Pregnancy, parturition and neonatal development: interactions between nutrition and thyroid hormones

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The primary role of thyroid hormones in the control and integration of metabolic homeostasis, particularly in adults, is well established. Throughout the life-cycle an individual's ability to alter synthesis, secretion or turnover of thyroid hormones in response to changes in nutrient intake and/or ambient temperature has a large impact on heat production and body composition (Ingram & Dauncey, 1986). This interaction is most striking during pregnancy and perinatal development when large perturbations in thyroid status within the mother, fetus or neonate may occur. Thyroid hormones are necessary to ensure normal development of the brain (Nunez, 1984), lung (Barker et al. 1988), muscle (Finkelstein et al. 1991), nerves (Vries et al. 1986), adipose tissue (Giralt et al. 1990), heart (Birk et al. 1992) and cardiovascular function (Walker & Schuijers, 1989) in both fetus and neonate, although their role varies with gestational age and maturity at birth. Alterations in thyroid-hormone regulation, therefore, can cause large changes in growth, development and maturation of a number of organs and tissues that ultimately determine if an individual will survive (Lucas et al. 1988; Symonds et al. 1989). Large changes in plasma thyroid-hormone concentrations can be detected by routine screening of infants for hypo- and hyperthyroidism, but this may fail to detect modest alterations in thyroid status at critical stages of development, which can be of clinical significance if associated with inadequate nutrition or inappropriate ambient conditions (Symonds et al. 1994).

Triiodothyronine (T3) is the metabolically-active thyroid hormone which influences gene expression, as well as organ or cellular metabolism, by binding to specific nuclear receptors for 3,5,3'-triiodothyronine (Oppenheimer et al. 1976). The ontogenesis of T3 nuclear receptors within fetal tissues such as the liver and brain occurs in tandem with maturation of the hypothalamic–pituitary–thyroid axis (Fisher et al. 1977). A primary factor determining thyroid status during perinatal life is nutrient supply from the mother to the fetus. Thyroid function can be modulated by changes in maternal energy intake (Riis & Madsen, 1985) or I status (Glinoer et al. 1992). A combination of enhanced nutrient intake with thyroid-hormone therapy has the potential to promote growth and development of premature babies, or those which have suffered from intra-uterine growth retardation and are small-for-gestational-age (Brock-Jacobson et al. 1977; Schonberger et al. 1981). Potential benefits of maximizing the metabolic effects of thyroid hormones also extend to other species. For example, the welfare of cattle and
sheep is compromised by poor thyroid function, which can result in an increased occurrence of disease (Cabello, 1980) and hypothermia (Cabello, 1983; Symonds et al. 1989a). Few studies have determined if metabolism of the fetus or neonate can be enhanced by thyroid-hormone therapy. Intramuscular injection of T₃, but not thyroxine (T₄), two to three times daily enhances summit metabolism in lambs (Alexander, 1970; Alexander et al. 1970). Similarly, subcutaneous T₃ injection into neonatal lambs maintained at thermoneutrality can increase O₂ consumption within 1 h of treatment, although the responsiveness of an individual appears to be directly linked to a low birth weight (Lynch et al. 1980). The important interaction between size at birth and thyroid status is emphasized by the finding that low plasma thyroid-hormone concentrations observed in small-for-gestational-age lambs are not due to a deficiency in thyroid-hormone production (Wrutniak et al. 1990). It is actually the result of increased T₄ and T₃ storage in extravascular sites, possibly in conjunction with a reduced amount of T₃ present in tissues such as muscle, adipose tissue and bone.

