Commentary

Placental pathology in thrombophilia: establishing clinico-pathological correlations

Women with thrombophilia are at an increased risk of not only venous thromboembolism, but various other complications including intrauterine foetal growth retardation, pre-eclampsia and foetal loss. Both inherited and acquired thrombophilias contribute to thrombotic events and their adverse outcome in pregnancy\(^1,2\). The major inherited thrombophilias include deficiencies of antithrombin, protein C, protein S, factor V Leiden, prothrombin G20210A gene polymorphism and hyperhomocystinaemia associated with methylene tetrahydrofolate reductase (MTHFR) C677T mutation. Acquired thrombophilias are mostly associated with antiphospholipid antibodies—both lupus anticoagulants and anticardiolipin antibodies. A recent systematic review of 25 studies revealed a positive association between early pregnancy loss and thrombophilia\(^3\). Data from late pregnancy loss analysed from 15 studies also showed significant association. The association was even stronger between thrombophilia and recurrent foetal loss\(^4\). The most frequently encountered heritable thrombophilias leading to pregnancy loss were factor V Leiden, hyperhomocystinaemia, prothrombin G20210A and protein S deficiency\(^4,5\). The only Indian study on thrombophilia and unexplained pregnancy loss was reported by Vora et al\(^6\) recently where 381 women were screened for heritable and acquired thrombophilia markers; 183 women had 2 and 198 women had >3 pregnancy losses. The strongest association was observed with anticardiolipin antibodies (\(P<0.001\)) followed by annexin V, lupus anticoagulant and anti β2 glycoprotein 1 (β2GP1). Amongst heritable thrombophilias the risk of pregnancy loss was highest with protein S deficiency, followed by protein C deficiency. A combination of >2 heritable factors was observed in 10.8 per cent and presence of both acquired and heritable risk factors in 20.7 per cent of patients\(^6\).

Histopathological examination of the placentas in women with recurrent pregnancy loss, intrauterine growth retardation and pre-eclampsia have revealed lesions due to vascular hypoperfusion. An organ once considered senescent after birth, usually discarded, is now increasingly being examined as an important diagnostic tool for maternal/foetal vasculopathies. The word placenta is derived from a Latin word meaning ‘flat cake’. It provides oxygen and nourishment to the foetus through regulation of maternal and foetal circulations. The cytrophoblast separates both the circulations and extends into the decidua basalis to form villi. Maternal blood in the intervillous space allows gaseous and nutrient exchange. Foetal blood is separated from the cytrophoblast by foetal endothelial cells\(^7\). Hence maternal blood flow in the placenta can be affected by both maternal and foetal thrombophilic gene mutations if the latter are expressed in the trophoblast.

A large variety of lesions can be seen in the placenta due to disturbances in the blood flow\(^8\). In conditions associated with maternal hypoperfusion the placenta may show perivillous fibrinoid deposition, subchorionic fibrinoid plaque, massive subchorial thrombosis, basal intervillous thrombus, intervillous lakes, retroplacental haematomas, maternal surface chorionic villous infarction and syncytial knots. Some of these lesions including small amounts of calcification may be seen in 3-36 per cent of term normal placentas, but are usually small and multifocal\(^8\). Some investigators recommend that extent of involvement by thrombohaemorrhagic or infarctive lesions should be estimated as percentage of the total maternal surface and pathologic sites sampled for histomorphology. Infarctions involving 25 per cent or more of the surface and villous loss >30 per cent are more likely to lead to underperfusion in the maternal placental circulation\(^8\). Although the above mentioned
lesions are common to intrauterine growth retardation, pre-eclampsia, placental abruption and thrombophilia, some investigators have observed an increase in the extent of villous infarction, which could be consequent to increased occlusive thrombi in spiral arterioles. Other placental lesions which have been seen in thrombophilic females are massive perivillous fibrin deposition (maternal floor infarction), subchorionic haemorrhage and uteroplacental vasculitis.

Placental pathology may occur as a result of disturbances in the foetal blood flow to the placenta and include intervillous thrombi, major foetomaternal haemorrhage, subamniotic haematoma and foetal arterial thrombosis. However, association between placental lesions and foetal thrombophilia is less well documented. In a study including 64 newborns of women with one or more of the following pregnancy complications: pre-eclampsia, placental abruption and intrauterine growth retardation, the maternal and neonatal blood was screened for heritable thrombophilic mutations. Foetal thrombophilic mutations were diagnosed in 19 of 64 newborns, 15 of whom had co-existent maternal thrombophilia. There was no statistically significant difference in the prevalence of thrombotic lesions of the foetal circulation between newborns with and without thrombophilia. The combination of maternal and foetal thrombophilia was also not associated with increased foetal vascular lesions of the placenta. Such a study raises doubts about thrombophilia alone being the single risk factor for at least foetal placental lesions.

In the study reported by Vora et al in this issue placentas from eight women with history of unexplained foetal loss were examined for any characteristic histomorphologic changes. At the same time extensive thrombophilia work-up was done for both heritable and acquired risk factors i.e., lupus anticoagulants, IgG/IgM antibodies for cardiolipin, β2 glycoprotein I and annexin V, protein C,S, antithrombin, factor V Leiden, prothrombin G20210A, MTHFR C 677 T, endothelial protein C receptor (23 bp insertion) and plasminogen activator inhibitor (PAI) polymorphisms. Six of these 8 women had risk factor for thrombophilia. Two women were homozygous for MTHFR C 677 T, one for PAI-1 4G/4G, while the remaining three had both heritable and acquired risk factors.

The primary pathology observed in the placentas was consequent to hypoperfusion and in order of frequency the lesions were thrombosis, infarction, stromal fibrosis in villi, calcification, haemorrhage and chorioamnionitis. What is intriguing is the presence of thrombosis and a large area of subchorionic haemorrhage observed in placentas of two women respectively, where no known risk factor for thrombophilia was detected. Though the study has been conducted on a small number of patients, it does substantiate similar observations. However, several issues need to be addressed. The authors speculate that there may still be several more risk factors for thrombophilia yet to be identified and added to the testing panel. Placental pathology at best is suggestive but not pathognomonic of maternal thrombophilia.

There are major issues which need to be addressed. Should all women with unknown pregnancy loss be subjected to thrombophilia screen and secondly in which cases should placental pathology be requisitioned? The placenta is a large organ, multiple areas need to be examined and extent of lesions must be calculated in terms of the percentage area involved. Since many of the lesions may be seen in small foci in term placentas, inadequate sampling may either miss pathologic lesions, or overestimate the pathologic association. Considering the two options i.e., extensive thrombophilia screen and labour intensive placental histopathological examination, a cautious stratified approach may be a feasible option. Most of the studies have been observational in nature, some comparing thrombophilic with normal gestations while others only reporting placental pathology in thrombophilic patients without controls. However, for establishing specific correlations randomized studies are necessary.

Yet, the data computed from a large number of studies, including the present one, have shown an association between placental pathology due to hypoperfusion and adverse pregnancy outcome. Thrombosis, infarction, villous atrophy and large haemorrhages have been observed consistently in women with thrombophilic risk factors. Hence in women with unexplainable pregnancy loss, if placental pathology reveals lesions of hypoperfusion, a thrombophilia screen in the patient may be necessary for diagnosis of maternal thrombophilia and for monitoring of subsequent pregnancies.

It remains to be seen whether anticoagulant interventions like administration of low molecular weight heparin (LMWH) significantly affect pregnancy outcome and/or extent of placental pathology in women identified with thrombophilic risk factor(s).
Again, randomized trials and not anecdotal data would give the answer.

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