The placenta as modulator of fetal prosperity
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Chapter 1:

Introduction
Introduction, Part 1: Placental development and Function

Historical Perspective

This thesis provides evidence for the important role of the placenta during pregnancy. The importance of normal placental development for normal fetal development has not always been as evident as it nowadays seems. The history of knowledge of placental development and function reflects the expansion in knowledge of human biology in general, from mythical beliefs and classical views to anatomical, functional and molecular biological evidence based data. Reverence to the prominent role of the placenta for mankind is reflected in an ancient creation myth of Mande-speaking people of southern Mali:

"Mangala tried to maintain this perfect creation, but chaos crept in; one of the male twins became ambitious and tried to escape from the egg. This chaotic character is called Pemba. He is a trickster figure who symbolizes the mischievousness of humans. Pemba's first trick was to steal a piece of the womb's placenta and throw it down. This action made the earth."

In contrast to these mythical beliefs, the Greek scientist Hippocrates in the fifth century B.C. strongly held to the view that the fate of the fetus was related to sickness of the mother and suffering due to delivery. Until the eighteenth century this paradigm predominated and scientists presumed that the placenta did not have a particular function. It was supposed to be the place where the mother's blood entered the umbilical cord to reach the fetus. In 1750 William Hunter was first to break this belief when he proposed that the function of the placenta is that of an exchange organ. When he acquired the body of a pregnant woman who had died near term, he was able to carefully examine the pregnant womb, and inject coloured wax into the uterine and umbilical blood vessels (Figure 1). This demonstrated the independence of the maternal and fetal circulation. His observations were first published in 1774 in "The anatomy of the Human Gravid Uterus." He held a fashionable obstetric practice in London and was appointed Physician-Extraordinary to Her Majesty, Charlotte of Mecklenburg-Strelitz, wife of King George III. It took until the second half of the nineteenth century to prove the functional concept of the placenta as an exchange organ. This was done by Sir Joseph Barcroft (1872–1947), who measured fetal blood volume and placental blood flow as well as oxygen and carbon dioxide pressures across the placenta in pregnant sheep. His interest in the influence of these parameters on fetal growth made him an experimental biologist far ahead of his time. In the 1970’s a wealth of information on endocrine regulation of pregnancy was generated by G.C. Liggins, through his work on animal models of parturition, hormonal influences of fetal lung maturation and fetal adrenal function. His work showed that the placenta is far more than
Figure 1: Figure I and II from plate X of "The anatomy of the Human Gravid Uterus" published by William Hunter in 1774, depicting the vasculature of the placenta. The maternal and fetal circulations are injected with coloured dye.

The legend states: TAB X.Fig I: *Uteri pars anterior et extima, prout se praebuit siccata, exhibens faciem vasorum uterinorum, qualem prae se ferunt eo loci, ubi Placenta utero adhaeret.* A view of the outside of the forepart of the womb, as it appeared when quite dry, exhibiting a specimen of the uterine vessels at the part where the placenta adhered. Fig II: *Facies interna Placentae, cujus vasa par funiculum umbilicalenum cera sunt repleta.* The inside of the placenta, which was injected by the umbilical vessels.

an exchange organ. It boosted an enormous amount of research dedicated to the influence of the placenta on fetal development and maternal adaptation to pregnancy. Currently the placenta is seen as a pluripotent organ with active roles in remodelling of maternal physiology, maintenance of pregnancy and fetal homeostasis, hormonal control of fetal growth and development as well as regulator of key processes of maturation and parturition.⁹
Introduction

Placental Structure

The human placenta is formed as early as 1-3 weeks post conception at the site of interaction of trophoblast cells and decidua. Trophoblast cells form the main placental constituent and are unique to gestation. Histologically, we distinguish cytotrophoblast cells (mononucleate) and syncytiotrophoblast cells (multinucleate). Functionally, we specifically annotate those trophoblast cells that infiltrate through the endometrium into the maternal tissue (extravillous or intermediate trophoblast cells). All trophoblast cells stem from embryonal origin. Decidual cells that form the lining of the placenta and are in direct contact with the maternal myometrium are from maternal origin.

Subtypes according to zonation

In relation to the degree of zonation of placental tissue and formation of a single discrete organ within the uterus, placentas are classified into four major types (Figure 2).

