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Placental Transport of Thyroid Hormone and Iodide

Kerry Richard, Huika Li, Kelly A. Landers, Jatin Patel and Robin H. Mortimer
Royal Brisbane and Women's Hospital and The University of Queensland, Australia

1. Introduction

1.1 The thyroid gland

The major role of the thyroid is to synthesise and secrete thyroid hormones (TH). It does this by a complex process that begins with extraction of iodide from circulating blood via the sodium iodide symporter (NIS) (Dai, et al. 1996). Intracellular iodide is oxidised, under the influence of a thyroperoxidase leading to iodination of the amino acid tyrosine on the abundant thyroglobulin that occupies thyroid follicles. Iodinated tyrosines are combined to form thyroxine (4 iodine atoms, T_4) and triiodothyronine (3 iodine atoms, T_3). Both T_4 and T_3 are secreted from the thyroid gland and circulate bound to a family of thyroid binding proteins so that only a tiny fraction of T_4 and T_3 remain unbound (Benvenga 2005). T_4 is avidly taken up by liver and deiodinated by a type 1 deiodinase (D1) (Bianco, et al. 2002) to the biologically more active T_3 and the biologically inactive reverse T_3 (rT_3). Most circulating T_3 is of hepatic origin. T_4, and to a lesser extent T_3 feed back at the pituitary level. Intrapituitary T_4 is deiodinated to T_3 by a Type 2 deiodinase (D2) and this together with T_3 from the circulation inhibits synthesis and secretion of thyroid stimulating hormone (TSH), also known as thyrotropin (Shupnik, et al. 1985). TSH is a highly glycosylated protein with alpha and beta chains and is under the tonic control of the inhibitory hypothalamic hormone somatostatin (Weeke, et al. 1975) and the stimulatory thyrotropin releasing hormone (TRH) (Shupnik, et al. 1986). TSH via thyroid cell membrane TSH receptors stimulates iodide uptake (Levy, et al. 1997) and TH synthesis and secretion. Serum TH levels are controlled by the pituitary feedback mechanism.

1.2 Thyroxine (T_4)

The thyroid gland is the only known source of T_4 in the body (Chopra 1996). T_4 is the most abundant iodothyronine in the circulation, present at around twenty times the concentration of T_3, up to one hundred times more than rT_3 and more than one thousand times the concentration of any other iodothyronine derivative. Iodine constitutes about 65% (by weight) of the T_4 molecule and T_4 accounts for up to 90% of protein bound iodine in serum. The extent of overall protein binding is great, such that the serum free T_4 concentration is

usually less than 0.1% of total T_4 concentration. The major TH binding proteins are; thyroxine binding globulin (TBG), transthyretin (TTR) and albumin as well as several minor carriers. The less biologically active T_4 is largely deiodinated in peripheral tissues to the bioactive form of TH, T_3 (Figure 1). Alternatively, T_4 may be converted to the inactive metabolite, rT_3. Both T_3 and rT_3 can be further metabolised in peripheral tissues to 3,3'-diiodothyronine (T_2).

1.3 3,5,3'-triiodothyronine (T_3)

T_3 was first discovered in human serum in 1951 (Gross and Leblond 1951) and was found to be several times more biologically potent than T_4 in producing the classic effects of THs (Gershengorn, et al. 1979). T_3 is formed by the removal of an iodine atom, by deiodinase enzymes, from the phenolic ring of T_4 (Figure 1). Like T_4, T_3 in serum is bound to TBG, TTR and albumin. As indicated above the main source of T_3 is peripheral conversion from T_4 in addition to some limited direct thyroid gland secretion.

1.4 3,3',5'-triiodothyronine (rT_3)

Reverse T_3 (rT_3) differs from T_3 in that iodine is removed from the inner or tyrosyl ring of T_4 rather than the outer or phenolic ring (Chopra 1996) (Figure 1). rT_3 was first found in the blood of rats in 1956, it has little or no activity when administered to animals and its metabolism is extremely rapid. The main source of rT_3 is inner-ring deiodination of T_4 in peripheral tissue, predominantly liver (Chopra, et al. 1975).

1.5 other thyronine derivatives

Besides T_4, T_3 and rT_3 several other thyronine derivatives are found in serum. These include three diiodothyronines (3,3'-T_2, 3',5-T_2 and 3',5'-T_2), two monoiodothyronines (3'-T_1 and 3-T_1) and two acetic acid analogues of T_4 (tetrac) and T_3 (triac) as well as the sulfate and glucuronide conjugates of T_4, T_3 and rT_3. Sulfate conjugates of iodothyronines are more actively deiodinated than the parent iodothyronine and sulfated T_3 loses its affinity for the thyroid receptor (Visser 1994).

1.6 Thyroid hormone receptors

Thyroid hormones act by binding to specific nuclear receptors that interact with DNA causing activation or repression of transcription (Tata and Widnell 1966). In the 1960s it was noted that nuclear RNA transcription preceded many of the physiological effects of T_3 and this led to the discovery of high affinity nuclear receptors for T_3 (Oppenheimer, et al. 1972; Samuels and Tsai 1973). The cloning from many species of multiple cDNAs encoding proteins with the characteristics of TH receptors (TR) brought about the realisation that there is a family of TRs (Evans 1988). These have molecular weights of 50 to 55kDa and bind T_3 with high affinities (Sap, et al. 1986; Weinberger, et al. 1986). The TR isoforms have substantial amino acid sequence homology with the steroid hormone receptors (Evans 1988). Levels of nuclear TRs correlate well with the developmental and tissue specific effects of T_3 (Chan, et al. 2002).

