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Eerdekens, Johan Verhaeghe, Veerle Darras, Gunnar Naulaers, Greet Van den berghe, Lies Langouche & Christine Vanhole

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**The placenta infetalthyroid hormone delivery: from normal physiology toadaptive mechanismsin complicated pregnancies**

An Eerdekens, UZ Leuven; Johan Verhaeghe, UZ Leuven; Veerle M. Darras, KU Leuven; Gunnar Naulaers, UZ Leuven; Greet Van den Berghe, UZ Leuven; Lies Langouche, KU Leuven; Christine Vanhole, UZ Leuven

Maternal-fetal thyroid hormone transfer

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Corresponding author: An Eerdekens, Neonatology, UZ Leuven, Herestraat 49, 3000 Leuven, an.eerdekens@uzleuven.be

Reprint requests: An Eerdekens, Neonatology, UZ Leuven, Herestraat 49, 3000 Leuven, an.eerdekens@uzleuven.be



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**Abstract**

**Context:** Thyroid hormones are indispensable for normal fetal development. Since the fetus depends to a large extent on maternal thyroid hormone supply through the placenta, this challenges maternal thyroid economy. Several molecular mechanisms are involved in placental thyroid hormone transport and metabolism. Chronic pregnancy complications, associated with utero-placental hypoxia, trigger the development of accelerated placental maturation in order to improve fetal-placental exchange to strengthen the offspring's chance of survival. This review provides an overview of normal maternal-fetal thyroid hormone supply and explores the presence of placental adaptive mechanisms in complicated pregnancies with chronical utero-placental hypoxia to improve the thyroid hormone supply to the fetus under pressure, to end with reflections about the long term health consequences.

**Evidence acquisition:** This work is based on a comprehensive literature review of the Pubmed and Embase database, including relevant articles from 1969 to June 2018.

**Conclusions:**The placenta is actively involved in fetal thyroid hormone delivery through a combination of stimulatory and inhibitory mechanisms. Parallel with histological adaptations to improve trans-placental fetal-maternal exchange, there are indications of placental adaptive mechanisms in thyroid hormone transport and metabolism in case of complicated pregnancies, from animal models and *in-vitro* experiments. Evidence from human *in-vivo* studies is limited due to heterogeneity in study populations, small study samples and technical limitations. Further research is necessary to reveal the role of the placenta in pathological circumstances. The placenta might thus be considered as the infants' black box of pregnancy. Results will contribute to more insights in the concept of fetal programming, which lays the foundations of optimum health, growth, and neurodevelopment across the lifespan.

## Introduction

Thyroid hormone (TH) is the general term for thyroxine (T4) and triiodothyronine (T3). From an evolutionary point of view, THs are crucial in developmental processes such as amphibian metamorphosis [1]. Animal models have shown the importance of THs in mammalian development, particularly in the brain [2]. Until mid-gestation, the fetus relies completely on maternal THs [3]. This review will first focus on the normal mechanisms of maternal-fetal TH supply, then emphasize the strain of pregnancy on maternal thyroid function and consequences in case of maternal thyroid insufficiency, give an overview of placental histological and molecular adaptations in TH transport and metabolism in complicated pregnancies due to chronic utero-placental hypoxia, such as gestational hypertension, (pre)eclampsia and HELLP syndrome, to end with a reflection on the long term health consequences in view of the developmental origins of health and disease. This work is based on a comprehensive literature review of the Pubmed and Embase databases, including relevant articles from 1969 to June 2018.



## Maternal thyroid hormone supply to the fetus

Until mid-gestation, the fetus is completely dependent on maternal TH supply. As early as the second month of human pregnancy, transfer of maternal THs towards the fetus is demonstrated by ultrafiltration of maternal serum in the exocoelomic cavity. These levels increase with increasing gestational age (GA) [4]. Although TH concentrations in fetal compartments during the first trimester are more than 100-fold lower than those in maternal serum, the fetal ratio of free to protein-bound hormones is much higher than in maternal serum. This results in a high biological activity level, which is important for the developing embryonic and fetal tissues [5]. At the end of the first trimester, the definitive hemochorial placenta is formed. At this stage, exchange of molecules between maternal and fetal circulations occurs by transport through the plasma membrane and cytoplasm of the trophoblast

cells (Figure 1) [6]. The transplacental TH supply is regulated by several factors: TH-binding proteins, TH transporters, deiodinases (DIO) and TH receptors.