MATERNAL NUTRITION, PREGNANCY AND THYROID STATUS

The quantity and energy content of food consumed is a major factor determining thyroid status (Dauncey, 1990), an interaction which continues during pregnancy despite a 50% decline in T₄ distribution space and secretion rate (Riis & Madsen, 1985). Thyroid function alters significantly during pregnancy, which can result in a pronounced decrease in maternal plasma concentrations of free T₄ and T₃ despite no change in the total amounts of these hormones (Glinoer et al. 1990). The extent to which this response may be related to changes in maternal food intake or alterations in fetal nutrient requirements has not yet been determined. Early abortion is associated with low concentrations of thyroid hormones in the maternal circulation, which indicates that maternal thyroid status is a primary factor determining whether pregnancy is maintained or aborts (Maruo et al. 1992). Interactions between maintenance of pregnancy and thyroid hormones appear to be linked, in part, to a woman's ability to increase their circulating concentrations during early pregnancy (Maruo et al. 1992). The potential importance of this adaptation is emphasized from the finding that thyroid hormones can stimulate the production of a number of placental hormones, including chorionic gonadotrophin, placental lactogen, progesterone and oestradiol-17β in placental tissue (Maruo et al. 1991). This in vitro placental response is confined to the early part of gestation and not observed near to term. Taken together these findings indicate that thyroid hormones play a primary role in maintaining function of the differentiated trophoblast, over a period in which growth and metabolic requirements are maximal (Robinson & Symonds, 1995). The ability to alter maternal thyroid-hormone production during early pregnancy could serve a dual purpose in promoting placental growth, as well as supplying T₄ to the fetus before development of the fetal thyroid (Sinha et al. 1992). In this respect, daily T₄ treatment of rats throughout pregnancy enhances placental and fetal growth (Spencer & Robinson, 1993).

The extent to which maternal thyroid function can be modulated in response to changes in energy intake before or after conception has not been determined. Short periods of improved nutrition before and during mating increase the proportion of ewes bearing twins, largely as a result of a higher ovulation rate (see Downing & Scaramuzzi, 1991), although it remains to be determined whether alterations in thyroid-hormone
secretion can influence ovarian function by modulation of gonadotrophin action. It is known that long-term periods of energy restriction before or after mating, leading to a pronounced loss of maternal body weight, result in an enhancement of placental weight (McCrabb et al. 1991; Robinson et al. 1994). This adaptation in placental development does not promote fetal growth, since nutrient restriction before conception followed by unrestricted feeding results in fetuses 'long-for-weight', compared with nutrient restriction up to mid-gestation that is associated with 'small-for-weight' fetuses (Robinson et al. 1994). The mechanisms mediating these alterations in fetal growth have not been determined but, given the strong link between energy intake and thyroid status in non-pregnant mammals (Dauncey, 1990), thyroid hormones are likely to have an important role.

During late gestation, both nutrient intake and ambient temperature have pronounced effects on thyroid status (Symonds et al. 1989b), which are closely linked to maternal plasma glucose concentrations (Fig. 1). In unshorn twin pregnant sheep, underfeeding, starvation or malnutrition result in a progressive decrease in plasma T3 concentration, which can be reversed following maternal glucose infusion, or chronic maternal cold

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**Fig. 1.** Influence of nutritional status on jugular venous plasma concentrations of (a) 3-hydroxybutyrate, (b) glucose and (c) triiodothyronine in twin pregnant unshorn and shorn ewes during late gestation. W, well-fed (1.5 kg chopped hay + 0.4-0.6 kg mixed barley concentrate/d); U, under-fed (1.2 kg chopped hay + 0.15-0.25 kg mixed barley concentrate/d); G, intravenous glucose infusion (0.6 mmol/min); S, overnight starvation; M, malnourished (0.5 kg chopped NH3-treated straw/d). Values are means with their standard errors represented by vertical bars. (Adapted from Symonds et al. 1989b, Clarke et al. 1995b; M. E. Symonds, unpublished results.)
exposure induced by winter shearing. At the same time as maternal plasma T3 and glucose concentrations decrease, with increasing energy deficit, an increase in plasma 3-hydroxybutyrate concentrations occurs (Fig. 1) as the ewe begins to exhibit clinical symptoms of pregnancy toxaemia (Symonds et al. 1986). The consequence of these reductions in maternal energy metabolism following food restriction is that fetal growth is compromised (Symonds et al. 1992, 1995). Conversely, chronic maternal heat stress during mid to late gestation lowers plasma T3 concentration and leads to a reduction in food intake, the combination of which inhibits placental growth. Under these experimental conditions no changes in maternal plasma concentrations of glucose or 3-hydroxybutyrate are observed and fetal weight at term is similar to that of control ewes (Bell et al. 1989).

