Assisted Reproductive Technologies Increase the Vasoconstrictor Responsiveness to Angiotensin II by an Epigenetic Mechanism

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Environmental influences acting early in life predispose to premature cardiovascular disease. In line with this concept, assisted reproductive technologies (ART) cause premature vascular ageing and arterial hypertension in mice and humans, but the underlying mechanisms are incompletely understood. In rodents, pathological events during pregnancy cause arterial hypertension in the offspring by increasing the vascular responsiveness to angiotensin II (ANG II). We speculated that a similar mechanism could be involved in ART-induced arterial hypertension. In aortic ring preparations of ART and control mice, we, therefore, assessed the vasoconstrictor responsiveness to stepwise increasing doses of ANG II in the presence of the eNOS inhibitor L-NMA. We also examined ANG II receptor (AGTR) type 1 and 2 expression (Western Blot) and AGTR gene promoter methylation (bisulfite sequencing) in the aorta. Finally, we measured mesenteric-artery responsiveness to acetylcholine and arterial blood pressure (carotid catheter). As expected, ART mice displayed endothelial dysfunction (P=.03, vs. control) and arterial hypertension (121.8±7.3 vs. 114.6±4.5 [mmHg], P=.02, vs. control). Most importantly, the vasoconstrictor response to ANG II, independently of endothelial function, was markedly increased in ART compared to control mice (0.32±0.05 vs. 0.22±0.04 [% of maximal KCl contraction], P<.01, vs. control). Moreover, and in line with this finding, in ART mice AGTR 1/AGTR 2 ratio of protein expression in the aorta was significantly increased (1.49±0.30 vs. 0.36±0.16, P<.008, vs. control) and the AGTR 1b gene promoter was hypomethylated compared with control mice (8.1±4.3 vs. 10.6±1.6 [% of methylation], P<.05, vs. control). Here, we show for the first time that ART increases the vasoconstrictor sensitivity to ANG II in the aorta. This is related to an epigenetically mediated imbalance between the expression of the vasoconstrictor (AGTR 1) and vasodilatator (AGTR 2) ANG II receptor. Hence, we identified a new mechanism contributing to ART-induced premature vascular ageing and arterial hypertension in mice. We speculate that this mechanism also contributes to ART-induced premature vascular ageing and arterial hypertension in humans.

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