a.Thyroid-hormone-binding proteins

Thyroxine-binding globulin (TBG), albumin and transthyretin (TTR) are the main serum TH-binding proteins. Apart from TBG, they are all synthetized in the placenta. Albumin has a low affinity, but high TH- binding capacity. Its function in TH transport within the placenta is not clear [7]. TTR mRNA and protein expression in the human trophoblast are already detected from 6 weeks of gestation, followed by a linear increase until 13-17 weeks before levelling off until term gestation [8]. Immunohistochemical data show that specifically on the syncytiotrophoblast layer, TTR expression peaks in the first trimester and progressively decreases throughout the second and third trimester [9]. Placental TTR expression and uptake might be enhanced by relative hypoxia observed in the first trimester of pregnancy, not coincidentally the moment when the fetus is completely dependent on maternal T4 [10]. TTR is also synthesized and secreted by liver, choroid plexus, pancreas and retina. It has greater affinity for T4 than T3 and also functions as a retinol-binding protein. The human placenta secretes TTR into both maternal and fetal circulations, suggesting the existence of a T4-TTR shuttle system [11]. This way, they might protect THs from metabolism during their transit through the throphoblasts. Indeed, *in-vitro* studies on placental cytosol showed that inhibition of T4 binding to TH-binding proteins resulted in increased deiodination of T4 into the inactive reverse T3 (rT3) by DIO3 [7].



b.Thyroid hormone transporters

Different transmembrane transporter families are responsible for active TH transport in and out of cells: monocarboxylate transporters (MCT), system L amino acid transporters (LAT) and organic-anion-transporting polypeptides (OATP). Among them, only MCT8, MCT10 and OATP1C1 have a high degree of specificity towards TH[12]. Currently, six TH transporters have been detected in the human placenta: MCT8 *(SLC16A2 gene)*, MCT10 *(SLC16A10 gene)*, LAT1 *(SLC7A5 gene)*, LAT2 *(SLC7A8 gene)*, OATP1A2 *(SLCO1A2 gene)* and OATP4A1 (*SLCO4A1 gene*) [13]. Their anatomical localization, ontogeny in the human placenta and relative affinity to THs are variable, complex and stillunder study [12]. Loss-of-function mutations in MCT8 in humans are responsible for the X-linked Allan-Herndon-Dudley syndrome, associated with severe psychomotor retardation[14]. In humans, MCT10 is more effective in T3 transport than T4 transport, compared to MCT8 [15].

Placental TH transporter expression increases with gestation and between 27-34 weeks, it reaches term levels. Remarkably, between 11 and 20 weeks, the time of trophoblast invasion, the expression is generally reduced. It may reflect the need to limit the pro-invasive effects of THs, thus preventing aggressive, uncontrolled trophoblast invasion in normal placentation. Increased expression with gestation may also fulfil the increased needs for other biological substances for fetal growth and development, such as amino acids [13].



c.Deiodinases

In general, T4 needs to be considered as a prohormone of T3, which in turn binds to the nuclear receptors and initiates TH action, although T4 also has some T3-independent non-genomic actions. In humans, approximately 80% of the daily T3 production is the result of extrathyroidal deiodination of T4. There are three types of the seleno-enzyme DIO. DIO1 functions both as an activating outer and inactivating inner ring deiodinase by converting T4 either to T3 or to reverse triiodothyronine (rT3), and both T3 and rT3 to 3, 3'-diiodothyronine (T2). DIO2 is an outer ring iodothyronine deiodinase, responsible for the conversion of T4 to T3. It therefore acts as a TH-activating enzyme. It also

catalyzes the conversion of rT3 to T2. DIO3 inactivates TH by catalyzing the inner-ring deiodination of T4 to rT3 and of T3 to T2, both biologically inactive [16] . DIO2 and DIO3 are expressed in the placenta [17, 18]. Although the activity level of DIO3 is approximately 200 times higher than that of DIO2, there seems to be interaction between both enzymes to provide the fetus with appropriate amounts of THs [19]. Since DIO3 is present on the apical membrane of the syncytiotrophoblast cells, DIO3 seems to play a pivotal role in protecting fetal tissues from excessive levels of THs by inactivating maternal THs [20, 21]. DIO2 is most present in the placental villous cytotrophoblast layer, on the fetal side of the chorionic villi, therefore suggesting a role in supplying T3 to the fetus in early gestation [12, 19]. Moreover, it has been suggested that placental DIO3 activity also contributes to the release of iodide ions into the fetal circulation for fetal TH synthesis [12].

