Clinical Translation of Extracellular Vesicles in pregnancy: What Are We Missing?

Carlos SALOMON – *University of Queensland, Australia*

While there is considerable contemporary interest in elucidating the role of placenta-derived extracellular vesicles in normal and complicated pregnancies and their utility as biomarkers and therapeutic interventions, progress in the field is hindered by a lack of standardized extracellular vesicle taxonomy and isolation protocols. The term “extracellular vesicle” is nonspecific and refers to all membrane-bound vesicles from nanometer to micrometer diameters and of different biogenic origins. To meaningfully ascribe biological function and/or diagnostic and therapeutic utility to extracellular vesicles, and in particular exosomes, greater specificity and vesicle characterization is required. The current literature relating to exosome biology must be interpreted in this context. Exosomes are a subtype of extracellular vesicle that are specifically defined by an endosomal biogenesis and particle size (40-120 nm) and density (1.13-1.19 g/mL(-1)). Exosomes are specifically package with signaling molecules (including protein, messenger RNA, microRNA, and noncoding RNA) and are released by exocytosis into biofluid compartments. Exosomes regulate the activity of both proximal and distal target cells, including translational activity, angiogenesis, proliferation, metabolism, and apoptosis. As such, exosomal signaling represents an integral pathway mediating intercellular communication. During pregnancy, the placenta releases exosomes into the maternal circulation from as early as 6 weeks of gestation. Release is regulated by factors that include both oxygen tension and glucose concentration and correlates with placental mass and perfusion. The concentration of placenta-derived exosomes in maternal plasma increases progressively during gestation. Exosomes isolated from maternal plasma are bioactive in vitro and are incorporated into target cells by endocytosis. While the functional significance of placental exosomes in pregnancy remains to be fully elucidated, available data support a role in normal placental development and maternal immunotolerance. Similarly, the role of exosomes in the etiology and progression of complications of pregnancy remains in a formative stage. Changes in the release of placenta- and nonplacenta-derived exosomes, their concentration in maternal plasma, composition, and bioactivity have been reported in association with pregnancies complicated by gestational diabetes and preeclampsia. The data, however, are confounded by the use of different isolation methodologies and vesicle subpopulations. The application of specific and well-characterized isolation methodologies is requisite to resolving the precise role of exosomes in complications of pregnancies and their ultimate clinical utility.