

**Review: The prevalence of factor V Leiden or prothrombin gene mutations was not higher in women with severe preeclampsia compared to matched controls.**

J.C. Livingston, J.R. Barton, V. Park, B. Haddad, O. Phillips and B.M. Sibai Maternal and fetal inherited thrombophilias are not related to the development of severe preeclampsia. *Am. J Obstet Gynecol.* 2001 July;185(1):153-157.

**Review written by Alan Karovitch MD from Ottawa, Canada**

**QUESTION**

Is the presence of maternal or fetal factor V Leiden (G/506A) mutation or prothrombin (G/20210/A) mutation or methylenetetrahydrofolate (MTHFR CC/667/TT) mutation increased in cases of severe preeclampsia?

**DESIGN**

Prospective cross-sectional study in patients with severe preeclampsia. Matched to similar gestational age, normotensive controls.

**SETTING**

Central Baptist Hospital, Lexington, Kentucky, USA.

**PATIENTS**

Women with severe preeclampsia. Defined as SBP  $\geq$  160 mmHg or DBP  $\geq$  110 mmHg with proteinuria or eclampsia or HELLP syndrome. Controls were women matched for gestational age with normal BP. They had no history of preeclampsia, hypertension, diabetes, venothrombotic events, renal disease or major fetal anomaly.

The average age was 24 years and the average gestational age was 34 weeks. Over 60% of patients were African-American. Mean arterial BP in patients was 124 +/- 29.9 and 88.5 +/- 25.7 in controls.

207 patients were recruited over a 16 month period. Enrollment was not consecutive since some patients refused to participate.

**MAIN OUTCOME MEASURES**

The main outcome measured was prevalence of factor V Leiden, MTHFR or prothrombin mutation in the patients with severe preeclampsia and in the umbilical cord blood of their fetuses. Outcomes were compared to matched controls.

**MAIN RESULTS**

207 women were included. 110 patients had severe preeclampsia. Blood was collected from the 110 preeclamptics and 75 fetal samples from those pregnancies. Blood from 97 controls and 80 fetal samples from those pregnancies were collected.

The frequency of factor V Leiden in patients with preeclampsia vs. controls was 4.4% vs. 4.3% (NS). For prothrombin mutation it was 0% vs. 1.1% (NS). For MTHFR it was

9.6% vs. 6.3% (NS). The combined percentages for all three mutations were 14.5% in the women with preeclampsia vs. 11.3% in the controls (also NS).

There was also no difference in the frequency of fetal thrombophilias and the development of preeclampsia.

There was no difference when looking at patient race, HELLP syndrome or eclampsia cases.

#### AUTHORS' CONCLUSION

This study was unable to demonstrate an association between either maternal or fetal mutations in regards to factor V Leiden, MTHFR or prothrombin genes and the development of severe preeclampsia. Previous case control data has shown an association with thrombophilias and preeclampsia. However other studies have not shown such an association. These negative studies often included women with mild preeclampsia or nonproteinuric hypertension.

Both fetal and maternal thrombosis may affect placental thrombosis therefore it is reasonable to evaluate fetal genotypes when looking at preeclampsia.

Previous studies largely looked at relatively homogeneous populations. This study had a very heterogeneous population and included many African-Americans who have an increased risk of preeclampsia but have a lower prevalence of these thrombophilic mutations. Different populations may be predisposed to preeclampsia by different mechanisms.

The power of the study may have been inadequate to show a difference since the number of patients for each ethnic group with severe preeclampsia was relatively small.

The authors conclude that their findings do not support routine screening of women with a history of severe preeclampsia for factor V Leiden, MTHFR or prothrombin mutations.

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#### COMMENTARY

Several studies have demonstrated an association between inherited thrombophilias and obstetrical complications (1-7). These include preeclampsia. Other studies have not shown such an association (8-10).

None of the data published to date is based on large prospective trials and as such most should be interpreted cautiously.

This study by Livingston et al. did not demonstrate an association between maternal factor V Leiden, MTHFR or prothrombin mutation and severe preeclampsia. I agree with the authors that there are several reasons why this may be so. The study may have been underpowered especially when looking at changes within different ethnic populations.

This study also included many African-American patients which makes it different than previous studies published. African-American patients are known to have a lower prevalence of the tested thrombophilias but may be at higher risk for preeclampsia for other reasons (11-13). Of course it just may be that these thrombophilias do not predispose women to preeclampsia. This is particularly important because this study only included women with severe preeclampsia as opposed to other studies that included women with mild disease.

This study also looked at the frequency of the three thrombophilias in the fetal circulation. The authors are the first to evaluate the risk of obstetrical complications associated with these fetal changes. However, they were unable to demonstrate an association between fetal thrombophilias and severe preeclampsia. Of course, once again, the power to do so may have been lacking in this study.

Obviously conflicting data exists. Large prospective longitudinal studies are required to clarify the question of risk of obstetrical complications and prevalence of inherited thrombophilias.

This study not only questions these associations but makes it abundantly clear that treating patients with these thrombophilias with anticoagulants in subsequent pregnancies cannot be justified until a large randomized trial addressing that specific issue is completed.

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