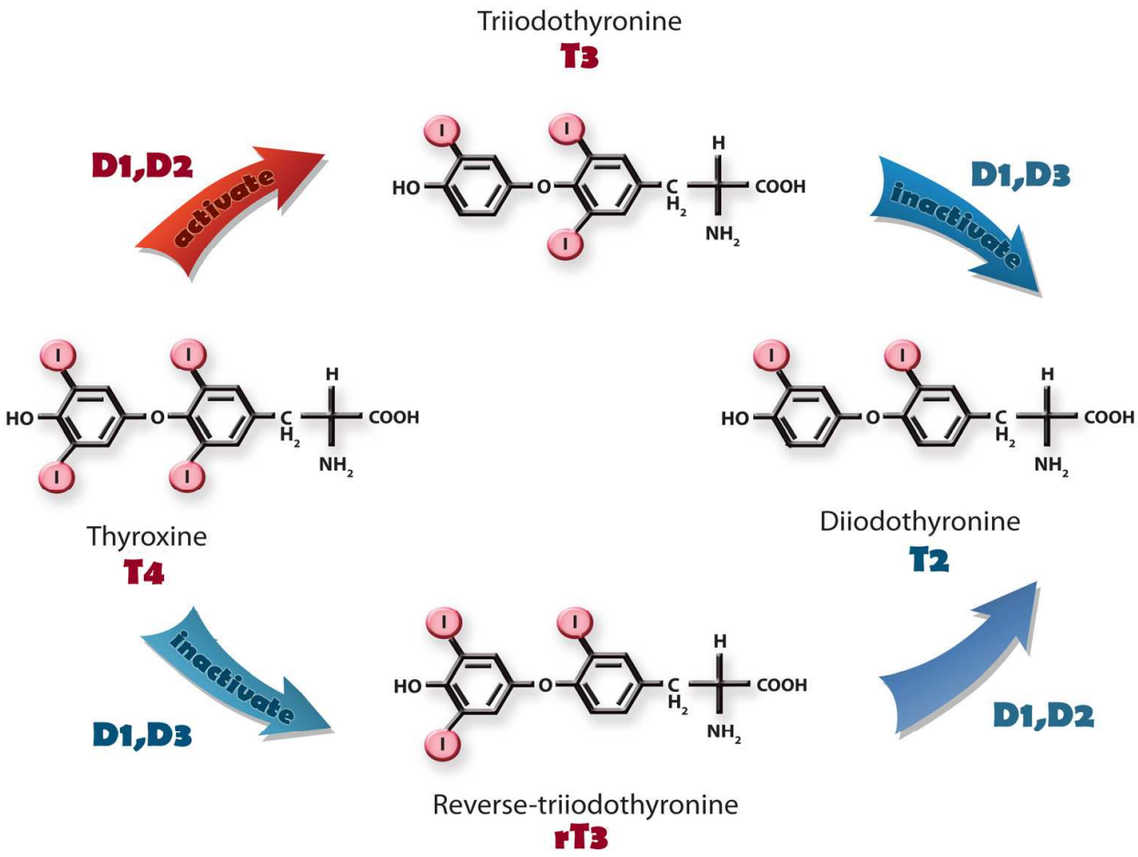

Fig. 1. Deiodination pathways of the thyroid hormones. D1, Deiodinase Type 1; D2, Deiodinase Type 2; D3, Deiodinase Type 3

2. Thyroid hormone and iodide are required for normal fetal development

2.1 Mild maternal thyroid dysfunction and impaired neuro-cognitive function in the offspring

There is now ample evidence that even mild maternal hypothyroidism is associated with impaired fetal neuro-cognitive outcome. World wide, the most common cause of maternal hypothyroidism is iodine deficiency (Andersson, et al. 2010; Pharoah and Connolly 1991). Severe iodine deficiency is well known to cause severe mental retardation, neuro-muscular impairment and short stature, a syndrome known as cretinism. While cretinism was described hundreds of years ago, the link between milder degrees of iodine deficiency and reduced intelligence of the offspring was first described described in the Himalayas in the early 20th century. Subsequent work in the highlands of Papua New Guinea by Pharoah confirmed the link between milder degrees of iodine deficiency and reduced neuro-cognitive function and provided evidence of correlations between reduced maternal T_4 (but not T_3) levels and reduced intelligence and coordination (Pharoah and Connolly 1991). A small, more recent Italian study (Vermiglio, et al. 2004) confirmed reduced IQ levels and a high incidence of attention deficit disorder in offspring of women from an area of moderate iodine deficiency. There was a strong inverse correlation between maternal mid gestation

free T_4 (FT_4) and offspring IQ. A Spanish study emphasised the importance of early iodine supplementation in preventing neurological damage (Berbel, et al. 2009).

A link between mild maternal hypothyroidism and impaired intellectual development of offspring was suggested in the 1960s. Over several years, from the late 1960s to the 1970s Man and co-workers published data from 1349 women whose serum T_4 was estimated by measuring butanol-extractable iodine during early and late pregnancy (Man, et al. 1991); three percent were hypothyroxinemic. Developmental and intellectual outcomes of progeny of 210 euthyroxinemic women, 15 hypothyroxinemic women adequately treated with thyroxine and 21 women inadequately treated with T_4 were compared at eight months, four and seven years of age. Mothers were well matched for intelligence, years of education and chronological age. At each age children of mothers with inadequately treated hypothyroidism had lower mean developmental and intellectual scores.

Subsequent studies using more precise measurements of TH status have yielded similar results. Haddow and co-workers (Haddow 1999) measured TSH levels in stored blood taken from over 25,000 pregnant women. Seventy-five women (0.3%) had levels at or above the 99.7th percentile; 47 were contacted and agreed to allow neuropsychological testing of their children at seven to nine years of age. Children of an additional 15 women with serum TSH levels between the 98th and 99.6th percentiles were also tested; 77 % of these 62 women had positive thyroid antibodies (markers of potential autoimmune thyroid disease). Results were compared with those of 124 women with normal thyroid function (14% of whom had positive antithyroid antibodies) and demonstrated significantly ($p=0.06$) reduced full-scale IQ scores, reduced verbal IQ scores ($p=0.06$) and word discrimination ($p=0.01$).

Children of women with normal thyroid stimulating hormone (TSH) levels but FT_4 levels less than the 10th percentile during early pregnancy (i.e. technically normal thyroid function) had significantly lower Bayley Psychomotor Development Index scores at ten months of age than children of women with higher FT_4 levels. Mothers with FT_4 levels below the 10th percentile had a significantly higher incidence of positive antithyroid antibodies (Pop, et al. 1999).

These, and other (Ghassabian, et al. 2011; Klein, et al. 2001; Kooistra, et al. 2006; Li, et al. 2010), clinical studies provide strong evidence of a relationship between reduced or low normal early pregnancy FT_4 levels and neuro-cognitive functioning of offspring. This relationship holds whether maternal thyroid dysfunction results from iodine deficiency or autoimmune thyroid disease. These findings suggest that maternal thyroxine is required for early fetal brain development and that maternal TH crosses the placental barrier.

2.2 Maternal hypothyroxinemia

Under normal circumstances maternal FT_4 levels rise in the mid first trimester in response to a surge in maternal human chorionic gonadotropin (hCG) levels (Fisher 1983) (Figure 2). HCG is a double chain glycosylated protein secreted by placenta from early pregnancy that shares a common alpha subunit with TSH. The beta subunits of each hormone and their cell membrane receptors are also significantly homologous. HCG stimulates the normal maternal thyroid via the TSH receptor to synthesise and secrete TH. Very high hCG levels as are seen in women with excessive pregnancy induced vomiting (hyperemesis) and women with placental malignancy (choriocarcinoma) can cause maternal hyperthyroidism. As

normal pregnancy progresses hCG levels fall and this is reflected in falling FT_4 levels (Figure 2). Impairment of maternal TH secreting capacity from iodine deficiency or autoimmune thyroid disease can blunt the physiological first trimester surge in maternal TH secretion, or if more severe can result in maternal hypothyroidism.