Figure 2: Placental subtypes according to zonation.

Depicted is a bicornate uterus, as this is the most common uterine form among mammals. Trophoblast cells, representing the predominant placental cell type are schematically represented by shaded areas.
In a diffuse type placenta, as in horse, pig, camel and whale, the placental trophoblast cells are distributed over the entire inner uterine surface. In cotyledonary placentas, specific for ruminants as sheep and cows, placental tissue is restricted to specific areas of the endometrium, called caruncles, that are dispersed over the whole inner uterine surface. On the interface of the endometrium and the fetal membranes the caruncles are covered by chorion, called cotyledon.

Figure 3: Placental forms of various species representing different taxonomic categories of the placenta-bearing mammalian phylogeny according to DNA homology. Formation of the discoid placental form is seen in bats, insectivores, rodents, primates and Xenarthra. Xenarthra means "strange joints", as these animals’ vertebral joints have extra articulations and are unlike those of any other mammals.
Zonary placentas show further concentration of placental trophoblast cells to form an equatorial band. The type with the most restricted zonation is the discoid type where there is a single plate. This is the human placental subtype. In Figure 3, taxonomic categories of the placenta-bearing mammalian phylogeny are arranged according to DNA homology. The discoid placental form of humans is shared, amongst other species, by the other primates and by rodents.

**Subtypes according to cellular structure**

When placentas are categorized by cellular structure, they can either be epitheliochorial, endotheliochorial or hemochorial, as depicted in Figure 4. Across species there is no general concurrence between the degree of zonation (the different forms depicted in Figure 2) and the three placental cellular structures. In all species the placenta consists of both a maternal and a fetal component. In epitheliochorial placenta, as in sheep and the other ruminants, maternal and fetal blood are separated by maternal endothelium, maternal connective tissue, the endometrium, the trophoblast, fetal connective tissue and fetal endothelium (Figure 4, left panel). This implies shallow implantation, with an intact endometrium, as the placenta forms at the inner surface of the uterine wall. Sub-endometrial development is observed in the endotheliochorial placenta, found in carnivores. In these species, the endometrium is destroyed during placentation and maternal and fetal blood are separated by maternal endothelium, maternal connective tissue, trophoblast, fetal connective tissue and fetal endothelium.

![Figure 4: Schematic representation of placental cellular structure of three placental subtypes.](image)
Chapter 1

Based upon cellular structure, human as well as rodent placenta is characterized as hemochorial, where maternal blood is separated from fetal blood only by trophoblast cells, fetal connective tissue and fetal endothelium. This placental structure exhibits the greatest extent of uterine tissue lysis, with the maternal endometrium, connective tissue and maternal endothelium all being lost. Unique for this type is that maternal blood is in direct contact with trophoblast cells. Since trophoblast cells are from embryonic origin this implies very close contact between two genetically different systems.

While human placenta is characterized by a monolayer of syncytiotrophoblast cells, rodent placenta has three layers: two layers of syncytiotrophoblast cells and one cytotrophoblast cell layer. Additionally, rodents have a Choriovitelline (yolk sac) placenta, implying the yolk sac persists until term. Transfer of immunoglobulins via the yolk sac confers passive immunity to the fetus.\textsuperscript{12;13}

In summary, human placenta is of the discoid hemochorial type, with the most extreme form of trophoblast zonation. Functionally the human placenta depends on the most extensive tissue replacement of the uterine wall, myometrium and maternal vascular endothelium as invasion of trophoblast cells into these structures in humans is far deeper than in most other mammalian species. This implies a high demand of maternal adaptation in the formation of a functional Fetal-Maternal-Placental Unit.

