Dear Sir,

Recent reports have identified an association between the presence of the factor V Leiden allele and spontaneous fetal loss and preeclampsia (1-3). In addition, the 5, 10-methylene tetrahydrofolate reductase (MTHFR) gene has also been found to be associated with early fetal loss and pre-eclampsia particularly when present in the homozgyous form or in conjunction with the presence of the factor V Leiden allele (3). The prothrombin 20210A gene mutation is associated with increased levels of plasma prothrombin and an increased risk for venous thrombosis and arterial disease but, to date, has not been investigated in high risk pregnancies (4, 5). It is generally known that underlying maternal hypercoagulability can be a significant risk factor for complications of pregnancy such as maternal deep venous thrombosis and pulmonary embolism, pre-eclampsia, spontaneous fetal loss, and intrauterine growth retardation (IUGR) (6-11). Indeed, the effects of the cumulative number and severity of placential lesions including vascular infaracts associated with placential thrombosis have been shown to be significant in the etiology of the IUGR pregnancy (6).

While the hemodynamic balance between maternal and fetal circulation is a critical component of the normal fetal development and pregnancy, few studies focus attention to the fetal circulatory contribution to this process. It is known that most of the coagulation factors (factors II, V, VII, VIII, IX, X, XI, XII, prekallikrein, high molecular weight kininogen and fibrinogen) are at low levels in the fetus, particularly prior to gestational week thirty four (12). Only factors V and VIII reach adult levels at birth (12). In addition, however, low levels of antithrombin III, protein S, protein C and tissue factor pathway inhibitor are found in the fetal circulation (12). Wilcox et al. have shown no overall difference between activated partial thromboplastin time, antithrombin III activity, fibrinopeptide A or thrombin-antithrombin complex concentrations between fetuses with placental insufficiency and those with no placental disease in Doppler defined umbilical placental insufficiency (13).

With the advent of polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) genotypic assays for the factor V Leiden allele, the prothrombin 20210A mutation and the MTHFR C677T gene mutations, we now have the capability to easily compare the prevalence of these mutations in our IUGR population with our normal (non-IUGR) population. It is thought that this information may provide some insights into the genotypic basis for IUGR as it relates to these control populations (3).

To examine the prevalence of the factor V Leiden allele, the prothrombin 20210A gene mutation and the MTHFR C677T gene mutation in our IUGR population we performed PCR-RFLP genotyping on archived placential tissue from 35 IUGR pregnancies. Pregnanacies previously identified with IUGR through antenatal ultrasound examination were considered for inclusion in this study. Estimated fetal weights were calculated using Hadlock's formula (14) and IUGR was defined by an estimated fetal weight of less than the tenth percentile for the gestational age. Placential tissue, harvested from IUGR pregnancies within 30 min of delivery, was collected from the region just below the chorialic plate to ensure adequate fetal component sampling and archived at ~70°C. For this study, chromosomal DNA was isolated and purified using the PureGene DNA Isolation Kit (Gentra Systems, Minneapolis, MN). We performed PCR-RFLP genotyping analysis for the factor V Leiden allele, the prothrombin 20210A gene mutation and the MTHFR C677T gene mutation (as previously described) on chromosomal DNA obtained from the 35 IUGR placenta (4, 15, 16). Unfortunately, maternal DNA was unavailable for analysis.

Interestingly, the factor V Leiden allele and the prothrombin 20210A gene mutation was identified in none (0/35) of the IUGR placentas. (Appropriate positive control samples were included to demonstrate the adequacy of the assay condition employed). These alleles are present in our population in 7.9% (factor V Leiden) and 2.0% (prothrombin 20210A) of our non-IUGR population (healthy blood donors and unselected surgical patients (17), and unpublished observations). The MTHFR C677T gene mutation was present in these IUGR placental samples at relative frequencies (25.7% wild type, 54.3% heterozygous, 20% homozygous) similar to that of other reported control populations (3).

These results suggest that there is no significant fetal contribution to the thrombotic nature of IUGR placental tissue (as it relates to these specific gene mutations) and that the three gene mutations presented here may manifest their greatest impact in IUGR pregnancies through the maternal component. Further studies are needed to determine the clinical impact that genotypic analysis of these genes may have in IUGR pregnancies.

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References

Dear Sir,

Resistance to activated protein C (APC), due to a factor V molecular anomaly (factor V Leiden), is the most common inherited risk factor involved in venous thrombosis, and is present in about 5% of the healthy Caucasian population (1). On the other hand, recently published studies show the increased risk of venous thromboembolism among users of different types of combined oral contraceptives (OC) (2, 3). When these two thrombotic risk factors, factor V Leiden and OC coincide, the thromboembolic risk increases substantially (4).

In our opinion, a correct estimate of the cost of this screening, in women using OC, should be based on the following data: 1) the yearly incidence of deep vein thrombosis in healthy women during their fertile years: between 0.8 (9) and 2 per 10,000 (7); 2) the prevalence of factor V Leiden in the normal Caucasian population, about 5%; 3) the incidence of deep vein thrombosis in women using OC, should be based on the following data: 1) the yearly incidence of deep vein thrombosis in healthy women during their fertile years: between 0.8 (9) and 2 per 10,000 (7); 2) the prevalence of factor V Leiden in the normal Caucasian population, about 5%; 3) the incidence of deep vein thrombosis in women who are factor V Leiden carriers and OC users, we can expect 30 thrombotic events/year/10,000 women. If this number of events is multiplied by 40 (increase in the mean thrombotic risk among women who are factor V Leiden carriers and OC users), we can expect 30 thrombotic events/year/10,000 women. If this number of events is multiplied by 40 (increase in the mean thrombotic risk among women who are factor V Leiden carriers and OC users), we can expect 30 thrombotic events/year/10,000 women. From this number we must subtract the 5.25 thrombotic events per year that these 5000 women would involve (6) and the corresponding economic cost (8), as much as $ 441,800 per avoided thrombosis, according to some reports (8).

In our opinion, a correct estimate of the cost of this screening, in women using OC, should be based on the following data: 1) the yearly incidence of deep vein thrombosis in healthy women during their fertile years: between 0.8 (9) and 2 per 10,000 (7); 2) the prevalence of factor V Leiden in the normal Caucasian population, about 5%; 3) the increase in thrombotic risk in factor V Leiden carriers who also take OC; 4) the sensitivity and specificity of the coagulation test for the diagnosis of factor V Leiden, nearly 100%, if the coagulation test is used early-onset pre eclampsia. Am J Obstet Gynecol 1995; 173: 1042-8. 5) the price of this test, approximately $ 6.00; and 6) the mean OC ingestion period per woman. From these data it can be calculated that to identify 5000 factor V Leiden carriers it would be necessary to study 100,000 women (prevalence: 5%), which would mean a cost of $ 600,000; and that the number of thrombotic events per year expected in these 5000 women of fertile age would be 0.75, if we use a mean prevalence of 1.5 thrombotic events/year/10,000 women. If this number of events is multiplied by 40 (increase in the mean thrombotic risk among women who are factor V Leiden carriers and OC users), we can expect 30 thrombotic events each year among these 5000 women. From this number we must subtract the 5.25 thrombotic events per year that these 5000 women