d.Thyroid hormone receptors

Kilby et al. showed the expression of TH receptor subtypes TRα1, TRα2, TRβ1 and TRβ2 mRNA in human placenta [22]. With exception of TRβ1, the expression increased with increasing GA. An increase in TRα1, TRα2, TRβ1 protein expression with advancing GA, assessed by immunohistochemistry, was also demonstrated. Although TRβ2 mRNA, which is considered to be largely pituitary-specific, was present in the placenta, no TRβ2 protein was detected. Endogenous nuclear saturation of T3 was 34% in the placenta, showing a direct action of T3 on placental cells [23].

e.Sulfotransferases and arylsulfatases

A broad range of biological substances are sulfated and desulfated by means of sulfotransferases and arylsulfatases. Sulfation of the phenolic hydroxyl group blocks the outer-ring deiodination of T4,

while it strongly stimulates the inner-ring deiodination of both T4 and T3, indicating that sulfation can be an important step in TH inactivation [24]. However, several studies have demonstrated a limited role of these enzymes in the formation and reactivation of sulfated iodothyronines in the placenta [12].

**Pregnancy is a challenging state for maternal thyroid economy**

Pregnancy requires maternal endocrine adaptation. Human chorionic gonadotrophin, a peptide hormone composed of an α- and β-chain, has a partial structural homology with TSH through the identical α-subunit. Therefore, it mediates direct stimulation of the thyroid gland ('spillover' mechanism), which leads to a small and transient increase in maternal free T4 (fT4) levels and a temporary decrease in TSH levels near the end of the first trimester. The thyroid gland, in turn, needs to respond to both the challenges of first, the estrogen-mediated rise in TBG, which requires an increased pool of T4 and simultaneously the increased renal iodine excretion.Iodine-sufficient pregnant women are able to maintain a plentiful store of iodine in the thyroid, but in iodine-deficient women, this adaptive mechanism fails, which can lead to thyroid dysfunction in the pregnant woman and her offspring.Also in the majority of patients treated for hypothyroidism, increased levothyroxine dosage in the first trimester of pregnancy is needed[25].Since the fetus is completely dependent on maternal TH supply until mid-gestation, it has been suggested that the increased maternal fT4 levelsin the first trimester may be functionally important for the developing embryo[4, 5]. During the second half of gestation, maternal circulating TSH levels return to pre-pregnancy levels and remain stable, unless there are underlying causes for thyroid insufficiency [25].The prevalence of thyroid disorders in pregnancy is high, affecting one in six pregnant Belgian women [26] and is caused by mild to moderate iodine deficiency, autoimmunity, thyroid autoantibodies and environmental contaminants such as organohalogens[27]. Mothers with thyroid insufficiency are more prone to pregnancy complications compared to euthyroid mothers. The evidence is obvious in overt hypothyroidism, which leads to several pregnancy complications including spontaneous miscarriage, preeclampsia, gestational diabetes, preterm delivery, induction and caesarean sections,decreased IQ and low

birthweight in the offspring[28].Subclinical hypothyroidism is associated with pregnancy loss and neurocognitive deficits, but there are conflicting data about other obstetrical complications, such as in isolated hypothyroxinaemia in pregnancy. Substantial study heterogeneity with a wide scatter in definitions, a broad variety of population characteristics including iodine status and the timing of recruitment and testingmight explain these controversies[29]. Moreover, these contradictions contribute to the persisting discussion whether or not to advocate universal TH screening during the first trimester of pregnancy.Based on two randomized controlled trials, it cannot be concluded that universal screening has an impact on maternal and infant outcomes. However, universal screening increases the number of women diagnosed with thyroid insufficiency compared with a targeted high-risk case finding approach and seems to be more cost-effective [28, 30].