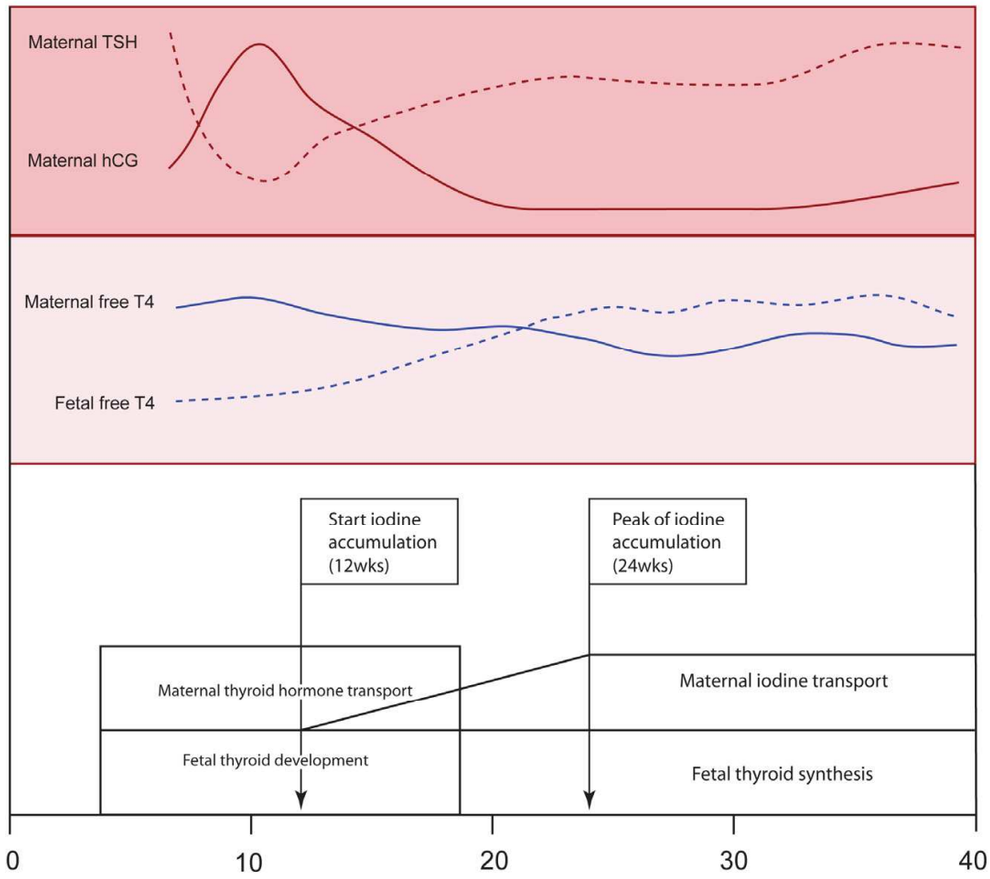

Fig. 2. Ontogenic changes in maternal and fetal thyroid gland and hormone function (compiled with data from (Fisher 1983; Fuse 1996)). hCG, human chorionic gonadotropin; TSH, thyroid stimulating hormone/thyrotropin; T_4, thyroxine.

Mild iodine deficiency is prevalent in many parts of the world, including some European countries, the USA and Australia and as discussed above is a common cause of maternal hypothyroxinemia. Iodine deficiency can be exacerbated by maternal smoking, which increases blood thiocyanate levels. Thiocyanate competitively blocks the sodium iodide cell membrane symporter (NIS) responsible for transfer of iodide into maternal and fetal thyroid and for materno-fetal transfer of iodide by the placenta (Manley, et al. 2005) . Thyroid autoimmunity is common in pregnant women. Autoimmune thyroid disease (AITD) is associated with autoantibodies to thyroperoxidase (TPO). This enzyme oxidises iodine in the presence of hydrogen peroxide, facilitating iodination of tyrosine and synthesis of TH. Enzyme activity is blocked by anti-TPO autoantibodies. About 10% of pregnant women have positive anti-thyroperoxidase antibodies at 14 weeks gestation and about 2.5% have asymptomatic hypothyroidism (Lazarus 2005).

2.3 Ontogeny of the human fetal hypothalamic-pituitary-thyroid axis

The thyroid gland is the first endocrine organ to develop in man where it originates as a thickening in tissue destined to become the tongue (Fuse 1996). This bud descends to the level of the larynx, forming two lobes connected by an isthmus. Recognisable thyrocytes are present by the end of 7 weeks gestation but mature thyroid follicles containing colloid do not appear until after 13.5 weeks gestation. The fetal thyroid appears to be able to accumulate iodine by about 12 weeks gestation (Figure 2). Iodine concentrating capacity increases from about 12 weeks, reaching a peak at about 24 weeks gestation. T_4 is synthesised by about 19 weeks gestation (Fuse 1996) (Figure 2).

The pituitary gland has two separate origins, the glandular component (appearing in the developing mouth at about 3 weeks gestation) and the neural primordium (extending from the hypothalamus about 5.5 weeks). The glandular primordium forms Rathke's Pouch, which loses its connection with the oral cavity by about 8.5 weeks. This adenohypophyseal primordium forms the anterior pituitary and forms a close association with the developing neural structure forming the neurohypophysis. Cells staining for the alpha subunit of TSH can be seen from 8-12 weeks gestation. The beta subunit can be identified by 13-15 weeks gestation. Immunoreactive TSH can be identified in fetal serum by 12 weeks gestation but levels are low until a rapid increase at 18-22 weeks.

These data suggest that while the fetal thyroid can concentrate iodine and synthesise TH in the late first trimester. TSH regulated TH secretion may not occur until as late as 18-20 weeks gestation (Figure 2).

2.4 Feto-maternal transfer of iodide and thyroid hormones

2.4.1 Iodide

Detectable iodine in the amniotic fluid of pregnant rabbits fed potassium iodide was reported in 1859 and in 1872 similar results were reported in man (quoted by (Gersten 1954). Transfer of radioiodine from the maternal to fetal circulations of the guinea pig was reported in 1955 (Logothetopoulos and Scott 1955) who noted that transport was blocked by sodium thiocyanate, suggesting an active transport process. In thyroid iodide is transferred from blood to the thyroid cell by the sodium iodide symporter (NIS) and iodide efflux from the thyrocyte is mediated by another transporter called Pendrin. NIS (Bidart, et al. 2000; Mitchell, et al. 2001) and Pendrin (Bidart et al. 2000) have been reported in trophoblasts and functional studies in a trophoblast cell line suggest that these are responsible for iodide influx and efflux in placenta (Manley et al. 2005). Sodium thiocyanate is a powerful inhibitor of NIS. Recently SLC5A6, a placental sodium/multivitamin transporter has been identified as an iodide transporter (de Carvalho and Quick 2011) but its role in placental iodide transfer is as yet unclear.

