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Maternal and Fetal Thyroid Function

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Conception is followed by a series of hormonal and metabolic changes that involve most maternal endocrine systems. With regard to thyroid metabolism, these include an increase in serum thyroxine-binding globulin and thyroid hormone concentrations, increased renal clearance of iodine, and increased production and turnover of thyroxine (T)¹. Fetal and maternal thyroid physiology differ, but the systems interact by means of the placenta and amniotic fluid, which modulate the transfer of iodine and small but important amounts of thyroid hormone from mother to fetus^{1,2}. In this article we shall review recent data and new insights regarding the changes in maternal and fetal thyroid function.

Thyroid Function in Pregnant Women

In pregnant women, renal clearance of iodide increases because of an increase in the glomerular filtration rate, and iodide and iodothyronines are transferred to the fetus. As a result, serum concentrations of inorganic iodide decrease. Women who live where iodine intake is marginal (<50 µg per day) may have an absolute or relative iodine deficiency and enlargement of the thyroid gland^{3,4,5}. Even in areas of iodine sufficiency, such as the United States, the thyroid increases 10 to 20 percent in volume during pregnancy⁴. The fetus needs increasing amounts of iodide as fetal thyroid hormone production increases during the second half of gestation^{1,2}. In addition to transporting iodide across the placenta, monodeiodination of iodothyronines within the placenta provides increasing amounts of iodide to the fetus as the placenta enlarges.

Serum concentrations of thyroxine-binding globulin increase in pregnant women during the first trimester as a result of reduced clearance by the liver because of an estrogen-induced increase in sialylation of thyroxine-binding globulin and an estrogen-stimulated increase in its synthesis⁶. The concentration plateaus after 12 to 14 weeks of pregnancy and is associated with concomitant increases in serum total T₄ and triiodothyronine (T₃) concentrations ([Figure 1](#)). Serum free T₄ concentrations increase slightly during the first trimester and then decrease. However, these changes are small, so that in most pregnant women serum free T₄ concentrations remain within the normal range for nonpregnant women^{4,7,8}.

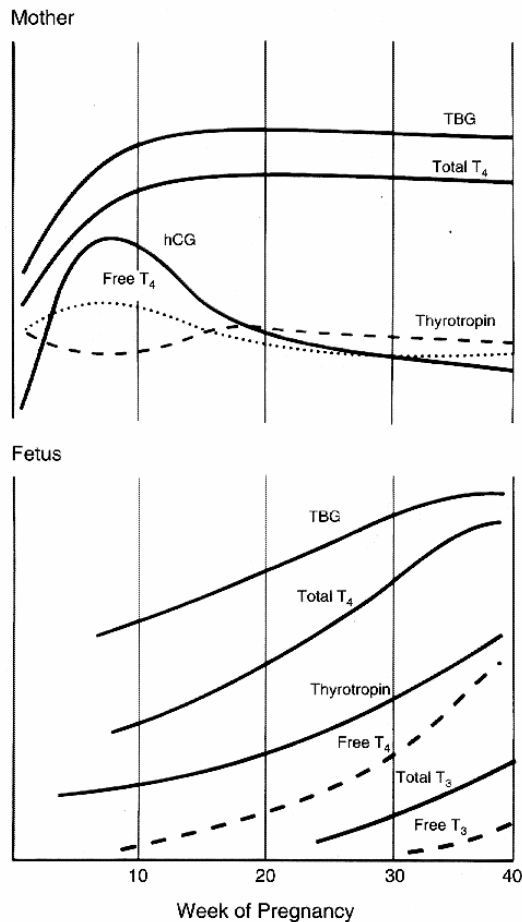


Figure 1. Relative Changes in Maternal and Fetal Thyroid Function during Pregnancy.

The effects of pregnancy on the mother include a marked and early increase in hepatic production of thyroxine-binding globulin (TBG) and placental production of human chorionic gonadotropin (hCG). The increase in serum TBG, in turn, increases serum T_4 concentrations; hCG has thyrotropin-like activity and stimulates maternal T_4 secretion. The transient hCG-induced increase in serum free T_4 inhibits maternal secretion of thyrotropin.

