7), 454-457

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

COMPARISON OF MEAN NORMAL PROTHROMBIN TIME (MNPT) BETWEEN DIFFERENT TRIMESTER OF PREGNANCY WITH NORMAL NON-PREGNANT REPRODUCTIVE AGE GROUP FEMALE SUBJECTS

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Article Received on 06/05/2021 **Article Revised on 27/05/2021** **Article Accepted on 17/06/2021**

ABSTRACT

Introduction: Pregnancy is hypercoagulable, most coagulation factors increase in normal pregnancy, hence the prothrombin time (PT) and the activated partial thromboplastin time (APTT) are shortened. Therefore INR will be affected in pregnant patients if Mean normal Prothrombin time established in Non-pregnant patients is utilised for calculating INR in pregnant patients. **Objective:** This study is done to compare the MNPT between different trimesters of pregnancy with normal non-pregnant reproductive age group female subjects and to identify whether the MNPT established for non-pregnant subjects for reporting INR can be used for pregnant subjects also or there is a need to establish a separate MNPT in pregnant patients for reporting INR. **Materials and Methods:** A total of 80 apparently healthy subjects were enrolled for the study and sub classified into 4 groups. The first group (Group A) is 20 normal pregnant women in first trimester, second group (Group B) is 20 normal pregnant women in second trimester, third group (Group C) is 20 normal pregnant women in third trimester and the fourth group (Group D) is 20 normal non-pregnant women of Reproductive age (15-45 years) group. The subjects on anticoagulant drugs like heparin, warfarin etc, hypertension, diabetes mellitus, severe liver disease, any other acute or chronic illness were excluded from the study. The Prothrombin test was analysed by semi automated photo optic method by Thromborel S reagent. **Results:** The mean normal prothrombin time of Group A (20 normal pregnant women in first trimester) was 11.39 seconds with SD of 0.39, Group B (20 normal pregnant women in second trimester) was 10.91 seconds with SD of 0.41, Group C (20 normal pregnant women in third trimester) was 10.05 seconds with SD of 0.41 and Group D (- 20 normal non-pregnant women of Reproductive age (18-45 years) group) was 13.01 seconds with SD of 0.45. **Conclusion:** It is concluded that prothrombin time is decreased in normal pregnancy when compared with non-pregnant women of reproductive age group. Since the degree of difference of MNPT between different trismester of pregnancy with non-pregnant women of reproductive age group is statistically significant, it is warranted to establish a separate mean normal prothrombin time in pregnant subjects for reporting INR.

KEYWORDS: Prothrombin time, coagulation, pregnancy, International Normalised Ratio (INR).

INTRODUCTION

Normal pregnancy is associated with significant change in coagulation system. It is characterised by increase in the majority of clotting factors, decrease in the natural anticoagulants and a reduction in fibrinolytic activity.[1-3] These changes in pregnancy result in a state of hypercoagulability which is likely to be due to hormonal changes.[4] The increase in clotting activity is greatest at the time of delivery with placental expulsion releasing thromboplastic substances which stimulate clot formation to stop maternal blood loss. Coagulation and fibrinolysis generally return to pre-pregnant levels 3–4 weeks postpartum.[1,2]

As most coagulation factors increase in normal pregnancy, the prothrombin time (PT) and the activated partial thromboplastin time (APTT) are shortened.[6] The prothrombin time is time required for a fibrin clot to form after the addition of tissue Factor (TF) (historically known as tissue thromboplastin), phospholipid and calcium to decalcified, platelet poor plasma. The Prothrombin Time (PT) test results are used for evaluation of extrinsic pathway of coagulation, for the measure of warfarin dosage, Liver disease and for assessment of Vitamin K status.