2.4.2 Thyroid hormone

Early human studies suggested that there was significant materno-fetal transfer of TH (Raiti, et al. 1967) and this was supported by detection of significant amounts of TH in cord blood of infants unable to synthesise TH (Vulsma, et al. 1989). Investigation of transfer of T_4 in the isolated perfused human placenta demonstrated that the abundant type 3 deiodinase (D3)

significantly limited transfer so that the fetal circuit T_4 reached only 0.008% of maternal levels. Inhibition of D3 by iopanoic acid increased fetal T_4 levels to 30% of those in the maternal circuit (Mortimer, et al. 1996). Membrane TH transporters were demonstrated in human trophoblasts and choriocarcinoma cell lines (Mitchell, et al. 1992) mediating uptake and efflux of TH. The identities of these transporters were subsequently ascertained.

There is now clear evidence of THs in fetal serum, coelomic and amniotic fluid and brain in early pregnancy, a time when the fetal thyroid gland has not yet developed the capacity to secrete TH (Calvo, et al. 2002). These studies were done in human tissues obtained from fetuses as early as 5-6 weeks gestation. The early feto-placental unit (up to 12-13 weeks gestation) consists of the fetus floating in amniotic fluid (AF) within an amniotic sac. This in turn is contained within an exocoelomic cavity containing coelomic fluid (CF) in which floats a prominent secondary yolk sac. The yolk sac, an extension of the fetal gastrointestinal tract and circulation, secretes and resorbs a variety of proteins. The CF is contained within a uterus lined by the early placenta. The early placenta is poorly vascularised, relatively hypoxic and covers the surface of the chorionic sac. The CF is protein rich, containing albumin and TTR whereas AF is essentially a low protein ultrafiltrate of maternal serum containing placental and yolk sac secretory products. Its volume is increased by urine secreted by the developing fetal kidneys.

With increasing gestational age, the yolk sac and the majority of the placenta regress and the exocoelomic cavity is largely obliterated by an expanding amniotic sac. The placenta forms a circumscribed disc-like structure and trophoblasts, the epithelial cells that mediate materno-fetal exchange, invade the uterine vasculature. This allows development of a mature maternal and fetal circulation within the placenta and a rise in placental oxygen levels. There is increasing evidence that the changing oxygen levels within the developing placenta have major effects on trophoblast function (Patel, et al. 2010b).

Human studies have provided considerable insight into TH levels in fetal serum (FS), CF and AF. It is clear that maternal TH crosses the placenta, entering the human embryonic cavities and fetal blood well before the fetal thyroid is secreting its own TH (Calvo et al. 2002; Contempre B 1993) (Figure 3). Total T_4 was detectable in several sets of CF fluid obtained between 5.8 and 11 weeks gestation, with set means ranging from 950 to 1280 pmol/litre. Total T_3 levels were very much lower (2.50 to 2.82 pmol/litre). rT_3 levels were high, ranging from 2.1 to 5.48 nmol/liter. T_4, T_3 and rT_3 were also found in AF sampled from 8 weeks on. Total T_4 ranged from 63 to 2041 pmol/litre, whereas total T_3 was 6 to 12 pmol/litre. rT_3 levels were again relatively high at 210 to 3430 pmol/litre. The high ratios of rT_3 to T_4 suggest active Type 3 deiodination (see below). The yolk sac synthesises and secretes the T_4 binding protein TTR and low levels of TTR were detected in CF from 7 weeks gestation, increasing with increasing gestational age. Mean free T_4 levels of 2.5 to 2.82 pmol/litre could be estimated in CF. Mean FT_4 in AF ranged from 6.45 to 20.43 pmol/litre.

These TH levels, expressed as a percentage of corresponding maternal levels in early pregnancy, are shown in Figure 3. Although fetal total T_4 is only about 5% of maternal levels and CF and AF levels are less than 1% of maternal values, free T_4 levels are much higher (approaching maternal levels) in these compartments due to very low TBG levels (Calvo et al. 2002).

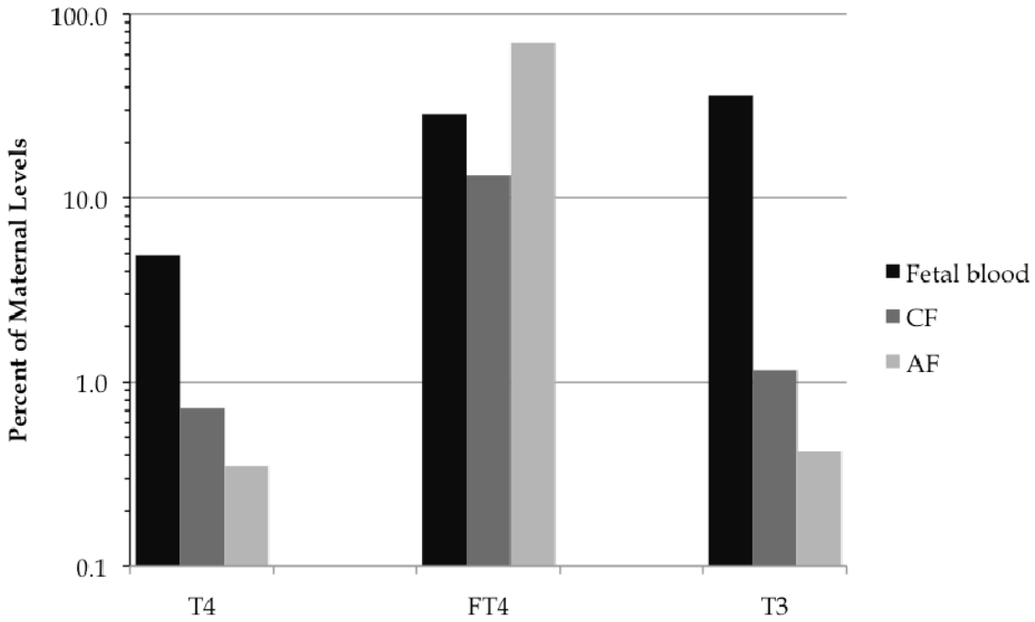

Fig. 3. Levels of total and free T_4 and total T_3 in first trimester fetal blood, coelomic (CF) and amniotic (AF) fluids as a percentage of maternal levels in the first trimester. (Data from (Calvo et al. 2002)).

Maternal T_4 and FT_4 levels increase during the first and second trimester. T_4 levels in CF correlate with those in maternal serum and in the second trimester fetal blood levels also correlate with maternal values. Interestingly T_3 and free T_3 levels in CF do not correlate with maternal levels (Calvo et al. 2002). These data strongly argue for significant transfer of maternal THs to the coelomic and amniotic fluids and into the fetal circulation. The significant gradient of total T_4 from maternal to fetal circulations and high levels of rT_3 in CF and AH suggest that active conversion of T_4 to rT_3 by D3 in placenta, placental membranes and the fetus strongly modulates fetal T_4 supply. Despite this fetal T_4 levels are strongly determined by maternal levels.

There is also strong clinical evidence that, at least in the presence of a hypothyroid fetus, transfer of maternal T_4 to the fetus continues throughout pregnancy. In 1989 Vulsma and colleagues reported that cord blood T_4 levels from infants with complete thyroid agenesis or a complete defect in organification of iodine and capacity to synthesise TH had T_4 levels of 30 – 75 nmol/liter, which must have been of maternal origin (Vulsma et al. 1989). Placental D3 levels appear normal in these infants (Koopdonk-Kool, et al. 1996).