Placental development

\textit{Implantation and Invasion}

Gestation starts with fertilization of an ovum. Seven to eight days post human conception the blastocyst nidates into the maternal endometrium.\textsuperscript{(Figure 5, top panel)} Buds of cytotrophoblast cells invade into endometrium, myometrium and spiral-shaped maternal blood vessels, thereby widening these maternal vessels into trumpet-like forms (Figure 5, lower panels). From the 6\textsuperscript{th} to 18\textsuperscript{th} week, villi are formed, which are lined by syncytiotrophoblast cells as well as a continuous layer of cytotrophoblast cells. The cytotrophoblast cell layer functions as a stem cell pool, continually differentiating either into syncytiotrophoblast by fusion, or migrating as extra villous trophoblast. On the apex of villi, the cytotrophoblast cell layer is formed into cytotrophoblast cell columns. The process of invasion continues into the second trimester, and is complete at 18 weeks.\textsuperscript{14}

The interstitial invasive trophoblast cells migrate and invade into the uterine tissue and anchor the placenta to the uterus. The syncytiotrophoblast vacuolizes and finally forms lacunae, ultimately to contain maternal blood. After extensive resorption of decidual epithelium, basement membrane and maternal vascular endothelium the maternal blood is able to circulate in
direct contact to syncytiotrophoblast. The function of cytotrophoblast cells, apart from entering endometrium and maternal blood vessels, is to form and sustain the placental villi after losing their invasive capacity by differentiation. The function of syncytiotrophoblast is covering the widening villous tree as exchange surface.

Figure 5: Functional developmental relations of placental cell types. Upper panel: Blastocyst at implantation phase. Lower three panels: schematic representation maternal uterine tissue and trophoblast villus and its cross section at 6-18 weeks, at 18-32 weeks and at 32 weeks gestation until term. Grey shading represents trophoblast localization. C = cytotrophoblast cells, S = syncytiotrophoblast, T = extravillous trophoblast cells, M = maternal blood vessel, E = Maternal endometrium, F = fetal blood vessel, V = villous mesenchyme cell.
Chapter 1

The immature villi are covered by syncytiotrophoblast as well as cytotrophoblast cells until 18 weeks of gestation. The villous stroma is compact, composed of mesenchymal cells with centrally located fetal capillaries. After 18 weeks, mature placental villi are covered only by syncytiotrophoblast as the majority of the cytotrophoblast cell layer starts to disappear. Physiologic changes during the process of differentiation of placental cell types continues through the second trimester with division and elongation of villi, proliferation and dilatation of capillaries. Towards term, there is thinning of the trophoblast cell layer, predominantly by disappearance of most of the cytotrophoblast cells (Figure 5, bottom panel). This results in a fall in resistance of the feto-placental vasculature which can be observed clinically by ultrasound Doppler. This decrease in resistance is generally accepted as an indicator of normal placental development as it favours placental perfusion to comply with the increasing demands with advancing gestation.

Placental growth
There are several reports in literature on normal placental weight. It has been established that placental weight increase accelerates after 12 weeks gestation and slows down again after 36 weeks. (see Figure 6)

Figure 6: Relation between Placental weight (90th, 50th and 10th percentile) and gestational age. Figure composed of data 22 to 28 weeks and 28 to 43 weeks according to Schuler-Maloney.
Introduction

Placental growth can be affected by all conditions that impinge on maternal supply and lead to hypoxia, hypoglycaemia or hypoproteinaemia. These conditions are anaemia, living at high altitude, maternal cardiac or pulmonary failure, malnutrition and vascular pathology. The most common uterine factor affecting placental growth is impaired uterine vascular adaptation related to preeclampsia: this is discussed in Part 2 of the Introduction "The placenta as the basis of gestational and fetal disease". Other uterine factors affecting placental growth are uterine malformations, primigravidity, an unfavourable implantation site and impaired vascular supply. Other factors associated with impaired placental growth are placental mosaicisms in chromosomal disorders, infection and infarction.

In general, impaired placental growth directly affects fetal growth. The only conditions where fetal growth is adversely affected without the concomitant decreased placental growth are umbilical cord anomalies, like abnormal insertion and coiling.