Pregnancy appears to impose a specific stress on thyroid function which makes it more sensitive to changes in nutrient intake than during non-pregnancy. For example, if women are on a marginal I intake of 100 μg/d symptoms of thyroidal ‘stress’ (i.e. goitrogenesis) only become apparent during pregnancy (Glinoer et al. 1992) and can persist for up to 1 year after parturition. An increased prevalence of thyroid disorders in women, compared with men, could be explained, therefore, by a combination of macronutrient (e.g. carbohydrate, protein) and/or micronutrient (e.g. I) deficiencies during pregnancy which can act to compromise the health and well-being of both mother and fetus. This interaction is particularly important in areas of the world in which environmental I deficiency is prevalent, and results in marked alterations in feto-maternal thyroid function interrelationships (Das & Ischei, 1993). In countries such as Bangladesh poor I intake is a primary risk factor for spontaneous abortion, stillbirth and early infant death (Anwar et al. 1995). Clinical problems associated with limited dietary I consumption may not be confined to developing areas of the world, but could extend to developed countries including the United Kingdom, where average daily I intake is only 140 μg/d (Lee et al. 1994), a value well below 1000 μg/d recommended as maximal by the World Health Organization/Food and Agriculture Organization Joint Expert Committee on Food Additives (1989). A failure to obtain sufficient I during pregnancy appears to have a much greater effect on thyroid-hormone economy in the fetus than mother (Obregon et al. 1991). The extent to which fetal rat tissues become depleted increases with gestational age as both extrathyroidal and intrathyroidal stores of thyroid hormones decline, an adaptation which is most noticeable in the placenta and fetal brain. After birth, when I availability is improved, the levels of T3 in the brain are restored (Obregon et al. 1991) but responses in other tissues remain to be determined, as do the longer-term consequences for growth and maturation.

FETAL DEVELOPMENT, THYROID STATUS AND NUTRIENT SUPPLY

The extent to which the hypothalamic–pituitary–thyroid axis attains complete functionality during fetal development is primarily dependent on length of gestation and maturity at birth. In rats, development of the thyroid axis occurs mainly after birth (Pracyk et al. 1992) and chronic maternal under-nutrition has little effect on fetal thyroid status, which is not impaired until the second week of postnatal life (Alaez et al. 1992). This contrasts with infants and lambs in which intra-uterine growth retardation is associated with low plasma concentrations of thyroid hormones at birth (Cabello & Levieux, 1981; Thorpe-Beeston et al. 1991b). Marked similarities in ontogeny of
thyroid-hormone production exist between human and ovine fetuses which act to maintain low rates of T₃ secretion (Fisher et al. 1977). One clear difference between these species is that in human subjects fetal plasma T₄ concentrations remain below the levels found in maternal plasma, although this difference becomes less obvious with increasing gestational age (Thorpe-Beeston et al. 1991a). In comparison plasma T₄ concentrations in the ovine fetus are twice the values recorded in maternal plasma (Slater & Mellor, 1981) and do not change over the final third of gestation (Fraser & Liggins, 1988). Maintenance of high circulating T₄ levels in ovine fetuses could be of benefit in maintaining fetal metabolism during periods of maternal malnutrition lasting 4–7 d, despite the onset of fetal hypoglycaemia (Mellor et al. 1977).

The importance of thyroid hormones in maintaining fetal growth is reduced with progressing gestational age in sheep (Fig. 2). This change coincides with the period in which expression of mRNA for hepatic growth-hormone receptor doubles (Klempt et al. 1993), which may be indicative of an increased fetal dependence on growth hormone or insulin-like growth factor-1 (Owens et al. 1994), rather than T₄ in maintaining whole-body growth. Evidence that pituitary and thyroid hormones have interactive influences on fetal growth is provided from studies on effects of hypophysectomy in fetal pigs (Latimer et al. 1993). This manipulation has no effect on fetal body weight, but if hypophysectomized fetal piglets are treated with T₄ growth is reduced by 25%. In fetal
Table 1. Effect of fetal thyroidectomy at 127 d of gestation on liver and brown adipose tissue (BAT) development in neonatal lambs

(Mean values with their standard errors)

