

# Interventions For Recurrent Embryo Implantation Failure: an Umbrella Review

Research Article

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## Letter to the Editor

We have read with great interest the review recently published in IJOG by A Almohammad et al [1], a collaboration of the Reproductive Medicine Unit of Sidra Medicine in Qatar with three research centres in Granada, Spain. Of the immunomodulatory uterine and endometrial and laboratory interventions the best results on live births rates (LBR), the gold standard index, were obtained with intralipid infusion improvement in 3/4 (75%), peripheral blood mononuclear cells 3/5 (60%) and in intentional endometrial injury in 2/3 (66.66%). Since this review thoroughly addresses the limitations of the analysis it should prompt a surge of new studies in the field of the dysfunctions of the early feto-maternal crosstalk.

Even if this review refers to repeated implantation failures derived from in vitro fertilization we estimate that your analysis can be extended to recurrent miscarriages as both conditions derive from an early failed crosstalk between the embryo and the womb (eg endometrium). For the sake of future analysis and based on our previous research on the clinical, cellular and functional associations between the components of the multifactorial interrelated vasodilator network [2-5] we suggest incorporating the microenvironment of endometrial vasoactive markers in future studies related to the following recurrent conditions, miscarriages and implantation failures. Those markers could be evaluated both in villous and/or decidual tissue obtained from recurrent miscarriage/implantation failure patients or in the pre-conceptional evaluation before pregnancy or embryo transfer.

On the other hand, from the point of view of the maternal systemic circulation, the association of a normal or defective maternal endothelium dependent vasodilation was tested in our study in 22 control women, in 25 with severe preeclampsia and in 29 with  $\geq 2$  sequential spontaneous miscarriages at  $27 \pm 6.9$ ,  $16 \pm 3.5$  and  $11 \pm 2.2$  months respectively after the end of their last pregnancy [6]. Our primary finding was the presence of endothelial dysfunction far from pregnancy in  $\approx 50\%$  of women with recurrent abortions and in those with a history

of previous severe preeclampsia. Another marker of vascular elasticity, the differential pulse wave index, is reduced women with recurrent miscarriages [7].

It is important to consider that the vasoactive approach not only provides possibilities to improve the outcome of spontaneous or IVF future pregnancies [8] but requires long term follow-up and management of women failing the stress test of pregnancy. Pell et al. demonstrated in 2004 that women with recurrent abortion presented an independent association with cerebrovascular disease [9] while in a 2013 report miscarriages had an increased risk of 1.1- 1.8-fold while  $\geq 4$  miscarriages or a previous stillbirth risks were 2.0- 4.0 fold for all outcomes [10], underscoring the fact that these events should be considered when evaluating a woman's future cardiovascular risk.

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