The Prothrombin time is reported as International Normalised Ratio (INR) which is the ratio of a patient's prothrombin time in seconds to mean normal prothrombin time, raised to the power of the ISI value.[7] INR = [Patient PT/Mean Noramal PT]^{ISI}. It is recommended by the WHO that MNPT should be

established for each lot of thromboplastin PT reagents by each laboratory, since PT results are dependent on the combination of reagent lot, instrument and technique followed at each laboratory.[8] Usually plasma from 20 normal healthy individuals independent of age/sex should be used to establish the MNPT. The Geometric mean of such PT results in seconds is mean normal prothrombin time (MNPT).[8]

The Prothrombin time test results will vary according to the type of thromboplastin reagent (Human, Bovine, Rabbit or Recombinant) used for the analysis because different thromboplastins will have different sensitivity index. The first WHO reference thromboplastin was assigned an ISI of 1.0. Hence individual thromboplastins are calibrated against WHO reference thromboplastin to assign them an International sensitivity index or ISI.

Most laboratories use mean normal prothrombin time established from non-pregnant patients for calculating INR in pregnant patients also. Since pregnancy is hypercoagulable, most coagulation factors increase in normal pregnancy, hence the prothrombin time (PT) and the activated partial thromboplastin time (APTT) are shortened. Therefore INR will be affected in pregnant patients if Mean normal Prothrombin time established in Non-pregnant patients is utilised for calculating INR in pregnant patients. To address this fact, this study is done to compare the MNPT between different trimesters of pregnancy with normal non-pregnant reproductive age group female subjects and to identify whether the MNPT established for non-pregnant subjects for reporting INR can be used for pregnant subjects also or there is a need to establish a separate MNPT in pregnant patients for reporting INR.

MATERIALS AND METHODS

This is a Prospective study conducted at Chengalpattu Medical College & Hospital. A total of 80 apparently healthy subjects were enrolled for the study and sub classified into 4 groups. The first group (Group A) is 20 normal pregnant women in first trimester, second group (Group B) is 20 normal pregnant women in second trimester, third group (Group C) is 20 normal pregnant women in third trimester and the fourth group (Group D) is 20 normal non-pregnant women of Reproductive age (15-45 years) group. The subjects on anticoagulant drugs like heparin, warfarin etc, hypertension, diabetes mellitus, severe liver disease, any other acute or chronic illness were excluded from the study. The study was approved by Instituitional ethics committee. After taking written informed consent from subjects enrolled for the study, 3 ml of blood was collected in sodium citrate tube for Prothrombin time test. The Prothrombin test was analysed by semi automated photo optic method by Thromborel S reagent. Thromborel S Reagent is prepared from human placental tissue factor combined with calcium chloride and stabilizers. The coagulation process is triggered by incubation of plasma with the optimal amount of thromboplastin and calcium. The time to formation of a fibrin clot is then measured in seconds.

STATISTICAL ANALYSIS

The Statistical analysis was performed using SPSS software version 23. Analysis of variance (ANOVA) and Tukey HSD post-Hoc test were used for statistical analysis. The minimum value of the level of statistical significance, p-value, in all statistical tests was set as 0.05.

RESULTS

Table 1: Comparison of Mean Normal Prothrombin Time Between Different Trimesters Of Pregnancy And Normal Non-Pregnant Reproductive Age Group Female Subjects.

Groups	Geometric Mean of Prothrombin Time In Seconds	P-Value
GROUP A - 20 normal pregnant women in first trimester	11.39 ± 0.39	<0.05
GROUP B - 20 normal pregnant women in second trimester	10.91 ± 0.41	
GROUP C - 20 normal pregnant women in third trimester	10.05 ± 0.41	
GROUP D - 20 normal non-pregnant women of Reproductive age (18-45 years) group	13.01 ± 0.45	

Table- 1 shows the comparison of mean normal prothrombin time between different trimesters of pregnancy and normal non-pregnant reproductive age group female subjects included in the study by ANOVA test. The mean normal prothrombin time of Group A (20 normal pregnant women in first trimester) was 11.39 seconds with SD of 0.39, Group B (20 normal pregnant women in second trimester) was 10.91 seconds with SD of 0.41, Group C (20 normal pregnant women in third trimester) was 10.05 seconds with SD of 0.41 and Group D (- 20 normal non-pregnant women of Reproductive age (18-45 years) group) was 13.01 seconds with SD of 0.45. A statistically significant difference ($p<0.05$) was observed for mean normal prothrombin time between different trimesters of pregnancy and normal non-pregnant reproductive age group female subjects.