2.5 Thyroid hormone and development of the fetal brain

Although fetal serum T_3 levels are very low at that time, T_3 and TH receptors have been identified in human fetal brain as early as 9 weeks gestation (Bernal and Pekonen 1984; Chan et al. 2002). Brain T_3 is locally produced by Type 2 deiodination of T_4 and rat studies indicate that brain T_3 in the hypothyroid rat fetus cannot be replenished by maternal T_3 administration but requires maternal T_4. T_4 enters brain via the cerebral circulation but a significant proportion also appears to be transferred through the choroid plexus, a potent source of cerebro-spinal fluid (CSF) transthyretin (TTR). TTR represents about 20% of CSF

protein and is the major TH transporter in CSF. Membrane TH transporters, notably monocarboxylate transporter (MCT) 8, are important mediators of neuronal T_3 uptake. Intracellular T_3 is translocated to the cell nucleus where it binds to TRs and, following homodimerisation or heterodimerisation with retinoic acid receptors, it binds to TH response elements present in many genes, positively or negatively regulating them. T_3 has major effects on neurogenesis, cell migration and myelination in the developing brain (Patel, et al. 2011).

3. Placental regulation of thyroid hormone transfer

3.1 Iodothyronine deiodinases

The deiodinases play an important role in coordinating TH action during vertebrate development and they regulate TH action within selected tissues during development and adulthood. Three deiodinases have been identified, deiodinase type 1 (D1), deiodinase type 2 (D2) and deiodinase type 3 (D3), and all are integral membrane proteins and are selenoenzymes that have regions of high homology surrounding the selenocysteine residue at the active site (Bianco and Larsen 2005). Interestingly, the deiodinases differ in tissue distribution, substrate specificities, catalytic profile, physiological functions and regulation. Of the three deiodinating enzymes, only D2 and D3 have been identified in the placenta (Koopdonk-Kool et al. 1996). Placental D3 activity is much greater (~200 times in first trimester and ~400 times at term) than D2 activity, however the activity and expression of both D2 and D3 falls as gestation progresses (Chan, et al. 2003; Koopdonk-Kool et al. 1996; Stulp, et al. 1998). D2 is an outer ring deiodinase (Nelson, et al.) found primarily in brain, pituitary, brown adipose tissue, thyroid and placenta with a preference for $T_4 > rT_3$ as a substrate (Figure 1). D2 converts the biologically inactive T_4 to the active T_3. Conversely, D3 catalyses inner ring deiodination (IRD) of T_4 and T_3 and is mainly present in placenta, brain and skin with T_3 being the preferred substrate over T_4 (Figure 1) (Gereben, et al. 2008). D3 inactivates T_3 to T_2 or T_4 to rT_3. T_2 and rT_3 were previously considered inactive metabolites because they do not bind TH receptors, however more recently rT_3 has been implicated in actin polymerisation (Farwell, et al. 2005) and T_2 in stimulation of mitochondrial respiration (O'Reilly and Murphy 1992).

D2 and D3 have been found to be present in the placenta throughout gestation (Chan et al. 2003). D2 has been localised to the villous cytotrophoblasts cells in the first trimester with expression in villous syncytiotrophoblasts (ST) variable and weak. In contrast, D3 has been localised to the villous ST cells and syncytial sprouts with expression in villous CTs focal and weak. In the third trimester villous ST expressed D2 and D3, whilst villous CTs were stronger for D2 than D3 (Chan et al. 2003). The localisation of the deiodinases suggests that they may regulate the amount of maternal TH reaching fetal circulation. D3 localised to the villous ST layer, which is in direct contact with the maternal circulation can protect the fetus from excessive maternal TH.

3.2 Placental TH membrane transporters

TH membrane transporters mediate cellular uptake and efflux of TH (Hennemann, et al. 2001; Visser, et al. 2008). Trophoblast membrane transport of TH was first reported in 1992 by Mitchell et al, using the human placenta choriocarcinoma cell line, JAR (Mitchell et al.

1992). Since this time significant findings in placental TH transporters have been made. TH transporters identified in the human placenta to date include the monocarboxylate transporters MCT8 (Chan, et al. 2006) & MCT10 (Friesema, et al. 2008), L-type amino acid transporters LAT1 (Okamoto, et al. 2002) and LAT2 (Park, et al. 2005) and organic anion transporting polypeptides OATP1A2 (Patel, et al. 2003) and OATP4A1 (Patel et al. 2003) (Sato, et al. 2003). However, their individual contribution to placental TH transport has yet to be elucidated.

3.2.1 MCT8 & MCT10

Freisema et al identified MCT8 as a TH transporter with a preference for T_3 over T_4 (Friesema, et al. 2003). Both MCT8 and MCT10 mRNAs have been identified in placenta however it is only recently that both mRNAs were identified in early human placenta (from 6 weeks gestation) and both increased in expression throughout pregnancy (Loubiere, et al. 2010). Immunohistochemical studies have localised MCT8 and MCT10 proteins to villous ST, CT and extra villous trophoblasts (EVTs) in first trimester placental tissue, with marked immunostaining of MCT10 in the CT layer (Chan et al. 2006; Loubiere et al. 2010). Both proteins localised to villous STs in term placental tissue.

3.2.2 OATP1A2 & OATP4A1

The expression of OATP1A2 and OATP4A1 in placenta and their ability to mediate transport of T_4, T_3 and rT_3 have implicated both proteins as TH transport mechanisms in the placenta (Patel et al. 2003; Sato et al. 2003). RT-PCR analysis revealed OATP1A2 mRNA increases in human placental tissue throughout gestation, whilst OATP4A1 decreases to mid-gestation followed by an increase towards term. Western blotting results suggest no significant change in both proteins throughout gestation.

OATP1A2 and OATP4A1 proteins have been localised to villous STs in the first trimester with OATP1A2 also found moderately strong in villous CT and extra villous trophoblasts (EVTs). In term tissue both proteins revealed diffuse, weak expression, with OATP4A1 preferentially localised to the apical surface in STs (Loubiere et al. 2010; Sato et al. 2003).

3.2.3 LAT1 & LAT2

LAT1 protein has been localised to the ST layer in placenta and LAT2 to the apical and basal membranes of ST at term (Hoeltzli and Smith 1989; Lewis, et al. 2007; Okamoto et al. 2002; Ritchie and Taylor 2001). Localisation of the proteins throughout gestation has yet to be elucidated. A more recent study of LAT1 mRNA expression in human placenta revealed that it increases with gestation, whilst LAT2 did not alter.

Considering in the first trimester STs are in direct contact with maternal blood, MCT8, OATP4A1 and LAT1 may be the key transporters for TH uptake from the maternal circulation as they are preferentially localised to the apical membrane of STs (Chan et al. 2006; Ritchie and Taylor 2001; Sato et al. 2003), whilst OATP4A1 and LAT2 may play more prominent roles later in gestation. TH membrane transporters in the placenta most likely act in concert to regulate the passage of TH transported from the maternal to the fetal circulation throughout gestation.