Although placenta and fetus develop under the same maternal influences, the Placental Ratio (PR), calculated as weight of the placenta divided by birth weight, has a non-linear relation with gestational age. Fetal weight normally has a maximal absolute increase between 32 and 37 weeks of gestation, while the placenta gains most of its weight between 20 and 34 weeks. As the fetus grows relatively more rapidly than the placenta, the PR decreases with advancing gestation and normally amounts 15% of neonatal birth weight at term. Population studies show racial differences in placental weight, but the PR at term is 15% for all ethnic groups. The PR is not an accurate clinical marker of fetal growth restriction, but is useful for functional comprehension and research purposes. A normal PR with a normal neonatal birth weight is a sign of adequate placental function. A normal or low PR in case of fetal growth restriction is typically found in case of placental dysfunction. This does not imply that fetal growth restriction is always accompanied by a low PR. Interestingly, in smoking mothers and mothers suffering from anaemia the PR is high, in spite of fetal growth restriction. When maternal smoking is stopped in the first trimester there are high PRs with an even normal fetal weight. Large placental size can reflect compensatory growth to support fetal growth in a hostile environment. In animal models a similar increased placental weight has been reported as a result of maternal undernutrition during placentation. Generally, placental size is maximum when constraints to maternal nutrition are discontinued after placentation is completed, suggesting a programming of placental size in the early phase of pregnancy. Human data from the 1944-1945 Dutch famine cohort support this hypothesis. Birth weight of children born to mothers exposed to the famine solely in the 1st trimester of pregnancy was
normal, in spite of an increase in placental weight. A further finding in this cohort, that increased placental weight at birth is associated with an increased risk of hypertension in adult life is in line with two other observations from long term follow up studies. Exposure to famine during pregnancy generally correlates with poor health, while the exact timing of the exposure determines which specific organ system is affected. In summary, both external and placental factors compromise fetal growth. The external and placental factors have opposite effects on placental development.
Functional Properties of Human Placenta

Transport and Metabolism
The most important placental function is to ensure maternal-fetal exchange of nutrients, gases and electrolytes. The bulk of maternal-fetal exchange is via the placenta; other routes as transamniotic passage or transfer via amniotic fluid are unlikely to be of great importance. For most substances, the placenta is not much of a barrier: water and electrolytes, glucose, fatty acids, catecholamines, immunoglobulins and water-soluble vitamins readily cross the placenta. Exchange of oxygen and carbon dioxide is by diffusion. Amino acid transport across the placenta has all the characteristics of active transport, since it occurs against a high fetal-maternal gradient. The placenta is active in the metabolism of carbohydrates, fat and amino acids. This requires extensive placental oxygen consumption which has been shown to be as high as in liver or brain.

Endocrine function of the Fetal-Maternal-Placental Unit
The remodelling and maintenance of homeostasis during pregnancy requires input of not only placenta but a concerted action between placenta, mother and fetus, commonly known as the Fetal-Maternal-Placental unit. This paragraph describes transport and metabolism of the major endocrine factors in the Fetal-Maternal-Placental unit.
In general, 97 – 99.9% of the total serum hormone pool is bound to carrier proteins of which the levels change during the course of pregnancy. For all steroid hormones as well as thyroid hormone metabolites it is the free hormonal concentration which determines the biological action, via their respective nuclear hormone receptors and changes in the total hormone pool during pregnancy should always be considered in the light of changing levels of hormone binding proteins.
The Fetal-Maternal-Placental unit is capable of synthesizing and secreting a broad range of growth factors, protein- and steroid hormones many of which are also produced by other endocrine organs, pituitary and brain. Due to the endocrine resemblance with the latter, the placenta has even been addressed as the third brain during pregnancy. Table 1 summarizes the broad range of endocrine factors produced by the placenta.
Steroidogenesis in pregnancy is a good example of the tripartite efforts of the Fetal-Maternal-Placental unit. Maternal cholesterol is metabolized by placental desmolase and 3-β-Hydroxysteroid Dehydrogenase (3βHSD), daily yielding substantial amounts (250-350 mg) of progesterone. Most of this enters the maternal circulation, but in the fetal compartment this progesterone is the substrate for the production of androgens and estrogens. Progesterone is converted to androgens by the fetal P₄₅₀-17α-hydroxylase and 17,20-lyase,
for which the placenta itself is deficient. The fetal produced androgens are in turn aromatised to estrogens in the placenta.