Table 2: Tukey Hsd Post-Hoc Tests For Multiple Pair Wise Comparisons.

Pairs		Mean Difference Of Prothrombin Time	P-Value
GROUP A	GROUP B	0.58	<0.05
GROUP A	GROUP C	1.44	<0.05
GROUP A	GROUP D	1.52	<0.05
GROUP B	GROUP C	0.86	<0.05
GROUP B	GROUP D	2.10	<0.05
GROUP C	GROUP D	2.96	<0.05

Table-2 shows Tukey HSD post-Hoc test. It shows multiple pair wise comparison and degree of difference of Mean normal prothrombin time between four groups.

DISCUSSION

The prothrombin time assay is one of the most commonly used coagulation test in clinical laboratories. The Prothrombin time is a screening test to evaluate the tissue factor and common coagulation pathways, so it is affected by the activity of coagulation factors II, V, VII, X and fibrinogen.[9] The PT is reported as international normalized ratio (INR) to provide test results adjusted for thromboplastin and instrument used. The test result is used for monitoring anticoagulant therapy with vitamin K antagonists such as warfarin. The Prothrombin time is prolonged with deficiencies of factors II, V, VII, X or fibrinogen and by antibodies directed against these factors as well as the presence of an antiphospholipid antibody (APLA), such as lupus anticoagulant. A mixing study is performed to differentiate between coagulation factor deficiency and the presence of inhibitors. If prothrombin time is corrected after the addition of normal plasma, congenital or acquired coagulation factor deficiency is implied, whereas if prothrombin time remains prolonged even after the addition of normal plasma raises the possibility of inhibitors.[10]

Pregnancy is hypercoagulable, most coagulation factors increase in normal pregnancy, hence the prothrombin time (PT) and the activated partial thromboplastin time (APTT) are shortened. In the present study there is decrease in mean normal prothrombin time in all trimesters of pregnancy when compared with non-pregnant women of Reproductive age (18-45 years) group. This decreased prothrombin time may be due to increase in concentration of most coagulation factors. Fuse, Y se at showed shortening of prothrombin time and activated partial thromboplastin time, increases in fibrinogen, platelet epinephrine, collagen aggregation, and plasminogen and a decrease in alpha 2-plasmin inhibitor in the third trimester when compared with those in the first trimester.[11] Another study by Hui C, Lili M et al also showed increase in levels of fibrinogen, thrombin time, fibronectin, prothrombin activated fragments 1+2 and thrombomodulin in early pregnancy.[12]

Pregnant women who have mechanical heart valves are at high risk of thromboembolic complications.[13,14] Many of the available anticoagulant agents may be used safely in pregnancy, but they are disadvantaged by competing efficacy and risks to the mother and fetus. Warfarin continued throughout pregnancy offers the best thromboembolic protection to the mother, but carries a higher risk of fetal loss and complications.[13] The Prothrombin time is reported as International Normalised Ratio (INR) which is the ratio of a patient's prothrombin time in seconds to mean normal prothrombin time, raised to the power of the ISI value.

Most laboratories use mean normal prothrombin time established from non-pregnant population for calculating INR in pregnant population also. In the present study, there is decrease in mean normal prothrombin time in all trimesters of pregnancy when compared with non-pregnant women of reproductive age (18-45 years) group due to increase in most coagulation factors. Therefore INR will be affected in pregnant population, if mean normal Prothrombin time established in non-pregnant population is utilised for calculating INR in pregnant population.

CONCLUSION

It is concluded that prothrombin time is decreased in normal pregnancy when compared with non-pregnant women of reproductive age group. Since the degree of difference of MNPT between different trismester of pregnancy with non-pregnant women of reproductive age group is statistically significant, it is warranted to establish a separate mean normal prothrombin time in pregnant subjects for reporting INR.

ACKNOWLEDGEMENTS: Nil.

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