**The placenta in maternal pregnancy-related vascular pathology**

Hypertensive disorders of pregnancy (gestational hypertension, (pre)eclampsia, HELLP syndrome) are characterized by chronic utero-placental hypoxia. In case of preeclampsia, this leads to increased placental secretion of several angiogenic factors in the maternal circulation, such as increased soluble fms-like tyrosine kinase-1 (sFlt-1) secretion, which has been associated with subclinical hypothyroidism. It has been postulated that increased secretion of these angiogenic factors alters maternal thyroid function, but more studies are necessary for further clarification [31].
Histological placental compensating mechanisms in chronic utero-placental hypoxia are well described, whereby premature aging is a known concept. The low oxygen levels induce branching angiogenesis, resulting in clusters of richly capillarized, short, highly branched terminal villi [32]. Tenney-Parker changes are an abnormal increase of syncytiotrophoblast (STB) knots at the surface of these villi and are a marker of premature aging. These STB knots originate from STBs, which form the epithelial layer of the placental villous tree. It is a multinucleated syncytium, generated and enlarged by the continuous fusion of the underlying cytotrophoblasts. In normal pregnancy, the frequency of STB knots increases as gestation proceeds, but in pregnancies with vascular complications they are more abundant and present earlier (Figure 2). It is hypothesized that sequestration of nuclei to

particular areas of the villus surface is a mechanism to prevent impingement on diffusional exchange [33]. In pregnancies with acute pathological manifestations, for example, acute chorioamnionitis, these changes are not present.

**Impact of complicated pregnancies on placental TH transport and metabolism**

Recent work in rodents has demonstrated placental compensation mechanisms in case of maternal TH deficiency to optimize TH provision towards the fetus. Placental OATP1C1 and MCT8 expression were upregulated in iodine-deficient hypothyroid pregnant rats compared to expression in their euthyroid counterparts. The hypothyroid rats showed decreased placental DIO3 mRNA expression and increased placental DIO2 mRNA expression [34]. In complicated human pregnancies, there are some indications of placental compensation mechanisms, although data are scarce and sometimes conflicting. This is due to the heterogeneity in study populations, relatively small samples and technical difficulties in studying this complex phenomenon (Table 1). Opposite results were reported considering MCT8 expression. MCT8 mRNA expression was increased in severe intrauterine growth restriction (IUGR) resulting in early delivery in one study, but could not be confirmed after increasing the sample. However, MCT8 protein expression was increased in IUGR in both studies [13, 35]. Data from IUGR placentas resulting in term birth compared with gestational-matched appropriately grown fetuses did not show any difference. However, in primary cultures of cytotrophoblasts, MCT8 protein expression was higher in IUGR compared with normal cytotrophoblasts [36]. Of note is that pregnancies with IUGR were only considered eligible for these studies in the absence of maternal hypertension, which might be a feature of abnormal placentation. Data on maternal or neonatal circulating TH levels were not available from these studies.

There are conflicting data about altered DIO regulation in complicated pregnancies. In one study, no difference was found in DIO2 and DIO3 mRNA expression and activity between placentas with IUGR and normal fetal growth [17]. Another study showed indications of loss of distribution of DIO3 activity across the placental bed in case of preeclampsia, together with low selenium levels in maternal and umbilical cord serum. There were no alterations in DIO2 and DIO3 mRNA expression