**Glucocorticoids**

In extra-uterine life, the Hypothalamus-Pituitary-Adrenal gland axis (HPA axis) is an integrative part of the stress system, where the adrenal cortisol secretion is regulated by a negative feedback system and all hormones involved are produced by discrete organs. The human placenta is an important source of both CRH and ACTH that act in a positive feed-forward mechanism on fetal adrenal cortisol production, bypassing the hypothalamic part of the fetal hypothalamus-pituitary-adrenal gland axis. This mechanism is predominant in the 5 weeks preceding parturition.64;65 This has led to the model of a placental clock, determining the duration of pregnancy. The increase in maternal plasma CRH, mainly due to the abundant production in placenta, saturates the CRH-binding proteins with a consequent rise in free CRH that acts as a parturition trigger.66;67 Overall corticoids are of key importance for regulation of the fetal environment. Total maternal serum cortisol increases to 3 times pre-pregnancy levels at term.68 The fetus is protected from high levels of maternal cortisol by the abundant presence of 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2) which oxidises cortisol to the bio-inactive metabolite cortisone.69;70 The net increase of bioactive glucocorticoid metabolites with advancing gestation is an oestrogen dependent process. 71 The changing balance between the expression of the glucocorticoid inactivating enzyme11β-HSD-2 (that decreases) and the glucocorticoid activating enzyme 11β-hydroxysteroid dehydrogenase -1 (that increases) results in an increase of bioactive glucocorticoids. In contrast to hydrocortisone, dexamethasone and betamethasone are not degraded by 11ß-HSD-2. From a clinical perspective, this is of particular importance since

Table 1, opposite page: The shaded left side of the table describes what is known of placental expression, regulation and function. The non-shaded right side of the table describes the non-pregnant expression and regulation. The most striking discrepancies in regulation between the pregnant and the non pregnant state are indicated. CRH = Corticotropin Releasing Hormone; Prost = Prostaglandins; IL1α/β = Interleukin 1α/β; ACTH = Adrenocorticotropic; Cort = Cortisol; 11-ß HSD1 = 11-ß Hydroxysteroid Dehydrogenase 1; 11-ß HSD2 = 11-ß Hydroxysteroid Dehydrogenase 2; TRH = Thyrotropin Releasing Hormone; TSH = Thyroid Stimulating Hormone; BAT = brown adipose tissue; D1 = Deiodinase 2; D2 = Deiodinase 3; INH = Inhibin A/B; FSH = Follicle Stimulating Hormone; P = Progesterone; hCG = Human Chorionic Gonadotropin; 3βHSD = 3-ß-Hydroxysteroid Dehydrogenase; GH = Growth Hormone; PRL = Prolactin; IGF1 = insulin-like growth factor 1 (somatomedin C); IGF2 = insulin-like growth factor 2 (somatomedin A); hPL = Somatomammotropin (Placental Lactogen); PAPPA = Pregnancy associated protein A

20
Table 1: Major endocrine factors in the Fetal-Maternal-Placental unit.

<table>
<thead>
<tr>
<th>Factor produced in placenta</th>
<th>Function</th>
<th>During pregnancy</th>
<th>In General</th>
</tr>
</thead>
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<tr>
<td>CRH</td>
<td>Maturation</td>
<td>Prost, IL1α, IL1β</td>
<td>Hypothalamus, Cort</td>
</tr>
<tr>
<td>ACTH</td>
<td>Maturation</td>
<td>CRH</td>
<td>Pituitary, CRH, Cort</td>
</tr>
<tr>
<td>Cort</td>
<td>Maturation</td>
<td>Estrogen</td>
<td>Adrenal cortex, ACTH</td>
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<tr>
<td>11-β HSD1</td>
<td>-</td>
<td>Estrogen</td>
<td>Liver, Cort</td>
</tr>
<tr>
<td>11-β HSD2</td>
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<tr>
<td>TRH</td>
<td>Maturation</td>
<td>Hypothalamus</td>
<td>TRH, T₄</td>
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<tr>
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<td>-</td>
<td>TRH</td>
<td>TRH, T₄</td>
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<tr>
<td>D₂</td>
<td>Increase of bioactive thyroid hormone metabolites</td>
<td>-</td>
<td>Brain, pituitary, muscle, BAT</td>
</tr>
<tr>
<td>D₁</td>
<td>Decrease of bioactive thyroid hormone metabolites</td>
<td>-</td>
<td>Brain, muscle, skin</td>
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<td>-</td>
<td>Ovarian follicle</td>
<td>FSH</td>
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<tr>
<td>Aromatase</td>
<td>-</td>
<td>Corpus Luteum</td>
<td>-</td>
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<td>P</td>
<td>Substrate for fetal androgen production</td>
<td>hCG</td>
<td>-</td>
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<td>3βHSD</td>
<td>Cholesterol metabolism</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Desmolase</td>
<td>Cholesterol metabolism</td>
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<tr>
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<td>Growth factor</td>
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prophylactic use of antenatal glucocorticoids in the event of threatening preterm delivery for prevention of respiratory distress syndrome has become one of the most undisputed and widespread perinatal interventions. There is however a need for caution in administrating glucocorticoids, as it has been shown that in humans neurodevelopmental outcome is adversely affected by postnatal administration. Also at repeated antenatal administration of glucocorticoids there is concern about adverse neurodevelopmental outcome while evidence of longer-term benefits remains insufficient.