T_4 requirements also increase during pregnancy. This is most evident in women with hypothyroidism who were treated with T_4 before becoming pregnant. In these women, the dose of T_4 has to be increased by 25 to 50 percent to maintain normal serum thyrotropin concentrations during the pregnancy^{9,10}. The specific reason for this increased need for T_4 is not known. The size of the extrathyroidal T_4 pool increases because of the increase in serum concentrations of thyroxine-binding globulin, but the increase amounts only to about 300 μg of T_4 and is largely achieved during the first trimester. Since the increased T_4 requirement is sustained until delivery, the increase in serum concentrations of thyroxine-binding globulin is unlikely to be the sole explanation. The increased requirement is probably also due to placental degradation of T_4 , the transfer of T_4 from mother to fetus, and increased maternal clearance of T_4 .

The negative-feedback control system of the hypothalamic-pituitary-thyroid axis functions normally in pregnant women, in that their serum thyrotropin concentrations during most of pregnancy are similar to those in nonpregnant women^{7,8}. In addition to the thyrotropin secreted by the maternal pituitary gland, the placenta produces large amounts of human chorionic gonadotropin, which has some thyrotropin-like bioactivity^{11,12}. The production of human chorionic gonadotropin begins during the first week after fertilization and is highest near the end of the first trimester, after which it declines. This increase causes a transient increase in serum free T_4 concentrations, which in turn decrease serum thyrotropin concentrations during the first trimester (Figure 1)^{11,12}.

The Placenta

Metabolism of Iodothyronines

Three enzymes catalyze the deiodination of iodothyronines in human tissues¹³. Type I deiodinase, which catalyzes the deiodination of both the outer and inner rings, is a selenoprotein expressed in adults in liver, kidney, thyroid, and pituitary gland¹⁴. This enzyme is responsible for most of the T₃ in serum. It also catalyzes the 5'-deiodination of 3,3',5'-triiodothyronine (reverse T₃), which is the rate-limiting step in the clearance of reverse T₃, as well as inner-ring deiodination, particularly of T₃ sulfate and T₄ sulfate (Figure 2 and Figure 3)^{15,16}. Type II deiodinase acts only on the outer ring and prefers T₄ and reverse T₃. It is expressed in brain, pituitary gland, brown adipose tissue, keratinocytes, and placenta^{13,17,18,19}. Type III deiodinase, present in high amounts in placental tissue, brain, and epidermis, catalyzes the conversion of T₄ to reverse T₃ and T₃ to 3,3'-diiodothyronine (T₂)^{13,20}.

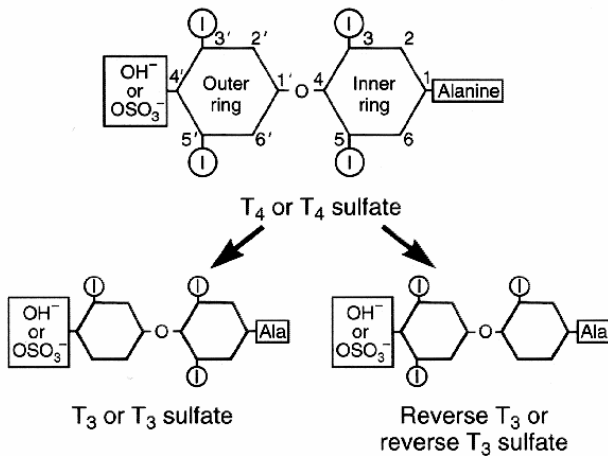


Figure 2. Structures of T₄, T₃, and Reverse T₃.

Sulfation at the 4'-hydroxyl position produces the sulfate conjugates of T₄, T₃, and reverse T₃.