and enzyme activities in both preeclamptic and normal pregnancies were comparable. This study took maternal TH function at birth into account, but could not demonstrate differences between preeclamptic and normal pregnancies. It was hypothesized that low selenium, associated with preeclampsia, alters enzyme regulation [37]. Recently, we studied DIO2, DIO3, MCT8 and MCT10 gene and protein expression in placentas of complicated pregnancies ending either in spontaneous preterm birth or indicated preterm birth due to pregnancy-associated vascular complications. Both maternal and cord blood TH levels were available and histological early maturation of the placentas was assessed. In the indicated preterm birth group, the placentas showed histological signs of early maturation and there was increased DIO2 mRNA and MCT 10 protein expression, together with decreased DIO3 mRNA expression. Moreover, the mothers of the indicated preterm birth group had slightly increased circulating TSH levels at birth and their infants had increased cord blood T3 levels, compared to the spontaneous preterm birth group, while cord blood (f)T4 levels were comparable between both groups [38]. These findings suggest the presence of placental compensation mechanisms in case of chronic placental hypoxia in order to optimize TH provision to the fetus in stressed conditions. An adaptive function for DIO2 was also demonstrated in cultured human placental cells and *in-vivo* and *in-vitro* rodent tissues. A rise in DIO2 activity was demonstrated after 48 h incubation in TH-depleted medium. Addition of T4, T3 or rT3 reversed the increase in 8-24 hours in a dose-dependent way [39]. The underlying mechanisms are mainly studied in rodent brain: down-regulation of DIO2 mRNA expression, mediated by the nuclear T3 receptor with probably a negative T3 receptor-binding response element in the promoter region of this gene, and substrate-induced enzyme inactivation [40]. It is hypothetical to extrapolate these findings to DIO2 and DIO3 regulation in human placenta and it warrants further studies. In neonatal TH insufficiency, as well as in neonates with congenital hypothyroidism due to a total iodide organification defect or thyroid agenesis, substantial amounts of T4 were found in cord blood, indicating maternal transfer of TH during late gestation [41]. In a small subgroup of these patients, placental DIO2 and DIO3 activities were not significantly different from those in euthyroid neonates [19]. Remarkably, although T4 levels were considerably lower in this subgroup compared to the levels of euthyroid neonates, T3 concentrations were in the same range. Currently, one can only speculate about the underlying mechanisms.

Finally, in IUGR, there are also indications of altered TTR expression. Fruscalzo et al. showed by immunohistochemistry that in IUGR and severe preeclampsia, there was a much stronger placental TTR signal compared to controls. They hypothesized that placental hypoxia is cause of increased TTR expression in placentas from pregnancies complicated by IUGR and preeclampsia [42], although conflicting data exist [9].

**Placental compensatory mechanisms in thyroid hormone metabolism: is their contribution beneficial on the long term?**

Although histological and metabolic placental compensation mechanisms are present in hypoxic circumstances, which may strengthen the offspring's chance of survival in uncertain times [33, 38, 42], there is strong evidence that fetal development in these conditions, often resulting in preterm birth, is an important predetermining factor in the development of chronic diseases in later life, such as hypertension, decreased glucose tolerance, altered renal function and neuropsychiatric and behavioral disorders. Altered or arrested development, epigenetic modifications of key genes involved in development and physiological regulation and altered development of the microbiome cause altered perinatal programming in several organ systems, in particular the cardiovascular and metabolic system [43]. These mechanisms are potentially exaggerated by the administration of antenatal or postnatal glucocorticoids in condition of preterm birth. Moreover, in animal models of IUGR, upregulation of the glucocorticoid receptor results in altered stress responses [43]. After birth, glucocorticoids generally inhibit the thyroid function, but animal studies suggest that the effect may be in the reverse direction during embryonic and fetal development [2]. In sheep, maternal or fetal administration of glucocorticoids in late pregnancy increases circulating fetal T3 and reverse T3 concentrations, but not T4 concentrations[44, 45]. T3 has maturational effects on the fetus and it has been suggested that increased T3 availability may mediate some effects of antenatal glucocorticoid treatment [45]. Nevertheless, the maturational effects of glucocorticoids on the hypothalamic-pituitary- thyroid axis come at the cost of decreased proliferation and a possibly permanently reduced thyroid size and number of pituitary TSH-cells and long-term effects on the function of the offspring's hypothalamic-

pituitary- thyroid axis, as demonstrated in rat [46, 47]. In human, maternal smoking and high maternal BMI were associated with disturbed fetal thyroid gland development and endocrine functionin the second trimester of pregnancy [48] and alterations in thyroid hormone function in former very preterm infants at preschool age were documented[49]. It is hypothetical whether these structural and functional alterations are contributing to the development of chronic disease in later life. Further studies are required to investigate the underlying mechanisms and long term effects.

**Conclusion**

During the first half of pregnancy, the fetus depends entirely on maternal TH supply, which is indispensable for normal fetal development and requires an adequate functioning maternal TH system. In case of maternal thyroid insufficiency, there is an increased risk of on the one hand pregnancy complications, including preeclampsia and preterm birth and on the other hand neurocognitive deficits in the offspring. Conflicting data about human placental TH transfer in pregnancies complicated with utero-placental hypoxia exist. Nevertheless, preterm infants, born as result of a complicated pregnancy due to chronic utero-placental hypoxia, are more prone to the development of chronic diseases later in life. There are indications that chronic intra-uterine stress, as is the case in conditions of chronic intra-uterine hypoxia, is activating the TH system in both the placental and fetal compartments to accelerate fetal development. This comes probably at the cost of long-term effects on the function of the infants' hypothalamic-pituitary- thyroid axis. As far as we know, the impact of the accelerated development of the preterm infant in relation to his TH system and the long term health implications hasn't been studied. It remains important to further explore the underlying mechanisms, since this may provide more insight in the developmental origins of health and disease in later life.

