ABSTRACT

Recurrent spontaneous miscarriage (RSM) refers to spontaneous abortion of three or more clinically diagnosed pregnancies within 24 weeks of gestation. In approximately 50% of these cases the cause remains unsolved, and the condition is known as idiopathic (IRSM). A complete understanding of endometrial receptivity in women with IRSM is lacking. The present study investigates the molecular mechanism responsible for a receptive endometrium during implantation window in IRSM. 66 women with IRSM and 50 fertile controls were included and the endometrium studied in terms of the receptivity markers expression, matrix and vascular remodelling and serum metabolic profile.

Aberrant endometrial histology, reduced expression of receptivity markers including, αvβ3 integrin, LIF, E-cadherin, MECA-79, Muc-1 and pinopodes, and altered endometrial perfusion were seen suggesting poor endometrial receptivity in IRSM. Further, altered endometrial remodelling factors and imbalance between MMP-9:TIMP-1 ratio in these women indicated excessive endometrial degradation. An imbalance between the expression of pro- and anti-inflammatory cytokines with a concomitant reduction in angiogenesis-related factors and cytokines were also observed. IL-10, VEGF and eNOS emerged to be the key factors contributing towards endometrial vascular dysfunction in IRSM women. A clear metabolic differentiation between IRSM and controls could be established using 1H NMR based metabolomics. A set of dysregulated metabolites were identified in IRSM which were found to be associated with increased inflammatory response and vascular dysfunction.

The presently available diagnostics options are unable to detect any potential threat to a subsequent pregnancy loss. There is, therefore, an urgent need to develop serum marker(s) for categorizing which women (with history of one miscarriage of unknown origin) are more at risk and which may pass through the pregnancy uneventfully. In view of this, the major factors found to be significantly dysregulated in the endometrium of IRSM women during implantation window (MMP-9, TIMP-1, IL-10, VEGF and eNOS) were assessed in serum. IL-10, MMP-9 and TIMP-1 offer promise as potential serum markers for prediction of women at risk of undergoing subsequent pregnancy loss. Summarizing the findings of the present work, a molecular mechanism regulating the process of endometrial receptivity during implantation window in IRSM is proposed.

Keywords: *idiopathic recurrent spontaneous miscarriage, endometrium, endometrial receptivity, extracellular matrix degradation, cytokine, vascular dysfunction, Interleukin-10, metabolic dysfunction*