3.3 Placental TH binding proteins

Thyroid hormone is extremely hydrophobic and carried in serum bound to three hepatically secreted binding proteins, thyroxine binding globulin (TBG), transthyretin (TTR) and albumin (Schussler 2000). Previously our group has described the synthesis of the TH binding proteins TTR and albumin by human placenta (McKinnon, et al. 2005).

3.3.1 Transthyretin (TTR)

Studies have reported high levels of TTR in fetal serum as early as 13 wks gestation (Fryer, et al. 1993) and considering little TTR mRNA is detectable in fetal liver at this time (Jacobsson 1989) we propose that the fetal TTR present may be of placental origin. Using placental explants and the choriocarcinoma cell line JEG3, we demonstrated that TTR was not only synthesised (McKinnon et al. 2005) but also secreted mainly through the apical cell membrane of these cells (Landers, et al. 2009).

We have also shown internalisation of TTR by placental explants and JEG3 cells which increased in the presence of T_4 (Landers et al. 2009). This increased internalization occurred under TTR: T4 ratios that favoured TTR tetramer formation (Landers et al. 2009) Similar increases have been described in astrocytoma cells (Divino and Schussler 1990b). Cross-linking studies of TTR bound to ^{125}I-T_4 suggest that TTR-T_4 is internalised by JEG3 cells as a TTR-T_4 complex. However, further research is required to confirm this finding and elucidate the mechanisms by which TTR or TTR-T_4 is internalised by the placenta. The protective role of TTR was postulated when binding of TTR to T_4 in placental cytosol was inhibited by addition of mefanamic acid, resulting in an increase in T_4 deiodination as determined by HPLC (McKinnon et al. 2005). The exact mechanisms of this are yet to be confirmed. TTR internalisation has previously been observed in ependymoma cells (Kuchler-Bopp, et al. 2000), chicken oocytes (Vieira, et al. 1995) and kidney proximal tubules (Sousa, et al. 2000) via megalin-mediated endocytosis. Receptor-mediated uptake of TTR was first described in HepG2 cells, primary rat hepatocytes, renal adenocarcinoma cells, neuroblastoma and transformed lung cells (Divino and Schussler 1990a). Similarly apical secretion of TTR has been described in the choroid plexus (Dickson 1986) and retinal pigment epithelium (Jaworowski, et al. 1995). Apical secretion of TTR by trophoblast cells into what would be the maternal circulation would increase local serum TTR concentrations at the surface of trophoblast cells. We propose that this would result in increased binding of maternal T_4 to placental TTR where TTR may serve to protect T_4 from deiodination and deliver T_4 or the TTR-T_4 complex to trophoblast cells of the placenta for eventual delivery to fetal circulation.

Many chemicals, including a variety of environmental pollutants, bind to TTR and displace T_4. These agents can cross the placenta and interfere with fetal thyroid function (Koopman-Esseboom, et al. 1994). Their role in interfering with TTR TH transfer is however yet to be investigated.

3.3.2 Albumin

There is an abundance of albumin during human pregnancy that comes into direct contact with the trophoblast cell layer. Early studies have demonstrated that maternal albumin is internalised by placental explants and in the syncytiotrophoblast layer the protein is either apically recycled into the maternal circulation or degraded (Lambot, et al. 2006). The exact role albumin plays at the trophoblast surface remains unclear and requires further investigation

particularly in first trimester tissue and in the presence of TH. Furthermore, the fate of albumin synthesized by placenta (McKinnon et al. 2005) is also of interest as, like TTR, it may also play a protective role for TH and aid in the transport of TH to fetal circulation.

4. Placental regulation of Iodide transport

4.1 Iodide transporters

It has been long recognised that maternal iodide crosses the placenta to the fetal circulation (Logothetopoulos and Scott 1956). Two transporters carry out placental iodide transport from the maternal to the fetal circulation: the sodium-iodide symporter (NIS) and Pendrin. Both transporters were first described in thyroid (Dai et al. 1996) followed by placenta (Mitchell et al. 2001) and kidney (Spitzweg, et al. 2001). NIS is a membrane-bound glycoprotein and the fifth member of the solute carrier family (SLC5A5)(Dohan, et al. 2003). As its name suggests, NIS simultaneously takes up two Na+ and one I^- ion from extracellular fluid (i.e. blood) into cells (Figure 4). This process is an active transport powered by the sodium gradient across the cell membrane generated by sodium potassium pumps, (Na+/K+ ATPase). Pendrin is an anion exchanger, encoded by the Pendred syndrome gene (PDS) (Manley et al. 2005; Royaux, et al. 2001; Scott and Karniski 2000) activated by high concentration of intracellular iodide (Yoshida, et al. 2004). Pendrin activity is dependent on NIS transporting iodide into the cells (Figure 4).

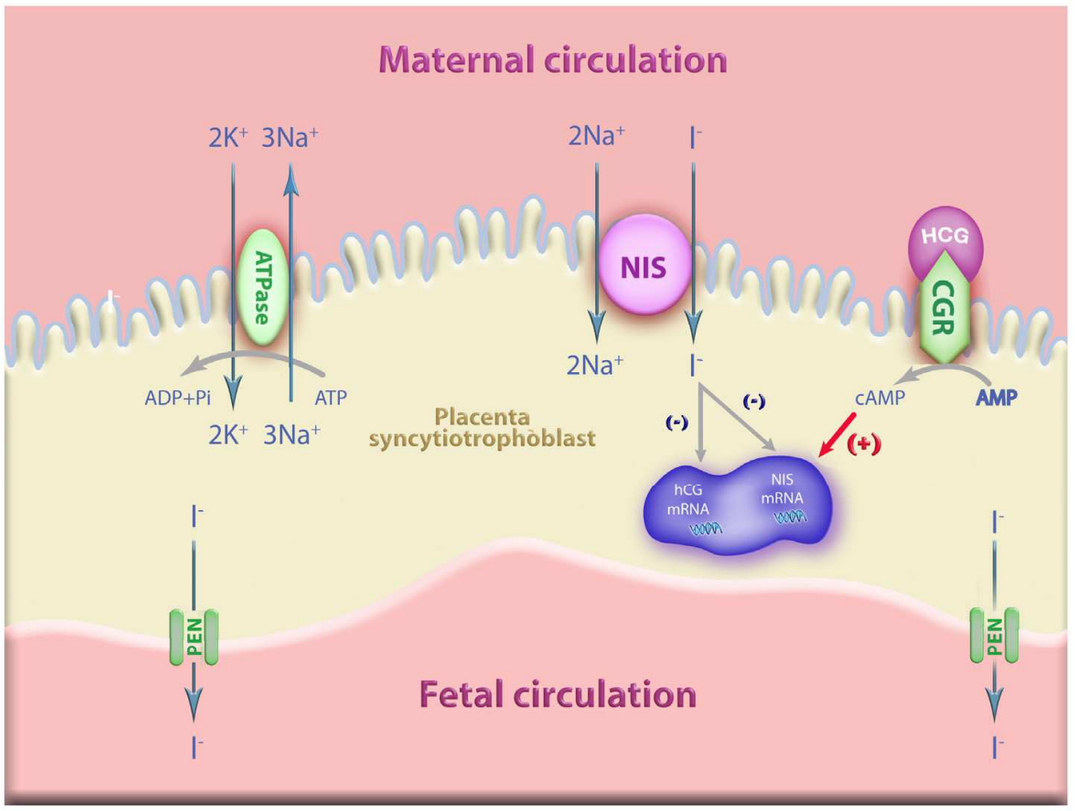

Fig. 4. Regulation of iodide transport across placental syncytiotrophoblast. NIS, sodium iodide symporter; PEN, Pendrin; hCG, human chorionic gonadotropin; CGR, chorionic gonadotropin receptor.