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**Figure legends**

Figure 1: Interactions between the maternal, placental and fetal compartment to provide the fetus with sufficient thyroid hormones for development and induction of fetal thyroid hormone metabolism

A. Maternal thyroid hormone secretion is increased triggered by placental secreted human chorionic gonadotrophin.

B. Maternal thyroid hormones are transferred through the placenta by means of 6 different thyroid hormone transporters: monocarboxylate transporters 8 and 10, L-type amino acid transporters 1 and 2, organic anion transporting polypeptides 1A2 and 4A1. Deiodinases type 2 and type 3 are present in the placenta and play a role in tight regulation of thyroid hormone transfer towards the fetus. Four different thyroid- hormone-binding proteins are present in the placenta: transthyretin, albumin, α-1-antitrypsin, α-1-acid-glycoprotein.

C. In the first half of pregnancy, only maternal thyroid hormones are present in the fetal compartment. Brain and thyroid structures are developed and from mid-gestation there is fetal thyroid hormone secretion under impulse of hypothalamic-pituitary-thyroid axis stimulation. Thyroid hormones are transported to target tissues through several thyroid hormone transporters. In the first and second trimester, further activation of the active hormone T3 is limited by predominance of enzymatic sulfation through sulfotransferase activity and limited deiodinase type 1 activity. In the third trimester, in preparation of birth, these mechanisms are reversed.

TRH: thyrotropin-releasing hormone, TSH: thyroid-stimulating hormone, T4: thyroxine, T3: triiodothyronine, rT3: reverse triiodothyronine, T2: diiodothyronine, DIO1: type 1 deiodinase (activating and inactivating properties), DIO2: type 2 deiodinase (activating properties), DIO3: type 3 deiodinase (inactivating properties), MCT: monocarboxylate transporter, LAT: L-type amino acid transporter, OATP: organic anion transporting polypeptide, TR: thyroid hormone receptor.

Figure adapted from Forhead [50].

Figure 2: Tenney-Parker changes: signs of premature aging in chronic uteroplacental hypoxia