During the second and third trimesters there are marked maternal-to-fetal gradients of free T₄ and T₃^{23,24}. For example, at delivery maternal serum free T₃ concentrations are twice those in cord serum²⁴. Newborn infants with thyroid agenesis or a total defect in thyroid hormonogenesis have cord serum T₄ concentrations between 20 and 50 percent of those in normal infants, values much lower than in maternal serum²⁵. The small amounts of T₄ transferred contribute to T₃ concentrations in the fetal brain and almost certainly minimize the effects of fetal hypothyroidism^{26,27,28}.

Thyroid Hormones in the Fetus

Development of Fetal Thyroid Function

Fetal thyroid function continues to mature throughout gestation. By 10 weeks after conception fetal thyroid follicles and T₄ synthesis are demonstrable. Increases in pituitary and serum concentrations of thyrotropin during the second trimester coincide with the development of the hypothalamic-pituitary portal circulation, which facilitates the modulation of pituitary thyrotropin secretion by hypothalamic thyrotropin-releasing hormone ([Figure 1](#)). The increased secretion of thyrotropin-releasing hormone, despite higher serum free T₄ concentrations, implies immaturity of the negative-feedback system that regulates the secretion of thyrotropin-releasing hormone and thyrotropin (e.g., the threshold or set point for T₄-induced inhibition of thyrotropin secretion is relatively increased)^{28,29}.

Thyroxine-binding globulin and T₄ are first detectable in fetal serum at 8 to 10 weeks of gestation and increase thereafter until they plateau at 35 to 37 weeks, at which time the serum total T₄ concentration is approximately 10 µg per deciliter (130 nmol per liter)^{28,29,30}. The progressive increase in serum concentrations of thyroxine-binding globulin presumably reflects maturation of the fetal liver and its responsiveness to estrogen stimulation. As serum concentrations of thyroxine-binding globulin increase in the fetus, there is a progressive increase in the extrathyroidal T₄ pool. In addition, serum free T₄ concentrations rise between 18 to 20 and 35 to 37 weeks of gestation, an increase caused by greater secretion of thyroid hormone. These changes in serum thyrotropin and free T₄ concentrations are caused by increased stimulation of pituitary thyrotropin secretion by thyrotropin-releasing hormone and enhanced thyroidal responsiveness to thyrotropin.

Metabolism of Iodothyronines

The ontogeny of the three deiodinases that catalyze the progressive deiodination of T₄ differs in the developing fetus. Type II and type III deiodinases appear at midgestation, whereas type I deiodinase is not evident until later^{13,29,30}. Accordingly, fetal serum T₃ concentrations are low (<15 ng per deciliter [0.2 nmol per liter]) before 30 weeks' gestation; they increase gradually to about 50 ng per deciliter (0.7 nmol per liter) at term ([Table 1](#))^{20,24,28,29,30}. Maternal serum values, by contrast, approximate 200 ng per deciliter (2.7 nmol per liter). The preterm increase in fetal serum T₃ concentrations is due to an increase in type I deiodinase activity. Serum concentrations of reverse T₃, T₄ sulfate, T₃ sulfate, and reverse T₃ sulfate in the umbilical cord at this time are high^{31,32,33}. The sulfated metabolites accumulate in fetal serum as a result of the very low type I deiodinase activity in fetal tissues and because the sulfated iodothyronines are not substrates for placental type III deiodinase³⁷. Although T₃ sulfate does not bind to nuclear T₃ receptors and therefore has no biologic activity,³⁸ its parental administration in rats after thyroidectomy increases serum T₃ concentrations and biologic responses³⁹. Thus, T₃ sulfate can be desulfated to T₃ in adult rats, probably by bacterial sulfatases in the gut⁴⁰. The liver, kidney, and brain of adult rats have sulfatase activity, and desulfation of T₃ sulfate to T₃ occurs in the liver and brain of fetal rats^{41,42}. Thus, T₃ sulfate could serve as a local source of T₃ in fetal tissues containing sulfatase.

Table 1. Iodothyronine Concentrations in Maternal and Fetal Serum and Amniotic Fluid.

