CHAPTER 1 contains the outline of the thesis.

In CHAPTER 2 the relation between angiogenic factors and multiple embryo implantation was investigated. We found that women with a multiple pregnancy from all embryos transferred had significantly increased concentrations of vascular endothelial growth factor-A (VEGF-A), an important regulator of angiogenesis in the endometrium, already prior to any treatment. High VEGF-A levels possibly stimulate angiogenesis at the embryo implantation site, thereby optimizing the environment for multiple embryos to implant.

In CHAPTER 3 a possible association between features of maternal body composition (height, weight and body mass index) and multiple embryo implantation was assessed. The results showed a significant association between maternal height and multiple embryo implantation. It could be speculated that this association is based on VEGF-A, which is an essential mediator of both angiogenesis in the endometrium (see CHAPTER 2) and long bone formation.

In CHAPTER 4 it was analyzed whether an association exists between multiple embryo implantation and breast cancer risk. It was found that women who had a multiple birth had a significantly increased risk to develop breast cancer compared with women who gave birth to singletons or remained nulliparous. In particular, women with a multiple birth from all embryos transferred were at risk. This supports our hypothesis of an association between the potential to successfully implant all embryos transferred and breast cancer risk, possibly through common angiogenic factors such as VEGF-A.

In CHAPTER 5 it was examined by means of individual patient data (IPD) meta-analysis, whether the administration of preconceptionally low-dose aspirin increases the chance for successful embryo implantation.
We found that aspirin does not increase pregnancy rates after IVF. It appeared that we could not obtain IPD from studies that reported the largest treatment effects, of which quality of randomization could not be confirmed. This highlights the need to create a method to ensure preservation of data sets from randomized controlled trials.

In CHAPTER 6 in an additional IPD meta-analysis it was investigated whether low-dose aspirin prevents the occurrence of hypertensive pregnancy complications, such as pregnancy induced hypertension and pre-eclampsia as well as preterm delivery. We concluded that low-dose aspirin does not prevent these complications. A remarkable finding was that low-dose aspirin even appears to have a harmful effect on embryo implantation, reducing the number of multiple implantations. This is possibly due to down-regulation of cyclo-oxygenase-2, a crucial enzyme in the embryo implantation process.

In CHAPTER 7 the development of a new method to standardize the injection speed during embryo transfer was introduced: pump-regulated embryo transfer (PRET). The results indicated that in manually performed embryo transfer, even after standardization by protocol, there is still a large variation in injection speed. The results also showed that a PRET device generates a reliable and reproducible injection speed and therefore brings new possibilities for further standardization and potential optimization of the embryo transfer procedure.

CHAPTER 8 contains a general discussion and provides implications for future research.