Letters to the Editor

Thrombophilias and adverse pregnancy outcome

Dear Sir,

Mousa and Alfirevic (2000) recently reported on the relationship between histological placental lesions and thrombophilia status in women with adverse pregnancy outcomes. Their results are interesting (with apparently thorough thrombophilia testing performed), but their conclusion, that the results do not support an association between thrombophilias and adverse pregnancy outcome, is misleading.

Firstly, this study only examined pregnancies complicated by intrauterine growth restriction, stillbirth, pre-eclampsia (PET) or abruption. If certain thrombophilias do indeed result in increased likelihood of pregnancy complications (e.g. PET), then the common mechanism would be expected to be related to trophoblastic invasion defects, just as in any other population complicated by this disorder. Therefore, examining the end result (i.e. the placenta), would be expected to show features of PET, not the underlying cause. Analogously, a head computerized tomography (CT) scan could diagnose, e.g. a thrombotic cerebrovascular accident, but the scan would not reveal much information about the underlying aetiology; however, this does not reduce the usefulness of the examination.

Secondly, the results themselves may not be as clear cut as presented and certain histological features may indeed be more common with certain thrombophilias. For example, massive perivillus fibrin deposition was present in six out of 11 cases which were anticardiolipin antibody (ACA)-positive compared with only six out of 36 from the thrombophilia-negative group ($z = 1.97, P < 0.05$). In fact, it is highly likely that the relative prevalence of the types of pregnancy complications and certain associated histological features will vary according to the type of thrombophilia and only larger future studies will provide such data. Nevertheless, this study highlights the importance of systematic examination of placental pathology in relation to high-risk pregnancy groups and provides some data on which further studies may be based.

References


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Dear Sir,

The findings of Mousa and Alfirevic (2000) cannot go unchallenged.

The crux of the paper asked whether there was a relationship between placental lesions and maternal thrombophilia. Unfortunately, there is scant regard to the precision, or otherwise, of placental histopathology. Diagnosis of placental lesions can be fraught with inter-observer and, to a lesser extent, intra-
observer variance even among placental pathologists (Khong et al., 1995; Grether et al., 1999). Clinico-pathological studies such as this are best performed when the histopathology is reviewed contemporaneously, preferably with at least two independent blinded observers (Grether et al., 1999; Beebe et al., 2000).

Infarction, massive perivillous fibrin deposition and intervillous thrombosis can be misleadingly similar. An experienced placental pathologist may be consistent in their naked eye assessment of these lesions without histological confirmation but junior pathologists and those less interested in the placenta may fail to differentiate them. Were blocks taken of abnormal as well as normal placentas the frequency of the placental lesions in each of these populations, no details were given regarding placental vascular thrombosis, is possible if an alternative, non-conventional, histological block of the placenta is taken (Khong and Chambers, 1992).

The maternal demographic details lack information on smoking or substance abuse, which may be associated with abruptio placentae, growth restriction or stillbirth (Raymond and Mills, 1993; Salafia and Shiverick, 1999). Despite this being a high risk obstetric population, no details were given regarding possible treatment of the mothers with aspirin, heparin or folate, all of which may affect outcome and placental pathology. A well-known cause of fetal thrombotic vasculopathy is maternal diabetes mellitus (Fox, 1997) but no information is provided as to whether either of the two women, one with fetal stem thrombosis and the other with thrombotic vasculopathy, were so affected. If histological examination of the placenta was performed as a routine clinical practice, as claimed in the Materials and methods section, why was placental histology 'incomplete or not performed' in some women; we would have liked to know and decide for ourselves whether the 23 women with incomplete or absent thrombophilia screening and/or placental histology may have skewed the results.

Other less serious defects in the study demonstrate a lack of understanding of the subject. No indication is given of whether the cases were a consecutive series or not; in itself, this may not be important but calibration of laboratory tests including placental histology (see above), can vary over time. For example, what are the inter- and intra-assay coefficients of variance for the coagulation assays? The authors write of low activated protein C resistance (APCR) as being abnormal; it is a high APCR or a low APCR ratio that indicates thrombophilic tendency. Pre-eclampsia/eclampsia, placental abortion, intra-uterine growth restriction (IUGR) and stillbirth are inter-related but Table V does not allow the reader to determine the frequency of the placental lesions in each of these complications in the absence of concurrence.

In summary, the article is seriously flawed and while the authors may well be correct in their conclusion and proposal, the scientific and medical community will be better served if more robust proof is forthcoming, preferably with interdisciplinary collaboration.

References

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Dear Sir,

Our study was a retrospective consecutive case series in which we analysed routinely collected data. We acknowledge methodological shortcomings of such an approach and agree with histopathologists that diagnosis, definitions and inter-/intra-observer variance of placental histology may be an important source of bias. We hoped that ‘routine’ placental histology, often used to guide our clinical decision making, would be robust enough to find some characteristic placental changes in women with thrombophilia. We were wrong. Nevertheless our conclusions are by no means ‘definitive’ and, like Khong et al. and Sebire, we are also looking forward to the large prospective studies with standardized protocols, internationally agreed definitions of thrombotic placental lesion and high internal and external consistency to confirm or refute our findings.

For the record, our study did not include diabetic women or women on folate, aspirin or heparin therapy. There were 19 smokers in our study group (24%), 11 of whom had had abnormal thrombophilia screen.

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