Summary,

This thesis is built in three sections. The first is an introductory section. In section two we used different methods and outcome variables searching for the answer if adverse early life conditions affect ovarian reserve. The third section concentrates on the effect of perinatal conditions on one of the most common causes of female infertility, Polycystic Ovary Syndrome (PCOS).

Summary of main findings

Section one: Introduction

In chapter 1 we lay out the concept of developmental origins of health and disease (DOHaD) and discuss this concept in an evolutionary perspective. We also give an overview of intrauterine oocyte development, follicle formation and hormonal regulation as well as programmed cell death. Finally, we elaborate the concept of ovarian reserve and the definition for PCOS.

By comparing birth weight differences between historical databases and contemporary databases using twin data in chapter 2, we showed that monozygotic (MZ) twins born before 1980 were less discordant than twins born after 1980, indicating that these older cohorts may be more susceptible to selection bias by selective survival of only fitter cohort members. Due to improvements in neonatal care, more at-risk babies survive the crucial pre-and perinatal period and reach maturity (1, 2). The survival of increasing numbers of low birth weight and preterm infants may, by virtue of case selection and altered postnatal environment, lead to a different spectrum of long-term sequelae when compared to historical peers. These babies do not require the adaptive mechanisms to survive today as they did decades ago. If these adaptive mechanisms are the causal connection between adverse perinatal circumstances and adult onset disease they are possibly not programmed to develop the diseases of the generations before them. Future research should take into account that selective survival may play a role in explaining differences in findings between cohorts from different historical eras. We found no evidence that voluntary versus mandatory enrollment was prone to selection bias.

Section two: Ovarian reserve

In chapter 3 we quantified ovarian reserve in a group of healthy adolescent volunteers born small for gestational age (SGA) or appropriate for gestational age (AGA) in a pilot study. For this purpose we measured LH, FSH, E2, AMH levels and the pituitary response to exogenous GnRH, all of which are established markers for ovarian reserve (3, 4). AMH in particular is documented as the most effective marker of ovarian reserve (5). Because we were unable to detect a clinically relevant or statistically significant difference in ovarian reserve between these young women born SGA and AGA, the results of this pilot study did not lead to continuation of this line of research. Our findings are in line with other published literature on this subject (6). A definite marker of ovarian depletion is natural menopause. We performed a case-control study investigating the influence of early environment on age at menopause before the age of 40 (POI) (chapter 4). We concluded that, in our study population, a preterm birth was significantly associated with menopause before the age of 40. Birth weight, however, was not related to the onset of menopause before the age of 40.

When quantifying the influence of birth weight on health and disease in later life, the effect of gestational age on birth weight is a considerable issue, due to the fact that gestational age is frequently not precisely known,
particularly in historical cohorts. Even when gestational age is reported, the best way to correct for gestational age is still a matter of debate as reference values for birth weight and gestational age are not available for all populations or ethnicities. By investigating the intra-twin differences in birth weight and their relationship with age at natural menopause in chapter 5 we found a solution for the confounding effect of gestational age regardless of ethnicity. Twins discordant for birth weight did not differ in age of onset of natural menopause. Mean age at menopause in this study was 48.5 y which is lower than the average of 51 y reported in international publications (7) but in agreement with other twin studies reporting age at menopause (8-10). While our study could not establish an association between age at menopause and birth weight, our findings may have limited generalizability due to the relatively young age at menopause in twins, which might in part be due to prematurity common in twins (11). Chapter 6, the final chapter of this section is the first systematic review, conducted according to PRISMA and MOOSE principles, on the effect of adverse intrauterine conditions, early childhood growth and famine exposure on the age at menopause. The final selection of this study included 11 published articles. Due to the differences in the definition of outcome variable and the reported risk estimates we were unable to pool data for statistical analysis. Nevertheless, we could conclude that famine during gestation and childhood as well as slow childhood growth is related to a younger age at menopause. Birth weight on the other hand, had no effect on age at menopause. To summarize the second section, we conclude that birth weight is not related to accelerated ovarian depletion. Premature birth and impaired childhood growth as well as famine exposure however, seem to result in an earlier age at menopause.

Section three: Polycystic Ovary Syndrome

Before investigating the role of specific early environmental influences on the etiology of PCOS, we quantified the genetic influences on the etiology of PCOS by computing the heritability of PCOS using twin data in chapter 7. We concluded that up to 79% of the pathogenesis of PCOS is caused by genetic variance. However 21% of the pathogenesis of PCOS can be attributed to environmental factors. Further understanding of non-genetic etiological factors such as perinatal conditions, could be of benefit for an early detections of women at risk of developing PCOS and the prevention of PCOS as well as PCOS related co-morbidity. In chapter 8 we investigated the effect of birth weight and age at menarche on PCOS and diminished ovarian reserve in a large retrospective cohort of all women undergoing IVF in The Netherlands between 1980 and 1995 (OMEGA cohort). In this cohort, self-reported birth weight was not related to PCOS or a diminished ovarian reserve. An older age at menarche, however, was associated with PCOS. A younger age at menarche was associated with indicators of diminished ovarian reserve. The case-control study in chapter 9, comparing markers of early life environment between women diagnosed with PCOS and a control group, could not establish a relation between self-reported birth weight or gestational age and PCOS. Chapter 10, the final chapter of this section contains the first systematic review conducted according to PRISMA and MOOSE principles on the effect of birth weight on PCOS. By pooling and analyzing data on 528,521 women from 13 studies, we conclude that birth weight is not related to the development of PCOS.
To conclude the third section we state that birth weight as a summary measure for gestational adverse conditions, is not a considerable factor in the etiology of PCOS.