The physiological functions of these two transporters are similar in placenta and thyroid. In thyroid gland, NIS is localised at the basal membrane of thyrocytes and takes up iodide from the blood stream into the cells (Caillou, et al. 1998; Castro, et al. 1999; Dai et al. 1996; Royaux, et al. 2000; Yoshida, et al. 2002). Pendrin is expressed on the apical membrane of thyrocytes and releases iodide into thyroid follicles for TH synthesis (Dohan and Carrasco 2003; Mian, et al. 2001; Spitzweg, et al. 2000). In placenta, NIS is localised to the apical membrane (maternal side) of syncytiotrophoblasts, which directly contacts with maternal blood and influxes iodide into the cells (Figure 4). Conversely, Pendrin is located in the basal membrane (fetal side) of syncytiotrophoblasts and effluxes iodide into the extracellular space (Bidart et al. 2000; Manley et al. 2005; Mitchell et al. 2001). Mutations of NIS have been found in patients previously found to have congenital hypothyroidism due to an iodide transport defect. Some of these NIS mutations have been confirmed to cause failure of membrane targeting (Kosugi, et al. 1999; Kosugi, et al. 1998; Matsuda and Kosugi 1997; Pohlenz, et al. 2000). Pendred syndrome, a recessively inherited disorder causing congenital deafness and thyroid goitre is caused by a genetic defect in the PDS gene (Everett, et al. 1997; Kopp, et al. 1999; Royaux et al. 2000; Taylor, et al. 2002).

4.2 Cell model for study of placental iodide transport

During development of the human placenta, cytotrophoblasts fuse to form multinucleated syncytiotrophoblasts that form the surface of the placental villi and are directly bathed in maternal blood. Syncytiotrophoblast cells conduct maternal-fetal nutrient and gas exchange and have a distinct endocrine function to produce and secrete pregnancy hormones such as hCG and placental lactogen. BeWo cells are a human trophoblast-derived choriocarcinoma cell line that shares many features with primary trophoblasts in culture. They form a well-differentiated monolayer, undergo syncytialization and, secrete hCG (Bode, et al. 2006; Liu, et al. 1997; Sullivan 2004). They have been used widely in placental transport studies, e.g. glucose (Antony, et al. 2007; Araujo, et al. 2008; Baumann, et al. 2007; Di Simone, et al. 2009; Mark and Waddell 2006), amino acid (Jones, et al. 2006a, b; Novak, et al. 2006), iron (Danzeisen and McArdle 1998; Gambling, et al. 2001), fatty acid (Johnsen, et al. 2009; Tobin, et al. 2009), and drug and toxicity studies (Araujo, et al. 2009; Hirano, et al. 2008; Magnarin, et al. 2008; Prouillac, et al. 2009). BeWo cells express both of the iodide transporters, NIS and Pendrin (Manley et al. 2005). NIS proteins are located in the apical membrane of polarized BeWo cells while Pendrin is located to the basolateral membrane. BeWo cells demonstrate significant uptake and efflux of iodide, with kinetic and inhibitory characteristics consistent with these transporters (Li, et al. 2007; Manley et al. 2005). The human JAr placental choriocarcinoma cell line has also been used in iodide transport studies but radio-labelled iodide (I^{125}) uptake was dependent on the presence of exogenous hCG in the culture medium (Arturi, et al. 2002a) limiting their use in many studies. The JEG-3 cell line also expresses both NIS and Pendrin, however JEG-3 cells do not take up measureable amounts of I^{125}, even after hCG treatment, since the NIS protein is not localized to the apical membrane (unpublished observation). Primary trophoblasts and placental explant cultures might appear to be the ideal model for iodide transport studies, but due to variations in sample quality and low NIS expression their use is limited. Clearly, BeWo cells possess the physiological properties required and are the best cell model for studies of iodide transport.

4.3 Regulation of placental iodide transport

In thyroid follicular cells, NIS is regulated by serum levels of the pituitary derived TSH (Ajjan, et al. 1998; Kogai, et al. 1997; Saito, et al. 1997). However, unlike thyroid, placental syncytiotrophoblasts not only express NIS but also produce hCG. NIS expression and iodide uptake is increased in Jar cells exposed to hCG, and withdrawing hCG from the culture medium, leads to decreased NIS expression and iodide uptake (Arturi et al. 2002a). In BeWo cells NIS mRNA and membrane protein is up-regulated by hCG, and is accompanied by increased levels of iodide uptake (Li et al. 2007). Clearly hCG is an important regulator of placental iodide transport. In thyroid, hCG can stimulate NIS expression, subsequently increasing iodide uptake and TH synthesis and secretion (Arturi, et al. 2002b; Kraiem, et al. 1994).

An inhibitory effect of excess iodide on iodide organification in the normal thyroid (Wolff-Chaikoff effect) was reported by Wolff and Chaikoff in 1949 (Wolff, et al. 1949). Following the discovery of NIS, persuasive evidence suggested that the inhibitory effect of iodide is associated with a decrease in NIS mRNA and protein levels, subsequently reducing iodide transport to the thyroid (Eng, et al. 1999; Eng PH 2001; Glatt, et al. 2005). In iodine deficient rats, NIS mRNA is up regulated in fetal thyroid, as well as in the placenta (Schroder-van der Elst, et al. 2001). In BeWo cells iodide also caused a significant decrease in NIS mRNA and apical membrane protein, followed by a decrease in levels of iodide uptake (Li et al. 2007). These studies suggest that self-regulation of iodide uptake by intracellular iodide occurs in thyroid and placenta. In BeWo cells, iodide decreases hCG mRNA expression and protein secretion. Interestingly cord blood TH levels in neonates of mothers with moderate iodine deficiency and hypothyroxinemia are significantly higher than maternal levels (Glinoer 1997; Glinoer, et al. 1992). Although no measurements of serum inorganic iodine concentrations were made in these cases it is tempting to hypothesise that in the face of moderate maternal iodide deficiency up-regulated placental NIS expression and increased materno-fetal placental iodide transport may allow the fetus to maintain normal TH levels. Excessive maternal iodide intake may, on the other hand, down-regulate NIS expression in placenta and reduce iodide transport to the fetus.

