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Commentary

The need to look beyond ANXA5 & apelin in pre-eclamptic placenta

The article by Dasgupta *et al*[1] deals with the analysis of placental pathology in pre-eclampsia in the context of foetal outcome. The authors have checked for immunomarkers such as ANXA5 and apelin to support their significance in the eclamptic placenta. Expression for these two proteins was analyzed semi-quantitatively by grading the intensity compared to control normal placentae. Pre-eclampsia still remains a major health issue in developing countries where proper antenatal care is not universally available[2]. The underlying pathobiology in the development of pre-eclampsia and eclampsia is not well defined and understood. Numerous factors have been hypothetically linked as the underlying possible aetiological factors in disease development. Understanding and defining the etiological factor is the foremost important step in the prevention and control of any disease. This condition is simply not only a maternal issue but also influences the foetal outcome[2,3]. The effects on the foetus ultimately will influence the physical and mental developments of the child if at all the neonates survive to adulthood[4].

The authors[1] have made efforts to analyze and understand the possible roles of the two selected proteins by studying their expressions by the trophoblastic and mesenchymal cells, and uterine vasculatures. Important observations made in this study were with respect to ANXA5 were (*i*) reduced ANXA5 expression in study groups compared to controls; (*ii*) no significant co-relationship between low ANXA5 expression with foetal growth restriction (FGR) compared to controls; and (*iii*) ANXA5 expression is related only to FGR and not to pre-eclampsia. However, the third observation although made conclusively, requires readdressal by studying more number of patients with pre-eclampsia and also placentae from mothers suffering from non-pre-eclamptic disease condition(s) giving birth to FGR neonates. It is also advisable to validate the ANXA5 status by studying other subtypes of annexins, like ANX2. Furthermore, Dasgupta *et al*[1], did not carry out analysis of maternal blood for the index proteins had not been carried out. The values in maternal blood samples are known to show variations with gestational age[5]. While analyzing the levels in blood and expression in placental tissue, it may be an ideal situation to understand the clinical parameters including associations with autoimmune disorders and primary coagulation disorders[6,7].

One important aspect to analyze and to emphasize critically is the role played by the shedding trophoblastic tissue *in utero*. One aetiologically important factor that has been hypothetically suggested in the development of pre-eclampsia, eclampsia and other pregnancy-related disorders is the stimulation of maternal endothelial cells by the deported trophoblastic knot tissue clumps, by inciting an inflammatory response[8]. Shedding of the trophoblastic knots is reportedly to be the result of rapidly proliferating superficial syncytial cells accompanied by shedding in large numbers. The underlying molecular mechanism of the shedding is poorly understood. Pre-eclampsia is one such condition associated with exacerbated trophoblast shedding into maternal blood[9-11].

In the reference manuscript, the analysis and statement made about apelin protein is brief and has not been delved into. The observation made was that apelin expression correlated with foetal outcome, rather than with placental pathology. More recent studies have made interesting observations with respect to apelin protein and apelin protein receptor J (APJ) expressions. Discrepancies have been reported in the patterns of distributions of rat preproapelin mRNA and apelin protein[12]. There are a few more studies citing the differences between apelin protein and APJ. Initially, apelin was thought to be the only ligand for APJ until recently when two research groups independently discovered, through the mining of long non-coding RNA transcripts, a short secretory peptide, called

Elabela (ELA)[13] or Toddler[14]. ELA, a ligand for APJ has similar properties as APJ. Genetics studies using the zebrafish model demonstrated the requirement of ELA signalling for the normal development of the heart, vasculature and lymphoreticular tissues. It was found that, ELA mutant phenotype is similar to APJ mutants, suggesting that ELA and APJ are genetically in the same biological pathway[13]. Hence, further studies are required before making a definitive remark in context to apelin expression in placental tissue of pre-eclamptic patients by studying other known as well as unknown ligands.

***Conflict of Interest*:** None.

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