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Perinatal reproductive endocrinology in singletons and twins

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Summary
Samenvatting



Over the last decades the intra-uterine environment has become more and more important as a possible starting point for development of diseases later in life. Hormones play a crucial role in the maintenance of these surroundings. In **chapter 1** this is described in more detail and we provide figures representing the assumed hormonal effects in twin and singleton mothers and children. Because the placenta is impermeable to most hormones, the fetal endocrine component is largely independent of maternal influences. Remarkably, it turned out that little was known about the actual reproductive hormone concentrations within these fetal surroundings. In multiples, it is even more complicated because circulating hormones both influence and are influenced by, at least two fetuses. We were interested in whether suggested effects later in life could already be measured at birth (cord blood) and at 6 weeks of age (urinary gonadotropins and ultrasonographically measured testicular volumes). We reviewed the existing literature and constructed graphs describing the hormonal changes that occur during gestation and within the first 6 months after birth (**chapter 2**). Solid data for singletons appeared to be scarce but for twins they are almost non-existent. We aimed to fill this gap by providing prospectively collected, hormonal profiles measured by the latest techniques and accounting for all reported possible confounders such as zygosity, ethnicity and gestational age at birth (**chapter 5**). Before starting this study there were two methodological issues that needed assessment. The first one was; how to measure hormones in newly born infants without the use of an invasive test, such as venous blood sampling. We compared urinary gonadotropins, corrected for creatinin, against serum concentrations as a gold standard. Urinary gonadotropins (corrected for creatinine) are a proper reflection of serum concentrations (**chapter 3**). In adult males testicle size is related to reproductive function, most importantly spermatogenesis which is mainly controlled by FSH. We were interested in whether infant testicle size is a representative of hormone exposure/ concentrations in young boys as well. Therefore, we measured testicle volumes and urinary gonadotropins at the age of 6 weeks. However, aside from converted data from orchidometer measurements there were no referential values for ultrasonographically measured testicular volumes in infants available. To obtain these data we measured testicles of 0 to 6 year old boys from different ethnic backgrounds (**chapter 4**). No differences were found either between the various ethnic groups or between the left and right testicle. Mean testicular volume increases significantly in the first 5 months, thereafter the volume decreases to 0.31 cm^3 at 9 months and remains stable until the age of 6. Visual inspection of the data during the first year gives the impression of two instead of one distinct hub, which was present in each of the four ethnical groups. We have no explanation, but future studies combining ultrasound testicular measurements and reproductive endocrine data are likely to be informative in this matter. In **chapter 5** we report that although mothers pregnant with a twin have higher estrogen concentrations at mid-pregnancy and at birth, their children have lower estrogen

levels compared to singletons. Our data strongly challenge the general assumption that maternal serum hormone concentrations are a proper reflection of actual fetal hormone exposure. We found no significant differences in concentrations of the various estrogens and progesterone between mothers of monozygotic (MZ) and dizygotic (DZ) twins. However, in cord blood DZ twin neonates had higher concentrations of estriol probably due to a larger placenta in DZ twins. These observations may strengthen the earlier suggested elevated estrogen exposure and increased risk of breast and testicular cancer in DZ twins compared to MZ twins. Opposite-sex twin children influence each other, however in a different manner than expected based on existing literature. Girls with a co-twin brother showed comparable, instead of the assumed higher, androgen concentrations compared to those found in girls of DZ girl-girl twins. On the other hand, boys with a female co-twin had lower cord blood LH and inhibin B concentrations compared to boys from a DZ boy-boy twin. Which endocrine compounds in opposite-sex twin pregnancies are responsible for this, is difficult to comprehend. A stronger estrogenic milieu as a result of the female co-twin is unlikely since estrogens were not found to be higher in the opposite-sex twin boys and fetal ovaries are virtually inactive with regard to steroid hormone production at time of birth. There seems to be no indication that fetal testicular tissue produces significant amounts of estrogens itself. Actually, from our study it appears that, in the twins some overall central suppression of the reproductive axis is present as girls in twin pregnancies have lower FSH and boys have lower FSH and LH concentrations in cord blood compared to singletons. At this moment we cannot point to any specific known mechanism and these findings merit further research. In order to evaluate the suggested effects later in life, in **chapter 6** we have evaluated the prevalence of PCOS in women from opposite-sex twin pairs compared to women from same-sex twin pairs. Androgens, originating from a male co-twin, might influence the female fetus in opposite sex-twin pairs. If overexposure to androgens during gestation results in a polycystic ovary syndrome (PCOS) like phenotype, the prevalence of PCOS should be higher in women from opposite-sex twin pairs. We found no significant difference in PCOS prevalence between opposite-sex and same-sex twin girls. If intrauterine exposure to androgens contributes to the development of PCOS, these androgens are more likely to come from the female fetus itself rather than from the male co-twin. This is compatible with the finding that PCOS is highly heritable as shown in Dutch twin families. Another possible source of androgens is the mother, but maternal androgen excess is unlikely to affect the fetus because excessive placental aromatase activity presents as an effective barrier. Furthermore, differences in FSH and inhibin B feedback mechanisms between adult male MZ and DZ twins were reported. We have re-evaluated these findings in **chapter 7** with regard to the genetic contribution of the various endocrine components of the hypothalamic-pituitary-testicular axis. Heritability estimates ranged from 56% (testosterone) to 81% (inhibin B and SHBG). For LH and FSH, the

heritability was estimated at 68% and 80% respectively. So although, all measured hormones were highly heritable, a difference in the FSH–inhibin B feedback system between males from MZ and DZ twins could not be confirmed. Finally, the general discussion (**chapter 8**) reflects on the main results presented in this thesis and provides suggestions for future research.