<table>
<thead>
<tr>
<th></th>
<th>W (kg)</th>
<th>Liver wt (g)</th>
<th>Wt of perirenal BAT (g)</th>
<th>GDP binding (pmol/mg mitochondrial protein)</th>
<th>$V_{O_2}$ (ml/min per kg W)</th>
<th>No. of lambs shivering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n 7)</td>
<td>4.69</td>
<td>100** 16</td>
<td>21.4* 1.3</td>
<td>180** 16</td>
<td>23.6* 3.0</td>
<td>1</td>
</tr>
<tr>
<td>TX (n 6)</td>
<td>5.29</td>
<td>155 13</td>
<td>31.9 5.4</td>
<td>98 16</td>
<td>15.5 2.1</td>
<td>3</td>
</tr>
</tbody>
</table>

W, body weight; $V_{O_2}$, O$_2$ consumption during non-rapid-eye-movement sleep at 15'; TX, thyroidectomized. Mean values were significantly different from those for TX animals (Student's t test): *P = 0.06, **P<0.05.

Sheep plasma T$_4$ concentrations are linearly correlated with fetal O$_2$ consumption (Fowden & Silver, 1995), which indicates that if T$_4$ levels are artificially elevated fetal metabolism will be enhanced and could limit nutrient availability for growth. During the final weeks of gestation thyroid hormones may actually act to limit growth of certain tissues, because fetal thyroidectomy at 127 d of gestation (term 147 d) results in lambs of normal body weight, possessing larger livers and more perirenal adipose tissue (Table 1). Similarly subcutaneous and perirenal adipose-tissue deposition is enhanced in ovine fetuses which have been hypophysectomized at 112 d of gestation (Stevens & Alexander, 1986).

Over the final stages of fetal development thyroid hormones are necessary for promoting maturation of many tissues or organs, including brown adipose tissue (BAT), liver and lungs. In ovine fetal hepatic tissue, for example, binding capacity of nuclear T$_3$ receptors, activity of the enzyme iodothyronine 5'deiodinase (EC 3.8.1.4; I 5'D) which converts T$_4$ to T$_3$, and glycogen content all increase dramatically during the last month of gestation (Fig. 3) despite little change in liver weight. The time-course of these changes parallels a rise in both hypothalamic thyrotrophin-releasing hormone (TRH) content (Polk et al. 1991) and rate of T$_3$ production (Fraser & Liggins, 1988). Thyroidectomy at 130 d of gestation has no effect on hepatic binding capacity of nuclear T$_3$ receptors (Polk et al. 1989), but causes a 30% reduction in I 5'D activity (Wu et al. 1990). Maternal nutritional status can act to modulate fetal I 5'D activities in liver and BAT, which are enhanced after chronic cold exposure or glucose infusion of under-fed ewes (Clarke et al. 1993, 1995a). The influence of maternal food intake on fetal nuclear T$_3$ receptor development is unknown, although their distribution on skeletal muscle is reduced during energy restriction of young pigs (Dauncey et al. 1988). A similar response could be observed in utero as maximal T$_3$ binding capacity is lower in runt (i.e. intra-uterine growth retarded) compared with normal-sized piglets (Dauncey & Geers, 1990).

From the limited data available, fetal thyroid status appears to be extremely sensitive to changes in nutrient supply, mediated via alterations in placental blood supply. Ligation of the maternal uterine vein and artery on day 17 of gestation in rats (term 22 d) significantly reduces plasma T$_4$ concentrations and fetal body weight (Wrutniak &
Cabello, 1983). In carunclectomized sheep fetuses, among the most dramatic fetal endocrine compromises are reductions in plasma T₄ and T₃ levels (Harding et al. 1985). This response is not directly linked to changes in fetal blood gas or glucose status or fetal size, although fetal hypoglycaemia and hypoxia enhance the fall in plasma thyroid hormone levels. Survival rates of carunclectomized fetuses are also low and are likely to be closely linked with suppressed thyroid function associated with placental insufficiency (Thorpe-Beeston & Nicolaides, 1992).

