The placenta as modulator of fetal prosperity
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Summary
The Placenta as Modulator of Fetal Prosperity

Chapter 1 introduces placental development and function in various species and elaborates on features like placental weight relevant for gestational diseases as fetal growth restriction and preeclampsia. The placenta is an endocrine organ, capable of synthesizing and secreting a broad range of growth factors, protein- and steroid hormones. Besides this, the placenta plays an important role in hormone metabolism and hormonal interaction between mother and fetus. Since thyroid hormone is crucial for fetal brain development, regulation of thyroid hormone metabolism during pregnancy is described.

In addition the role of placental tissue in the development of gestational hypertensive disease as preeclampsia is described. It is stated that no single genetic disorder will explain the full spectrum of preeclampsia. This complex genetic disease deserves a sophisticated approach that investigates gene expression in its full context. We propose the use of non-selective high-throughput analysis of gene expression in placental tissue using both publicly available and in-house made Serial Analysis of Gene Expression (SAGE) libraries.

In Chapters 2 and 3 of this thesis we evaluate the clinical significance of placental weight and birth weight. Placental and birth weight are closely related and are associated with obstetrical pathology and adverse neonatal outcome.

Placental weight is addressed in Chapter 2 and we illustrate the pivotal importance of placental function for fetal growth with so far unpublished data on placental weight. In this review we reinterpret the study of Kloosterman on 80,000 consecutive birth weights and 30,000 placental weights. We conclude with Kloosterman that pregnancies with heavier placentas last longer. Furthermore, it appears that birth weight of children from primiparous women compared to those from multiparous women and of twin children compared to singleton children is lower and that this difference is associated with smaller placentas. Therefore we conclude that the placenta is in control of fetal growth. This concept has motivated longitudinal investigations on placental volume and the relation of placental volume to fetal outcome.

In Chapter 3 we explore an alternative parameter in the classification of Birth Weight. Birth weight is an important obstetrical determinant for neonatal outcome since it is related to perinatal mortality, neonatal morbidity, but also childhood intelligence and future health. In daily practice, birth weights are dichotomized by defining growth restriction below a centile threshold,
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for instance the 5th or 10th centile. The determination of centile thresholds, however, is subject to a considerable numbers of outliers in the reference curve at lower gestational ages. Most of the tertiary care study populations investigated in clinical studies indeed are of lower gestational ages. Birth Weight Ratio (BWR) is a parameter that does not suffer the shortcomings of centile thresholds. We define BWR as the ratio of observed birth weight divided by the mean birth weight of the reference growth curve. We show that difference between BWRs calculated by either the Gardosi or the Kloosterman birth weight charts is smaller than the differences between centile scores, and less dependent of weight. This illustrates the dependency of centile scores on the type of chart. We demonstrate that application of the BWR allows for a more consistent classification of newborn weight. Obviously, the BWR is more appropriate to describe fetal growth restriction and increases discriminative power for statistical analysis, since it is a continuous variable.

In Chapter 4 we investigate an aspect of the interaction between glucocorticoids and thyroid hormone in neonates. We studied preterm neonates receiving dexamethasone treatment for weaning off the ventilator as a model for thyroid hormone and glucocorticoid interaction because they may still partly show maturational aspects that normally occur at the end of term gestation. These infants are known to be at risk of hypothyroxinemia because of prematurity as well as because of severe neonatal disease. We found significantly decreased TSH and T₃ levels and significantly increased reverseT₃ levels after dexamethasone administration. We conclude that dexamethasone administration has an effect on thyroid function and on thyroid hormone metabolism. Whether this also occurs in the antenatal period has to be established in future research.

In Chapter 5 we assess whether and to what extent thyroid function is affected in pregnant women with early and severe hypertensive disorders and in their growth restricted newborns. These women were enrolled in a randomized clinical intervention trial evaluating the use of plasma volume expansion. We observed low fT₄ levels in 33% of these women at admission followed by a spontaneous normalization during pregnancy in almost all of
them. We found no correlation between cord blood fT₄ and maternal fT₄, and in contrast to other studies, we found no gestational age effect of cord blood fT₄ levels. We conclude that women with severe hypertensive disorders of pregnancy may transiently have lower fT₄ levels without evidence of a thyroid disorder. Their neonates have lower fT₄ levels not related with their mothers’ thyroid hormone status.

Chapter 6 reports the data generated by SAGE on placental tissue obtained from a normotensive pregnancy and a pregnancy with PE and HELLP syndrome. Comparison of SAGE profiles identified differentially expressed transcripts, a subset of which is validated on 36 placental tissue samples. Further downstream analysis and nearest centroid classification results in a 7 gene molecular placental signature specific for HELLP syndrome. This distinct placental molecular signature indicates that HELLP is not a PE variant but a separate disease entity and partly explains why studies aimed at identifying a common cause for gestational hypertensive disorders lack statistical power. The transcripts involved (CTNNAL, FLT1, GSTP1, LEP, PAPPA2, S100A8 and WWTR1) correspond to diverse molecular pathways, exemplifying the multigenic molecular basis of the disorder.

Chapter 7 describes genes that are differentially expressed during three time points in gestation, 12, 28 and 40 weeks of gestational age. Using K-means clustering we assign the placental transcripts to 3 mutually exclusive clusters of gene expression profiles with predominant expression in the first, second and third trimester. Mapping to gene ontology classes shows that genes involved in protein synthesis are relatively overrepresented in the first trimester. The gene ontology classes representing processes like development, angiogenesis, cell adhesion and apoptosis are rather evenly distributed over the three clusters. The prospected sequence of gestation specific events was not reflected in the clustered expression profiles. Extensive up regulation of ribosomal proteins is the most striking feature in the first trimester.

Chapter 8 discusses the main findings of this thesis and indicates aims for future research.