**Thyroid hormones**

Thyroxin (T₄), the principal product of the thyroid gland, is produced under the classic negative feedback-controlled Hypothalamic-Pituitary-Thyroid axis (HPT axis). The hypothalamic Thyrotropin Releasing Hormone (TRH) stimulates the synthesis and release of Thyroid Stimulating Hormone (TSH), which in turn stimulates thyroid hormone secretion by the thyroid. T₄ is metabolised by Iodothyronine Deiodinases type 1, 2 and 3, that specifically deiodinate the inner or outer ring. Iodothyronine Deiodinase type 1 (D1) and Iodothyronine Deiodinase type 2 (D2) can both deiodinate the outer ring producing bioactive T₃ and clearing the inactive metabolite rT₃. D1 is mainly expressed in liver, kidney and thyroid, where it is mainly responsible for maintenance of plasma levels of T₃. Additionally, D1 can deiodinate the inner ring. D2 is expressed in thyroid, muscle, brown adipose tissue, pituitary, brain and placenta, where it is responsible mainly for local provision of T₃. Iodothyronine Deiodinase type 3(D3) only has inner ring deiodination capacity and is present in brain, muscle, skin, fetal liver, the pregnant uterus and in placenta, especially in syncytiotrophoblast and cytotrophoblast cells. Inner ring deiodination lowers the concentration of bioactive T₃ by converting T₄ to rT₃, and T₃ to T₂. The intracellular concentration of bioactive T₃ is the resultant of the tissue specific levels of D2 and D3, but also of transport of plasma T₄ and T₃ into the cell. Brain, and also liver highly express MCT8, a member of the monocarboxylate transporter family, which mainly transports T₃ into the cell. Apart from uptake and deiodination, there are several other processes that influence the levels of bioactive thyroid hormone metabolites such as sulfation, glucuronidation, oxidative deamination, decarboxylation and ester link cleavage. The bioactive thyroid hormone metabolite T₃ exerts its function through nuclear thyroid hormone receptors. At least three forms of thyroid hormone receptors (TRα1, TRβ1 and -β2) have thyroid hormone binding properties. Interaction of thyroid hormone with the thyroid hormone receptor results in the regulation of transcription of thyroid hormone target genes. These genes encode proteins involved in both developmental as well as basic metabolic processes.
Optimum thyroid hormone levels are indispensable especially for development of the central nervous system as they induce maturation of different cell types i.e. neurons, astrocytes, oligodendrocytes and microglia. Thyroid hormones are essential for fetal development and are produced by the human fetus as early as 12 weeks. We know from both animal and human studies that fetal coelomic fluid, amniotic fluid and brain tissue contain significant amounts of free T4, before the onset of fetal thyroid hormone production. This is presumed to be of importance since the α1, β1 and -β2 receptor as well as iodothyronine deiodinases are expressed in human brain in significant amounts as early as 7 to 8 weeks gestation. The only possible source of thyroid hormone for the fetus so early in gestation is the mother. Evidence that thyroid hormones are able to cross the placental barrier comes from the work of Vulsma et al who showed that cord blood from fetuses who are unable to synthesize thyroid hormones, due to thyroid agenesis or a total iodide organification defect, contains substantial amounts of thyroid hormone. At term this is considered to be 30-40% of the fetal thyroid hormone pool. After 16 weeks, there is significant thyroid hormone secretion from the fetal thyroid, and serum T4 levels increase and reach a plateau at 35 weeks. At all times serum levels of bioactive thyroid hormone are lower in the fetus compared to the mother. In pregnant women, the function of TSH is mimicked by hCG that cross-reacts with the TSH receptor. Mirroring the hCG rise in the first trimester, TSH levels are relatively low in this period. During pregnancy, the most prominent change in maternal thyroid function is a rise in mean total T4 from 100 nmol/L to 140 nmol/L as a result of the oestrogen-induced TBG production by the liver. Free T3 only increases slightly, whereas free T4 even shows some decrease. Placental deiodination of T4 to rT3 by D3 is a dynamic process and is considered the main regulator of the maternal-fetal T4 transfer. D3 activity per cell decreases during pregnancy, but due to placental growth total placental activity increases. It is assumed that placental D3 activity prevents the untimely exposure of the developing embryo to excessive levels of thyroid hormone. The intracellular trophoblast requirement for T3 is supplied by D2 activity, which at all stages of pregnancy is 200-fold less than D3 activity. Since thyroid hormone provision to fetal cells is dependent on both the maternal and the fetal thyroid function, neurodevelopmental disabilities are most severe in combined maternal and fetal hypothyroidism. The most dramatic example is that of endemic cretinism where both mother and fetus are profoundly hypothyroid as a result of iodine deficiency. Fetal thyroid hormone deficiency can cause neurodevelopmental defects, especially if this starts early in development before the onset of fetal thyroid hormone production. Even mild maternal hypothyroxinemia during pregnancy is
associated with adverse neurodevelopmental outcome in the offspring.\textsuperscript{105-107} As thyroid disease shows higher prevalence among women in child-bearing age, a current hot topic is whether thyroid hormone function should be evaluated during early pregnancy, aimed at achieving thyroid hormone levels in the high normal range, by treatment if necessary.\textsuperscript{106;108;109} Some authors favour defining a pregnancy-specific TSH reference range by lowering the upper limit from 4.0 mU/L to 2.5 mU/L.\textsuperscript{110} Since optimal timing and nature of screening is still not established, others advocate case finding of subclinical hypothyroidism in risk groups.\textsuperscript{108} On the other side of the spectrum, also fetal hyperthyroidism is not without risk. It can result in permanent neurological and skeletal injury,\textsuperscript{111;112} and long term neurodevelopmental studies of the children are needed to establish the benefit of treating pregnant women with thyroid hormone.