**MANIPULATION OF THYROID FUNCTION IN THE NEWBORN AND ADAPTATION AT BIRTH**

In species that have a mature hypothalamic–pituitary–thyroid axis at birth, parturition is an important stimulus in initiating the postpartum surge in thyroid hormones. Normal delivery at term is associated with a 3–6-fold increase in plasma concentration of T₃, but only a 25% rise in T₄ values (Simila et al. 1975; Clarke, 1994). This dramatic elevation in T₃ levels is the result of both an increase in thyroidal T₃ production (Polk et al. 1987; Fraser & Liggins, 1989) and hepatic I ₅'D activity (Symonds, 1995). For infants the rise in thyroid-hormone concentrations after birth is closely associated with that of thyro-
trophin (TSH; Simila et al. 1975), but within 24 h TSH secretion declines (Zegher et al. 1994), although plasma T₄ and T₃ concentrations remain elevated (Simila et al. 1975). A similar relationship is not observed in lambs for which changes in fetal or neonatal TSH levels do not appear to be correlated with changes in thyroid-hormone secretion (Sack et al. 1976; Fraser et al. 1985). An increase in plasma TSH concentration may not be observed until several hours after the postpartum surge in thyroid hormones (Cabello & Levieux, 1980). One important stimulus for thyroid-hormone secretion in lambs is cutting of the umbilical cord (Sack et al. 1976), and any delay in time between delivery and cord-cutting greatly reduces the increase in thyroid-hormone concentration, despite TSH levels rising. Other factors, such as corticosteroids, can act to promote T₃ production (Fraser & Liggins, 1989), but it is not known if cortisol has a direct effect on the thyroid gland or acts indirectly by changing TSH secretion (Zegher et al. 1994).

Irrespective of the precise mechanisms responsible for altering thyroid function at birth there is a clear interaction between initiation of independent thermoregulation, thyroid status and maintenance of body temperature after birth (Symonds et al. 1995). A primary factor determining adaptation at birth is type of delivery, as vaginally-delivered lambs are able to maintain body temperature over the first few hours of life (Cabello, 1980; Symonds & Lomax, 1993), which is not the case for those delivered near-term by caesarean section (Sack et al. 1976; Symonds & Lomax, 1993). Similarly caesarean-section-delivered infants exhibit lower axillar, interscapular and skin temperatures than those born per vaginum (Christensson et al. 1993). These responses appear to be linked to reduced postpartum surges of thyroid hormones and catecholamines (Irestedt et al. 1982; Symonds et al. 1994). Differences in endocrine status between vaginally- and caesarean-section-delivered lambs include responsiveness of the hypotalamic-pituitary axis because, in contrast to pre- or full-term vaginally-delivered lambs (Wrutniak & Cabello, 1985), TRH administration has no effect on plasma concentrations of thyroid hormones in caesarean-section-delivered lambs (Bird et al. 1994). The route of delivery also has a marked influence on the hypotalamic-pituitary-adrenal axis as caesarean-section-delivered lambs have adreno-corticotropic hormone levels nine times higher than those delivered vaginally, but plasma cortisol concentrations are similar between groups (Clarke, 1994).

The importance of thyroid hormones in preventing an accelerated fall in body temperature after birth has been demonstrated in caesarean-section-delivered lambs (Polk et al. 1987). This effect has been attributed to a decreased rate of O₂ consumption by BAT, for which a comparable response is observed in thyroidectomized fetuses born per vaginum, and results in an appreciable fall in body temperature after birth (Fig. 4). In addition the thermogenic activity of BAT is greatly reduced and these lambs have an increased reliance on shivering thermogenesis in order to maintain metabolic rate (Table 1). Thyroid hormones are not only necessary for the functional development of BAT but are essential for maturation of lungs (Barker et al. 1990) and skeletal muscle (Finkelstein et al. 1991), which if either are compromised will contribute to metabolic deficiencies after birth. This point is illustrated from the finding that altered fetal thyroid development is associated with hypothermia in newborn piglets (Berthon et al. 1993), a species which does not possess BAT (Trayhurn, 1993).