IODOETHYRONINE	MATERNAL SERUM†	AMNIOTIC FLUID		FETAL SERUM	
		20 WK	TERM	20 WK	TERM
		<i>ng/dl</i>			
T ₄	12,000	250	570	3,100	11,000
T ₃	200	8.6	6.6	13	49
T ₂	2.2	5.8	6.2	—	11
Reverse T ₃	24	130	69	250	270
T ₄ sulfate	1.8	28	—	—	21
T ₃ sulfate	2.9	6.6	—	6.7	12
Reverse T ₃ sulfate	3.8	8.6	—	—	50

*Data were obtained from Abuid et al.,²¹ Ballabio et al.,³⁰ Chopra et al.,³¹ Wu et al.,^{32,33} Meinhold et al.,³⁴ and Klein et al.^{35,36} To convert values for T₄ to nanomoles per liter, multiply by 0.013; to convert values for T₃ and reverse T₃ to nanomoles per liter, multiply by 0.015; to convert values for T₂ to nanomoles per liter, multiply by 0.019; to convert values for T₄ sulfate to nanomoles per liter, multiply by 0.012; and to convert values for T₃ sulfate and reverse T₃ sulfate to nanomoles per liter, multiply by 0.014.

†Values are for midgestation.

In fetal rats and sheep, brain tissue, brown adipose tissue, pituitary tissue, and perhaps skin contain substantial amounts of type II deiodinase by midgestation (before the increase in serum T₃ concentrations)^{43,44,45}. This allows for the possibility of the conversion of T₄ to T₃ by local tissues and the potential for varying local-tissue supply of T₃^{26,27,43,45}. Type II deiodinase activity increases in fetuses with hypothyroidism, whereas the activities of types I and III deiodinase decrease²⁷. These changes favor shunting of T₄ to brain tissues, where deiodination to T₃ is increased and degradation of T₃ is decreased. Thus, although fetal thyroid development is largely independent of maternal influences, even limited transfer of thyroid hormone from mother to fetus may protect a fetus with hypothyroidism^{25,26,27,45}. In rat fetuses with hypothyroidism, the increased type II deiodinase activity in association with T₄ derived from the mother can normalize brain T₃ concentrations^{26,27,45}.

The Importance of Iodothyronines in Amniotic Fluid

In addition to being linked by the umbilical cord, the mother and fetus are linked by the amniotic cavity and amniotic fluid, providing a second pathway for fluid and molecular exchange. The amniotic-fluid volume is the net balance of inflow, consisting of fetal urine and lung fluid, and outflow, consisting of fetal-maternal transamniotic fluid exchange and fetal swallowing^{46,47}. The pattern of iodothyronines in amniotic fluid reflects the effects of type III deiodinase activity in placental and fetal tissues, and the iodothyronine concentrations in amniotic fluid thus reflect both maternal and fetal thyroid hormone metabolism (Figure 3)^{34,35,48,49}. Reverse T₃ and T₄ and their sulfate conjugates account for more than 95 percent of the total iodothyronines in amniotic fluid (Table 1). The T₄ concentrations increase progressively during gestation, whereas reverse T₃ concentrations decrease.

At term, T₄ concentrations in amniotic fluid are about 0.6 µg per deciliter (8 nmol per liter) (Table 1), much lower than in maternal or fetal serum. The reverse T₃ concentration, in contrast, is about three times the concentration in maternal serum and one quarter that in cord serum^{48,49}. In fetuses with congenital hypothyroidism, iodothyronine concentrations in amniotic fluid largely reflect maternal thyroid function^{48,49}. Since protein and thyroxine-binding globulin concentrations are low in amniotic fluid, the free T₄ concentration

is slightly higher than in maternal or fetal serum^{34,35,49} and the free reverse T₃ concentration is much higher than in maternal serum.

Concentrations of T₃ in amniotic fluid are relatively low ([Table 1](#)), and T₂ concentrations (the product of inner-ring deiodination of T₃ or outer-ring deiodination of reverse T₃) are two to three times higher than in maternal serum and only slightly lower than in fetal serum³⁴. These results illustrate the effects of type III deiodination on the maternal T₄ and T₃ entering the amniotic fluid.