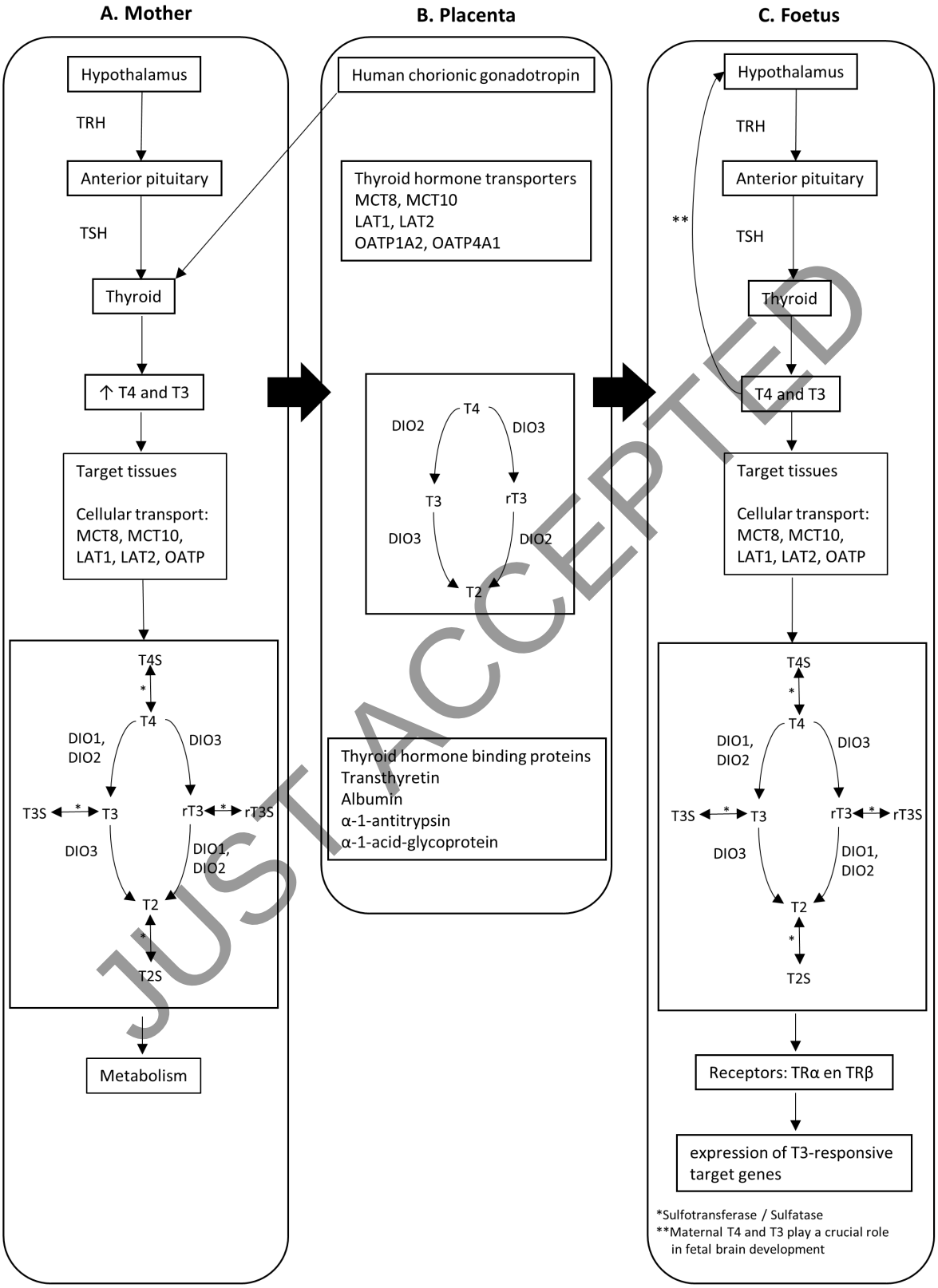
Hematoxylin & Eosin staining of placenta samples of 2 pregnancies ended at gestational age of 25 weeks. Pictures taken with enlargement x 10. Panel A: Premature placenta. Panel B: Signs of premature aging: Tenney-Parker changes. Compared to the premature placenta, the average area of the villi is smaller, reflecting increased villous branching. Syncitial knotting is present (arrows).