Infants born premature and/or small-for-gestational-age are known to be at increased risk from respiratory and thermoregulatory disorders. These complications tend to be associated with a low birth weight and plasma T₃ concentrations, despite normal TSH
levels (Nagashima et al. 1985), and can be exaggerated by diseases linked to immature lung development, including hyaline membrane disease or respiratory disease syndrome (Uhrmann et al. 1978; Abbassi et al. 1984). Placental insufficiency is thought to be a primary factor contributing to poor fetal thyroid status (Cabello & Levieux, 1981) as a consequence of poor fetal nutrition, including fetal hypoxia. Oxygenation of the fetus can be improved by maternal $O_2$ administration (Paulick et al. 1992), although subsequent effects on thyroid status have not been determined. TRH is known to have synergistic effects with glucocorticoids in stimulating lung maturation (Liggins et al. 1988) and its use in preventing chronic lung disease in very-low-birth-weight infants is increasing (Ballard et al. 1992b). Maternal TRH treatment in conjunction with betamethasone in cases of premature births can result, however, in a suppression of the normal postnatal surge in thyroid hormones (Ballard et al. 1992a). This effect could be related to an altered sensitivity of the pituitary–thyroid axis to TRH observed in pre-term individuals (Wrutinak & Cabello, 1985). Moreover, prenatal TRH treatment in rats, with or without dexamethasone can decrease pup survival rate during a 14 d period of exposure to hyperoxia (Rodriguez-Pierce et al. 1992). These findings indicate that alternative strategies aimed at stimulating thyroid-hormone secretion before or after birth should be developed. One simple method of increasing plasma $T_3$ concentrations in caesarean-section-delivered lambs to values similar to those of lambs born per vaginum is to give an oral dose of 20 ml milk (Table 2). This manipulation stimulates lipolysis and enhances the thermogenic activity of BAT in conjunction with a higher colonic temperature. A greater understanding of the interactions between feeding, gut function and thyroid secretion could be of great benefit in the management of pre-term infants, as intravenous administration of nutrients has no effect on plasma concentrations of thyroid hormones, but stimulates activity of the sympathetic nervous system (Weinstein et al. 1987).
Table 2. Effect of feeding on thermoregulation in near-term caesarean-section-delivered lambs
(Mean values with their standard errors)

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Peak response §</th>
<th>Plateau binding (pmol/colonic mitochondria)</th>
<th>BAT GDP protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T₃ (nm)</td>
<td>T₄ (nm)</td>
<td>NEFA (mm)</td>
</tr>
<tr>
<td>Milk-fed (n 6)</td>
<td>4.80⁺</td>
<td>0.37</td>
<td>126</td>
</tr>
<tr>
<td>Control (n 5)</td>
<td>4.02</td>
<td>0.45</td>
<td>121</td>
</tr>
</tbody>
</table>

T₃, triiodothyronine; T₄, thyroxine; NEFA, non-esterified fatty acids; BAT, brown adipose tissue.

⁺,⁻ Mean values for T₃ and NEFA in the same row with different superscript letters were significantly different from those for pretreatment (Student's paired t test): abP<0.05, cP<0.01.
Mean values were significantly different from those for milk-fed animals (Student's t test): *P<0.05, **P<0.01, †P=0.078, ‡P=0.068.

‡ Milk-fed lambs were given 20 ml formula milk orally 70 min after birth.
§ Peak value measured up to 100 min after treatment.
In conclusion, the increased occurrence of premature births and caesarean-section deliveries resulting from changes in clinical practices in Europe and North America is directly contributing to conditions whereby thyroid function can be compromised after birth. An increasing number of studies are showing that compromised lung function, respiratory acidosis and infant mortality can all be reduced following thyroid-hormone therapy (Mashiach et al. 1978; Schonberger et al. 1981; Adamovich et al. 1992). Manipulations of this kind will have a large impact on metabolic homeostasis and nutrient utilization, which will not only determine perinatal outcome, but are likely to have much-longer-term consequences. The ability to alter thyroid-hormone production at specific stages of fetal or neonatal life is likely, therefore, to have considerable benefit in terms of reducing clinical interventions as well as minimizing losses to the agricultural industry.

The author would like to thank Jane A. Bird, David S. Buss, Lynne Clarke, John J. Gate and Samantha J. Lyke for their dedication to this work, plus Michael A. Lomax for his continued guidance and encouragement. The financial support of The Wellcome Trust, BBSRC, MRC, MAFF and the University of Reading are gratefully acknowledged.

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Printed in Great Britain