The injection of T₄ into amniotic fluid increases thyroid hormone concentrations in amniotic fluid and fetal serum: the injection of 700 µg of T₄ to five pregnant women at term caused a 13-fold increase in amniotic-fluid T₃ concentrations and a 30-fold increase in reverse T₃ concentrations measured 20 to 24 hours later (at the time of delivery), indicating that amniotic fluid T₄ is accessible to both inner-ring and outer-ring deiodinases³⁶. Maternal serum T₄, T₃, and reverse T₃ concentrations did not increase, but cord serum T₄ and T₃ concentrations increased and the neonatal surge in thyrotropin secretion was blunted. Maternal iodothyronines in amniotic fluid can therefore enter the fetal circulation. Late in gestation, fetal swallowing appears to account for most of the transfer of thyroid hormones from amniotic fluid to the fetal circulation. Early in gestation any transfer of thyroid hormone from amniotic fluid to the fetus would presumably occur transdermally, although such transfer has not yet been demonstrated.

Effects of Thyroid Hormone on the Fetus and Neonate

Thyroid hormones have important roles in embryogenesis and fetal maturation. In rats, maternal thyroid hormone reaches the embryo and fetus from the earliest days of gestation. Moreover, fetal rat tissues, including brain, contain T₄ and T₃ before fetal thyroid hormone is produced^{26,50}. The administration of serum from rats with either hypothyroidism or hyperthyroidism induces malformations in rat-embryo cultures in vitro⁵¹. Finally, the progeny of pregnant rats with hypothyroidism, when studied as adults, have abnormalities in brain amino acid metabolism, marker enzymes of neuronal and glial cells, and calmodulin-regulated phosphatase activity, although postnatal growth and brain weight are not altered^{52,53,54}.

In humans living in iodine-deficient areas, maternal hypothyroxinemia is common and is associated with neonatal hypothyroidism and defects in IQ and neurologic function in the offspring^{55,56}. These infants are referred to nosologically as having endemic cretinism. The proximate cause of endemic cretinism is iodine deficiency, but aggravating factors include dietary goitrogens (such as thiocyanate), selenium deficiency, and autoimmune hypothyroidism^{55,56}. The manifestations of endemic cretinism range from goiter or mild mental retardation in euthyroid subjects to severe mental deficiency and neurologic defects in those with variable degrees of hypothyroidism^{56,57}. Two subtypes of endemic cretinism have been described, neurologic cretinism and myxedematous cretinism. People with neurologic cretinism have mental and neurologic abnormalities but appear euthyroid; those with myxedematous cretinism, in contrast, have hypothyroidism^{55,56}. The neurologic abnormalities are similar in both types and presumably represent the combined effects of maternal, fetal, and neonatal hypothyroidism^{56,57}. Neurologic damage in the absence of neonatal hypothyroidism has been postulated to be due to maternal hypothyroxinemia early in gestation⁵⁷.

Both low and normal IQs have been found in the children of women with hypothyroxinemia during pregnancy who live in iodine-sufficient areas (the United States and Japan)^{58,59}. Nuclear T₃ receptors that are relatively saturated with T₃ have been identified in rat and human fetuses early in gestation, particularly in brain tissue,^{60,61,62,63} and brain mutation in newborn rats and humans is dependent on thyroid hormone^{64,65}. The presence of occupied T₃ nuclear receptors in brain tissue early in fetal development supports a role for maternal thyroid hormones in the maturation of the brain.

