in vitro fertilization (IVF) has seen a rapid rise in its use for the treatment of infertility over the past decades. IVF allows subfertile couples to achieve pregnancy resulting in the birth of a child. However, it is known that IVF is, among others, associated with increased prevalences of preterm birth, low birthweight and multiple birth. These conditions are risk factors for impaired health later in life in IVF offspring. More general, David Barker - who coined the developmental origins of health and disease (DOHaD) theory – demonstrated how parental and environmental factors may influence fetal development in such a way that it may result in an increased vulnerability for health related problems in later life. This implies that components related with IVF, such as the in vitro culture procedure, controlled ovarian hyperstimulation (COH), the underlying parental subfertility, but also preimplantation genetic screening (PGS) all could affect the health of IVF offspring. COH induces the growth of multiple follicles, bypassing the natural selection of the development of one dominant follicle, and leads to higher progesterone and oestrogen levels preceding in vitro culture procedure and during early embryo development. During the in vitro culture procedure oocytes, sperm and embryos are handled outside the human body, possibly affecting their developmental phenotype by epigenetic programming. In addition, in PGS the embryo is manipulated even further than in IVF. PGS has been developed to boost chances of a successful pregnancy for couples undergoing IVF. Although this is not the case. PGS requires embryo biopsy allowing the screening for aneuploidies. Only screened embryos for euploid are transferred to the womb.

This thesis evaluates the possible long-term effects of ovarian hyperstimulation, the in vitro culture procedure and PGS on the health and development of IVF offspring. It is based on the Groningen ART-cohort study and the PGS-trial. The Groningen ART cohort consist of three groups: 1) children born after controlled ovarian hyperstimulation-IVF (COH-IVF, n= 57); 2) children born after modified natural cycle-IVF (MNC-IVF, n= 48); 3) children from subfertile parents who eventually conceived naturally (Subfertile-naturally conceived; Sub-NC, n= 68). The cohort was used to disentangle the effects of COH (comparing the COH-IVF with the MNC-IVF group) and the in vitro procedure (comparing the MNC-IVF with the Sub-NC group) on health and development of singletons and twins born to subfertile couples. The PGS-trial consists of two groups of children who were born after IVF with or without PGS.

In chapter 2 the following question is addressed: are cognitive and neurological development, anthropometrics and blood pressure (BP) levels of 4-year-old COH-IVF twins (n= 48) worse than those of age-matched COH-IVF singletons (n= 103)? Cognitive development was evaluated with the Kaufman test (primary outcome intelligence quotient [IQ]). Neurological development with the Hempel test. Anthropometrics and BP were measured. IVF twins had a lower weight, a shorter height and a lower IQ score compared to IVF singletons. These differences disappeared after adjustment for confounders. Neurodevelopment and BP did not differ between the two groups. The study indicated that the generally observed less favourable health and development in twins is also observed in IVF conceived twins compared to IVF conceived singletons.

The studies described in chapter 3 and 4 investigated the possible effects of ovarian hyperstimulation and the in vitro culture procedure on asthma and asthma medication use in 4-year-old and 9-year-old children born to subfertile couples. Participants were singletons of the Groningen ART cohort of whom parents filled out a questionnaire on asthma. At the age of 4 years the rate of asthma medication was higher in the COH-IVF group than in the Sub-NC group (adjusted odds ratio [OR] [95% CI]: 1.96 [1.00, 3.84]). At the age of 9 years the prevalence of asthma did not differ in the three groups: COH-IVF (8%); MNC-IVF (0%); and Sub-NC (6%). Adjustment for confounders did not alter the results. At 9 years of age neither ovarian hyperstimulation, nor the in vitro culture procedure were associated with asthma.

In chapter 5 visual acuity of 11-year-old IVF offspring is addressed. The proportion children wearing glasses on medical indication was highest in the COH-IVF group (23%), followed by the MNC-IVF group (12%) and the Sub-NC group (8%). After adjustment for confounders the proportion of COH-IVF children wearing glasses on medical indication was four times higher than of Sub-NC children (adjusted OR [95% CI]: 4.0 [1.13, 14.06]) and two times higher than of MNC-IVF children (adjusted OR [95% CI]: 2.4 [0.74, 7.87]). This suggests that COH is associated with refractive errors.

In chapter 6 the BP percentiles (which take sex, age and height into account) and anthropometrics of 9-year-old children of the Groningen ART cohort study are assessed. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) percentiles did not differ between the three groups, but were all above the expected 50th percentile. No differences were observed regarding height, weight and heart rate. Adjustment for confounders did not alter the results.

The study described in chapter 7 investigated the possible effect of parental subfertility on the BP of the offspring at the age of 9 years. We compared the BP percentiles of the pooled Groningen ART cohort study (n= 149) with the BP percentiles of another longitudinal study of children of fertile couples (n=277). SBP and DBP percentiles were higher in the subfertile group (mean [SD], SBP percentile 60.6 [19.2], DBP percentile 62.5 [18.6]) than in the fertile group (mean [SD], SBP percentile 56.0 [24.5], DBP percentile 56.1 [23.3]). This result suggests that parental subfertility is associated with higher BP values in the offspring.

The study in chapter 8 is part of the PGS-trial; it investigated whether day-3 cleavage stage PGS affects neurological development, cognitive development, anthropometrics and BP of 9-year-old IVF offspring. Forty-three children born after IVF with PGS (PGS group) and 56 children born after IVF without PGS (control group) took part in the study. The children’s neurological condition was assessed with the MND-assessment (focussing on minor neurological dysfunction), and their cognitive development with an IQ test.
Behaviour was analysed with a parental questionnaire. BP and anthropometrics were measured. No differences between the two groups were observed in neurodevelopment, cognitive development, anthropometrics and BP.

Overall, the results of our studies regarding the IVF procedures and PGS are reassuring. We found no differences in cardiovascular health and asthma prevalence between singletons conceived after IVF with and without ovarian hyperstimulation and naturally conceived children to subfertile couples at the age of 9 years. In addition, day-3 PGS does not seem to have an adverse effect on child health. However we did find that children conceived with conventional IVF, i.e. IVF with ovarian hyperstimulation, are at increased risk of refractive errors and that subfertility is associated with a less favourable cardiovascular risk profile.