Table 1: Overview of TH-compensating mechanisms in human placentas

| Study | Study population | Study object and method | Number of patients | Results | Maternal and neonatal TH status |
|---|---|---|---|---|---|
| Chan (35) (2006) | IUGR placenta with GA-matched AGA placenta | MCT8 (q PCR, WB) | **AGA** 28-34 w GA: n=6 37-40 w GA: n=16 **IUGR** 26-32 w GA: n=6 37-38 w GA: n=4 | Increased MCT8 mRNA and protein expression in early-onset IUGR placenta | Unknown |
| Loubière (13) (2010) | IUGR* placenta compared with GA-matched AGA placenta | MCT8, MCT10, OATP1A2, OATP4A1, LAT1, LAT2, CD 98 (qPCR) | **AGA** 27-34 w GA: n=9 37-41 w GA: n=40 **IUGR** 25-32 w GA: n=17 37-38 w GA: n=5 | Increased MCT8 protein expression in early-onset IUGR placenta Decreased MCT10 mRNA expression in early-onset IUGR placenta | Unknown |
| Vasilopoulou (36) (2010) | Primary cultures of IUGR** and AGA cytotrophoblasts | MCT8 and MCT10 (qPCR and WB) | **AGA** > 35 w GA: n=27 **IUGR** > 35 w GA: n=14 | Increased MCT8 protein expression in IUGR cytotrophoblasts | Unknown |
| Chan (17) (2003) | IUGR placenta compared with AGA placenta | DIO2 and DIO3 (qPCR and specific DIO activity assays) | **AGA** 27-28 w GA: n=3 29-34 w GA: n=6 37-40 w GA: n=20 **IUGR:** 25-38 w GA: n=18 | No differences in DIO2 and DIO3 mRNA expression and activity | Unknown |
| Kurlak (37) (2013) | Preeclamptic pregnancies compared with normotensive term pregnancies | DIO2 and DIO3 (qPCR and specific deiodinase activity assays) | Placentas of preeclamptic pregnancies (n=23) and normotensive term pregnancies (n=27) | Maternal and cord blood selenium levels significant reduced in preeclampsia Loss of distribution of DIO3 activity across the placental bed in placentas of preeclamptic pregnancies | Cord blood TSH levels significantly higher in preeclampsia |
| Eerdekens (38) (2018) | Blood and placenta samples of complicated pregnancies ending in preterm delivery and healthy term controls | Maternal and cord blood TH levels, MCT8, MCT10, OATP1C1, DiO1, DIO2 and DIO3 gene and protein expression by PCR and WB; placental maturity scores | Spontaneous preterm birth: n=31 Indicated preterm birth due to pregnancy-associated vascular complication: n=45 Healthy term controls: n=41 | Decreased DIO3 gene expression, increased DIO2 gene and MCT10 protein expression and increased signs of placental premature aging in placentas of the indicated preterm birth group | Increased maternal TSH levels and increased cord blood T3 levels in the indicated preterm birth group |
| Fruscalzo (42) (2012) | Retrospective case-control study comparing placentas of pregnancies complicated with early-onset | TTR (immuno-histo-chemistry) | **Idiopathic IUGR**: n=4 **IUGR + preeclampsia**: n=4 **IUGR + preeclampsia + HELLP:** n=3 **Controls**: n=5 | Idiopathic IUGR and IUGR + preeclampsia: strong staining for TTR | Unknown |

| | | | | | |
|---|---|---|---|---|---|
| | IUGR with AGA placentas§ | | | | |
| Zhu (9) (2016) | Placental tissues from uncomplicated and preeclamptic pregnancies | TTR expression by immunohistochemistry and image analysis | 6-12 w GA: n=6<br>12-37 w GA: n=9<br>37-41 w GA: n=9 | The mean TTRoptical density of the syncytio-trophoblast layer of the severe preeclampsia group was lower than that of controls | Unknown |
| Kilby (22) (1998) | Fetal thyroid function and placental expression of TH receptors in IUGR and AGA pregnancies | fT4, fT3 and TSH in cord blood; TRα and TRβ (qPCR, WB and immuno-histo-chemistry) | **Blood samples:** 22-25 w GA: n=11<br>28-38 w GA: n=15 IUGR (24-35 w GA): n=15 **Placenta samples:** 7-12 w GA#: n=15<br>13-21 w GA#: n=11 27-41 w GA: n=10 | Increased immunostaining for TRα1, α2 and β1 in IUGR placenta | Decreased cord blood fT4 and fT3 levels in IUGR |

IUGR = intrauterine growth restriction; GA = gestational age; AGA = appropriate growth for gestational age; MCT = monocarboxylate transporter; LAT = system L amino acid transporter; OATP = organic-anion-transporting polypeptide; CD98 = LATs obligatory associated protein; w = weeks; PCR = polymerase chain reaction; TSH = thyroid-stimulating hormone; TTR = transthyretin; fT4 = free thyroxine, fT3 = free triiodothyronine; TR = thyroid hormone receptor, qPCR = quantitative real-time PCR; WB = Western Immune Blotting; TH = thyroid hormone; * IUGR defined in the absence of maternal hypertension; ** IUGR defined in the absence of maternal hypertension or thyroid disorders; § Controls all with isolated fetal malformations; # after surgical termination of pregnancy



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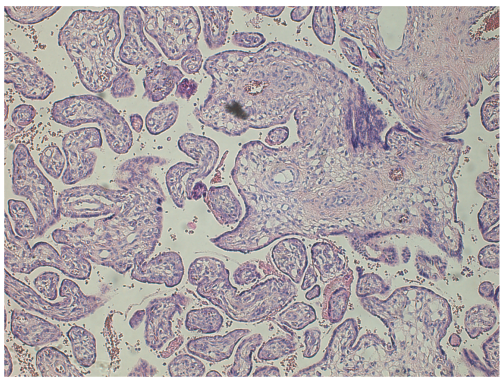

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