With the advent of newborn screening for congenital hypothyroidism, it has become clear that size, weight, appearance, behavior, extrauterine adaptation, and immediate postnatal development are usually normal in infants with hypothyroidism, even those with thyroid agenesis^{66,67}. The usual manifestations of intrauterine hypothyroidism are increased serum thyrotropin concentrations and low or low-normal serum T₄ concentrations; in addition, bone maturation is delayed at birth in approximately 60 percent^{66,67,68}. Some newborns may have subtle signs of hypothyroidism, but fewer than 5 percent of cases are diagnosed clinically in the neonatal period. The classic symptoms and signs of hypothyroidism develop progressively during the early weeks and months of extrauterine life. The absence of symptoms and signs in most affected neonates suggests either that metabolism and development in the fetus are not dependent on T₄ or that the small amounts of maternal thyroid hormone in the fetal circulation are sufficient to prevent most clinical manifestations of thyroid deficiency.

Newborn infants with congenital hypothyroidism who are identified by screening programs and treated promptly usually have IQs in the normal range at five to seven years of age, as well as normal growth and development^{69,70,71}. However, low-normal or occasionally low IQs have been reported in some children with congenital hypothyroidism who had very low serum T₄ and very high thyrotropin concentrations and delayed bone maturation at birth, suggesting that hypothyroidism in utero may lead to some degree of irreversible retardation^{71,72,73}. Delaying treatment has the same effect on the IQ⁷².

Low serum T₄ concentrations during the first year of treatment in infants with congenital hypothyroidism are also associated with lower IQs at five to seven years of age^{70,73}. These results and information obtained from late-treated infants before the advent of newborn screening suggest that newborn infants with severe hypothyroidism, if untreated, lose 3 to 5 points of IQ monthly during the first 6 to 12 months of life^{71,72,73,74,75,76,77}. There is some evidence that more aggressive early treatment may be beneficial; increasing the dose of T₄ in infants with congenital hypothyroidism from 7 to 9 µg per kilogram of body weight per day to 8 to 10 µg per kilogram per day increased the IQ at the age of five to seven years by 4 to 5 points⁷⁴.

Although serum T₄ concentrations of 2.3 to 5.4 µg per deciliter (30 to 70 nmol per liter) seem to be protective in the fetus,²⁵ much higher concentrations (10 to 16 µg per deciliter [130 to 205 nmol per liter]) are required to minimize IQ damage in infancy. A better understanding of the role of thyroid hormones in brain development is required before this paradox can be resolved.

Conclusions

The role of thyroid hormones in fetal growth and development and maturation of the fetal brain remains unclear. Infants with congenital hypothyroidism are born with low serum concentrations of thyroid hormone and high thyrotropin concentrations, but if identified by newborn screening programs and treated appropriately, most will have normal physical and intellectual development. This indicates either that any consequences of intrauterine hypothyroidism are largely reversible or that the fetus is protected in some way from the hypothyroxinemia. There is limited but still important placental transfer of maternal T₄ to the fetus, and recent studies have characterized T₃ nuclear receptors and an iodothyronine deiodinase that catalyzes the conversion of T₄ to T₃ in brain tissue early in fetal life. The current hypothesis is that in fetuses with hypothyroidism, maternal T₄, by means of compensatory alterations in iodothyronine metabolism, provides sufficient T₃ to the brain to prevent irreversible damage in most instances. The occurrence of neurologic cretinism in areas of severe iodine deficiency (when both fetal and maternal T₄ synthesis are impaired), as well as the results of studies in animals, supports this hypothesis. Nonneurologic fetal tissues appear to have a limited dependence on thyroid hormone.

Pregnancy increases maternal requirements for T₄, which necessitates a 25 to 50 percent increase in maternal T₄ production in euthyroid women. In women with hypothyroidism or women who live in areas in which iodine deficiency is endemic, fetal brain development is normal if normal maternal concentrations of serum free T₄ are maintained during gestation either by iodine supplementation, where appropriate, or by suitable adjustments of

exogenous T₄ treatment. Placental T₄ transfer does not seem sufficient in all cases, however, to protect the brain of fetuses with hypothyroidism, but early intensive postnatal treatment of infants with evidence of intrauterine hypothyroidism will normalize childhood IQs. Whether treatment in utero of the occasional fetus with hypothyroidism is necessary or desirable remains to be demonstrated.

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Source Information

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