\textbf{Influence of glucocorticoids on fetal and placental thyroid function}

In vivo evidence of interaction of the HPT- and Hypothalamic-Pituitary-Adrenal gland axis (HPA axis) was established by the combined glucocorticoid and thyroid hormone treatment in pregnant sheep that has a supra-additive effect on pulmonary maturation.\textsuperscript{113;114} The extent of HPA- and HPT axes cross-talk is species-specific and depends on the developmental stage.\textsuperscript{115} From animal experiments there are numerous examples but for obvious reasons the data for humans with basically normal thyroid and adrenal function are limited. It has been shown that glucocorticoids directly influence the HPT axis. Apart from the expected suppression of the HPA axis\textsuperscript{116} due to the physiological negative feedback system there is evidence of a similar suppressive effect of glucocorticoids on the HPT axis.\textsuperscript{117;118} Physiological levels of corticosterone are known to inhibit TSH secretion.\textsuperscript{119} In euthyroid subjects, a five-day course of Dexamethasone increases rT\textsubscript{3} serum levels.\textsuperscript{120} In clinical practice, antenatal glucocorticoids have temporary suppressive influences on fetal breathing movements,\textsuperscript{121} variability of heart rhythm\textsuperscript{122} and fetal behaviour\textsuperscript{123} and there is a measurable effect on brain perfusion.\textsuperscript{124} Interestingly, suppressed thyroid function can have the same effects, suggesting that the glucocorticoid effect may in part be mediated by thyroid hormones. There are currently no studies substantiating this point, but there are data showing a negative effect of postnatal dexamethasone on thyroid hormone metabolism.\textsuperscript{125} On the molecular level this could be explained by induction of D\textsubscript{3}\textsuperscript{115}, or alternatively by suppression of D1.\textsuperscript{126} Both would lead to a lowering of the bioactive metabolites, with influences both in fetus and placenta.

In summary, the placenta is able to modulate key processes regarding the Hypothalamic-Pituitary axes during pregnancy.