5. Importance of oxygen in placental thyroid hormone and iodide transport

5.1 Changes in placental oxygen concentration through gestation

The adaptive processes of the developing placenta have long been studied demonstrating that under rapid physiological changes specific genes and associated proteins are affected, leading to altered nutrient, hormone and waste exchange between the mother and fetus. Many of these physiological changes relate to changing oxygen concentrations in the placenta that relate to placental vascularisation by the end of the first trimester of pregnancy. In the first trimester, EVT cells invade into the decidua, occluding uterine spiral arteries (Jauniaux, et al. 2003). This restricts blood flow into the intervillous space (IVS) resulting in a low oxygen environment that is essential for placental and embryonic development (Burton, et al. 1999; Genbacev, et al. 1997; Huppertz and Peeters 2005; Osol and Mandala 2009). Measurements with oxygen sensitive probes during ultrasonography at 8 weeks gestation have established that the oxygen concentration within the IVS is <20 mmHg or 3-5% O_2 (Rodesch, et al. 1992). Oxygen concentrations within the underlying

maternal decidua are approximately 60 mmHg or 8-10% O_2. Between weeks 11-12 of gestation, uterine spiral arterioles become patent, allowing significant maternal blood flow and increasing oxygen levels (Carter 2009; Jauniaux, et al. 2000; Rodesch et al. 1992). Recent in vitro studies have demonstrated the capacity of EVTs to initiate apoptosis of vascular smooth muscle cells (VSMC) and endothelial cells. This may represent the mechanism of the physiological modification of the uterine spiral arterioles that leads to the increased vascular compliance and circumference of early pregnancy (Ashton, et al. 2005; Harris, et al. 2006; Moffett-King 2002; Zygmunt, et al. 2003). The resulting increased blood flow and growth of the vascular and capillary network meets the demands of the growing fetus (Burton 2009).

Many placental transport processes are regulated by low oxygen levels, including hormonal, glucose, amino acid (system A – a sodium dependant transport process of amino acids) and iodide transporters. Here we describe potential placental adaptations to T_4 uptake through regulation of TTR expression and iodide uptake through regulation of the NIS cell membrane transporter.

5.2 Low oxygen in the placenta and NIS expression and function

As described earlier, placental iodide transport to the developing fetus is essential to allow the fetal thyroid to produce TH from about week 12 of gestation. We have demonstrated down regulation of mRNA and protein expression of the NIS transporter in human BeWo placental cells cultured at 1% oxygen in comparison to controls cultured at 8% oxygen (Li, et al. 2011). A significant reduction in iodide uptake in cells cultured at low oxygen was also observed (Li et al. 2011). This suggests that the increasing oxygenation of the placenta at about 12 weeks gestation may up regulate NIS expression leading to increased iodide transport at a time when the developing fetal thyroid requires maternal iodide. hCG expression measured in the same study mirrored the expression of NIS. hCG regulates Pax8, an essential protein that must bind to the NIS promoter and enhancer region to up regulate NIS transcription (Schmitt, et al. 2001). This highlights the complexity of placental NIS expression, with oxygen concentrations and hormonal expression both playing a role in NIS regulation.

5.3 Low oxygen, the placenta and transthyretin (TTR) expression and function

As described above, the low oxygen environment within the placenta clearly regulates a number of important genes including those related to specific transport processes. Recently, our group demonstrated that low oxygen levels up-regulate expression, secretion and re-uptake of TTR (Patel, et al. 2010a). Human placental JEG-3 and primary trophoblast cells cultured under low oxygen conditions (1-3% O_2), showed an increase in TTR mRNA and protein expression. Using fluorescent and ^{125}I labelled TTR, increased up-take into trophoblast cells was observed using the same low oxygen culture conditions. The uptake studies were conducted in the presence of excess T_4 which causes TTR tetramerisation, a process that appears critical for significant TTR uptake by cells (Landers et al. 2009). This study was the first to demonstrate physiological regulation of trophoblast TTR uptake. Although speculative at this stage, this could suggest increased transplacental delivery of thyroxine (T_4) during the first trimester of pregnancy, when fetal requirement for maternal T_4 is higher (as detailed earlier in this chapter) and when a physiological low oxygen environment is present.

Increased concentrations of placental TTR protein have been demonstrated in patients with preeclampsia (Gharesi-Fard, et al. 2010). This increased TTR expression probably relates to placental hypoxia, which is common in pre-eclampsia, but further investigation of TTR in the cause and/or diagnosis of pre-eclampsia is warranted.

6. Conclusion

Adequate supplies of maternal TH and iodide are essential for normal fetal brain development, with TH critical in the first trimester and iodide from the second trimester on. It is increasingly apparent that even very mildly reduced maternal T_4 levels may impair the offspring's neuro-cognitive function. Impaired maternal thyroid function from iodine deficiency or autoimmune thyroid disease is common and may represent a major public health issue. The mechanisms underlying materno-fetal transport of iodide and TH are slowly being unravelled. NIS and Pendrin mediate iodide transfer in placenta, as they do in the thyroid gland. HCG, iodide and placental oxygen levels regulate placental NIS. NIS transport is blocked by thiocyanate, a component of tobacco smoke, which may exacerbate marginal iodide deficiency in smoking mothers.

TH transfer appears to involve trophoblast membrane TH transporters but the important role of placental TTR requires further evaluation. There is increasing evidence that placental TTR participates in a shuttle in which TTR secreted by the apical trophoblast membrane is taken up by the trophoblast. This shuttle appears to be involved in TH transfer but whether this is by carriage of TH across the placenta, delivery of TH to the membrane transporters or both is as yet unclear. The low placental oxygen level of early pregnancy up regulates both TTR expression and reuptake. Many agents interfere with T_4 binding to TTR and impair fetal thyroid function but a role in interfering with placental transfer of TH is yet to be studied. Placental D3, which converts T_4 to the biologically inactive rT_3, is an important modulator of TH transfer. The interaction of TTR, if any, with the deiodinase requires investigation.

Lastly, TTR is up regulated in placentas of women with pre-eclampsia. While this may be the effect of placental hypoxia, which is prevalent in this condition, its role as a marker of pre-eclampsia deserves further attention.

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This book contains the total of 19 chapters, each of which is written by one or several experts in the corresponding field. The objective of this book is to provide a comprehensive and most updated overview of the human placenta, including current advances and future directions in the early detection, recognition, and management of placental abnormalities as well as the most common placental structure and functions, abnormalities, toxicology, infections, and pathologies. It also includes a highly controversial topic, therapeutic applications of the human placenta. A collection of articles presented by active investigators provides a clear update in the area of placental research for medical students, nurse practitioners, practicing clinicians, and biomedical researchers in the fields of obstetrics, pediatrics, family practice, genetics, and others who may be interested in human placentas.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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