INSUFFICIENT PLACENTAL VASCULARIZATION CAUSES DEFECTIVE HEART DEVELOPMENT IN SHEEP EMBRYOS IN VITRO PRODUCED

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An increased risk of aberrant placentation is associated with assisted reproduction. An adequate vascular development is the key to placental function. Here we investigate: 1) the vascular growth in developing placentas from in vitro produced sheep embryos (IVP) in comparison to in vivo developed controls (CTR) and, because placental vasculogenesis affects cardiovascular development 2) gross morphology of the heart in related foetuses. First, the levels of transcripts involved in vascular growth (FGF2, FGF2R, VEGF, ANG1, ANG2, TIE-2) in placentas collected on day 22 of pregnancy and subsequently (day 26), the number, area and diameter of placental vessels were analyzed. A reduced expression of FGF2, ANG2 and TIE-2 ($p<0.05$), indicative for defective maturation of vessels and lower vessel number (0.78 ± 0.02 fold relative to CTR; $p<0.01$), area (0.22 ± 0.04 fold relative to CTR; $p<0.05$) and diameter (0.55 ± 0.05 fold relative to CTR; $p<0.01$) was observed in IVP placentas. Second, around 30% thinner ventricular wall was noted in hearts from IVP embryos either on day 22 (0.64 ± 0.06 fold relative to CTR; $p<0.01$) and 26 (0.72 ± 0.06 fold relative to CTR; $p<0.05$). Similar reduction of ventricular wall thicknesses and similar placental vascular defects were observed in mouse lacking HOXA13, which is a transcription factor of TIE-2. Relevantly, we observed a severe reduction of HOXA13 transcript ($p<0.01$) in IVP placenta on day 22. We demonstrated defective cardiovascular development in IVP embryos. This defect is due to lower expression of factors regulating placental vessel growth.