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ANXA5: a key to unlock the mystery of the spectrum of placental-mediated pregnancy complications?

“There is growing evidence of the ANXA5 M2 haplotype being associated with placenta-mediated pregnancy complications including preeclampsia, fetal growth restriction and recurrent pregnancy loss.”

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Background

Placental-mediated pregnancy complications, miscarriage, fetal growth restriction and preeclampsia are a spectrum of disorders sharing overlapping clinical and pathological features. All are associated with thrombotic pathogenic processes, ranging from microvascular fibrin deposition in the glomerular vessels in preeclampsia, to placental infarction in fetal growth restriction. However, a number of disease mechanisms contribute to these outcomes, and it is not clear how critical the thrombotic process is across the various components of the spectrum of disease and between pregnancies. Some predictive and risk factors are known, but the only established preventative measures that exist are antithrombotic agents – low-dose aspirin and low-molecular-weight heparin. However, their efficacy is modest. This approach assumes that antithrombotic processes will impact on the disease outcome, yet the contribution of thrombosis may be highly variable. The benefits of intervention with antithrombotic agents may be best seen in those women where thrombosis is a major factor in the pathophysiology. Identifying those women most likely to benefit from treatment would allow stratification of treatment based on disease process, which in turn may provide more effective use of interventions. Such a stratified or precision medicine approach is already widely used in cancer care, where the direction of oncological research has moved

away from analysis of treatment response in cohorts sharing the same diagnosis based on the organ affected and tumor histology, to treatment based on biomarkers specific to the molecular pathology of the tumor. It may now be time for obstetrics to adopt such a personalized medicine approach. However, this requires a biomarker with clinical utility to guide treatment. Recent research suggests that ANXA5 may be such a biomarker.

Placenta-mediated pregnancy complications

The placenta-mediated pregnancy complications, noted above, constitute a spectrum of relatively common yet enigmatic obstetric disorders. They share similar, but by no means the same, prothrombotic factors and have a placental origin. However, these are multifactorial conditions where a number of pathological processes, other than thrombosis, have been identified. The contribution of these processes is variably expressed across the spectrum of disease and between affected pregnancies. Therefore, interventions focused on a single possible disease mechanism would only be anticipated to be effective where that mechanism plays a dominant or major role. Applying an intervention without stratifying by pathological mechanism may underlie the lack of consistency between different intervention trials in conditions where more than one process may result in the same final outcome. Miscarriage is a good example of this



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as the same outcome may result for a large number of different pathological processes of which a thrombotic mechanism is only one.

Recurrent miscarriage is a serious health issue, which has a significant impact on women's quality of life. It is defined as three or more consecutive early pregnancy losses. Although multiple etiologies are known, and genetic components play a significant role, half of cases are not associated with any of the known risk factors [1]. Currently no single predictive biomarker has been identified to guide treatment. Antithrombotic interventions in unselected patients have generally not been shown to be effective [2–5].

Preeclampsia is a common and serious obstetric disorder with multifactorial pathophysiology [6] focused on endothelial damage, microthrombosis, vasoconstriction and oxidative stress. There is a genetic component, however, the relative weight of maternal and placental genetic factors in susceptibility remains unclear [7]. Preeclampsia has multiple phenotypic variants, including preterm and term onset, which each likely represent different genetic architectures [8].

“Such stratification of those at risk of placental thrombosis offers the opportunity to bring a stratified medicine approach to obstetrics allowing better targeting for antithrombotic interventions, in particular on groups with homogeneous pathological mechanisms.”

Fetal growth restriction is the reduction in fetal growth velocity leading to failure of the fetus to achieve its genetic growth potential. It is associated with significant perinatal mortality and morbidity [9] and occurs in 3–7% of pregnancies [10]. Genetic components are known to play a significant etiological role [11]; however, the most common underlying cause is placental insufficiency with substantial overlap with the features seen in preeclampsia, including placental thrombosis and infarction. This highlights thrombotic processes as potential risk factors. Intervention with low-dose aspirin has a limited effect likely due to the heterogeneity of the disease process, however, given its prevalence and unfavorable fetal outcomes, risk stratification is highly desirable for better more specific treatment, but is not available due in part to lack of appropriate biomarkers.

ANXA5

ANXA5 is a protein with anticoagulant functions. Although dispersed throughout the body, ANXA5 is highly expressed on the apical surfaces of the syncytiotrophoblast, where it lines the placental villi at the maternal–fetal circulation interface and is integral to placental thrombomodulatory function [12–14]. It prolongs phos-

pholipid-dependent coagulation reactions by displacing coagulant proteins from phospholipid surfaces [14].

Expression of the protein has been considered in placenta-mediated pregnancy complications, because thrombosis and placental dysfunction are key features of their pathogeneses. Theoretically, low levels of this anticoagulant in the placenta would reduce the ‘shielding’ of phospholipids, thereby facilitating phospholipid-dependent coagulation activation with risk of thrombosis and placental infarction [15]. Of interest is the expression of ANXA5, which varies by the haplotype of the *ANXA5* gene. M2 is a common haplotype, giving rise to low levels of circulating ANXA5 protein [6]. Recently it has been reported that the prevalence of the M2 haplotype is increased in women with placenta-mediated pregnancy complications [16].

The origin of ANXA5 protein in placental villi is either maternal circulation, trophoblastic production or a combination of both [6]. Placental expression will be dependent on both maternal and paternal genetic contributions. Therefore this may constitute a mechanism for the paternal contribution to the disease process and may offer an explanation for change in paternity being a risk factor for preeclampsia [17–19].

There is growing evidence of the *ANXA5* M2 haplotype being associated with placenta-mediated pregnancy complications including preeclampsia [6], fetal growth restriction [20] and recurrent pregnancy loss [15,16], although not all studies are consistent [13]. However, the maternal and paternal M2 haplotype status might offer the opportunity to provide a biomarker for pregnancies at risk of placental thrombosis and therefore allow antithrombotic treatment to be stratified based on the parental haplotype status.

Future perspective

We have few biomarkers available in pregnancy for placenta-mediated pregnancy complications. Further as the placenta is key to the disease process, a specific biomarker reflecting the risk of placental thrombosis (rather than solely that of the mother) may be of value in stratifying disease. Thus, determining parental M2 haplotype status provides a novel opportunity to explore whether this could be an important biomarker to guide treatment. Further, with increasing availability of cell-free fetal DNA testing, noninvasive prenatal identification of high-risk patients may be based directly on the placental genotype. Such stratification of those at risk of placental thrombosis offers the opportunity to bring a stratified medicine approach to obstetrics allowing better targeting for antithrombotic interventions, in particular on groups with homogeneous pathological mechanisms.

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