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Fetal thyroïdology

Michel Polak, MD, PhD, Professor of Pediatric Endocrinology [a,b,*], Dominique Luton, MD, PhD, Professor of Obstetrics and Gynecology [c]

[a] Pediatric Endocrinology, Gynecology and Diabetology, Necker Enfants-Malades Hospital, AP-HP, Paris, France
[b] INSERM U845, IMAGINE affiliate, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
[c] Obstetrics and Gynecology, AP-HP, GHU Nord, Hôpital Beaujon and Bichat, Paris and Clichy, Université Paris VII, Paris, France

Advances in prenatal imaging techniques and in fetal hormonology now allow for identification of disorders of thyroid function in the fetus. These can potentially be treated in utero by giving drugs to the mother. This review shows the feasibility of in utero treatment of fetal thyroid disorders, either indirectly by treating the mother or by giving the necessary drugs directly to the fetus. For goitrous fetal hypothyroidism leading to hydramnios, repeated intra-amniotic injections of thyroxine have been reported to decrease the size of the fetal thyroid. Experience with such procedures is limited but positive. The risk that direct in utero treatment of the fetus may provoke premature labor or cause infection should be carefully evaluated. In women with Graves' disease, autoimmune fetal hyperthyroidism can generally be treated in a noninvasive way by optimizing treatment of the mother, such as by increasing the dose of antithyroid drugs. Follow-up of the efficacy and the possible long-term consequences of medical interventions to normalize thyroid function of the fetus are of great importance. Specialized care of the fetus should be provided by skilled teams with extensive experience in prenatal care.

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 * Corresponding author. Pediatric Endocrinology, Gynecology and Diabetology, Necker Enfants-Malades Hospital, AP-HP, Paris, France.
 E-mail addresses: michel.polak@nck.aphp.fr (M. Polak), dluton@free.fr (D. Luton).

We will here summarize recent aspects of thyroid physiology and availability of new tools to assess fetal thyroid function. Those are the basis for fetal thyroid dysfunctions treatments that we will describe as well.

Development of the normal thyroid gland function

The thyroid gland develops at ∼24th day of gestation in Human and its maturation can be divided into two phases.[1] The first phase involves embryogenesis of the thyroid gland and the hypothalamic-pituitary-thyroidal (HPT) axis. The second phase involves further development of the HPT axis including hormone production and regulation.

The thyroid gland originates from the median anlage and from two lateral anlagen. The single median anlage gives rise to the vast majority of the thyroxine-producing follicular cells: it evolves from an outpouching of the floor of the pharynx and at the tip of the foramen cecum at the base of the tongue (between the first and second branchial arches). As the thyroid gland develops it descends through the tissues of the neck, remaining connected to the foramen cecum by the thyroglossal duct, which generally solidifies and subsequently becomes entirely obliterated (during gestational weeks 7–10). The two lateral anlagen (one on each side of the neck) derive from the posterior aspects of the fourth branchial pouches (sometimes called the fifth pouches) and they eventually fuse with the median anlage. The lateral anlagen may give rise to a few thyroxine-producing cells but are the main source of the calcitonin-secreting cells (parafollicular or C cells).

From the functional standpoint, the thyroid can be envisioned as a structure that extracts and concentrates the iodine that reaches the gland through the bloodstream to convert it into thyroxine (T_4) and triiodothyronine (T_3). Fetal T_4 is detected by the 11th week of gestation and progressively increases throughout gestation. Placenta and pancreas produce thyrotropin-releasing hormone (TRH) early in the gestation and hypothalamic TRH synthesis is present at midgestation. Maternal TRH as well as iodine, maternal thiourea drugs, thyroid antibodies, and limited but significant amounts of thyroid hormones cross the placenta.[2] Thyroid-stimulating hormone (TSH)-like activity by the human chorionic gonadotropin secreted by the placenta has minimal effect on the fetal HPT axis. Fetal TSH level starts progressively to increase, at approximately 18 weeks of gestation to a peak value of 10 mU/L at term. At the same time T_4 levels begin to increase steadily until the end of gestation. Fetal serum T_3 remains low until the 30th week of gestation, and then slowly increases until birth.

TRH is a tripeptide secreted by the supraoptic and paraventricular nuclei of the hypothalamus and travels to the anterior pituitary through the hypophyseal portal venous system. Once at the anterior pituitary, TRH binds to TRH receptors and stimulates the synthesis and secretion of TSH-β subunit. TSH, after binding to the thyroid stimulating hormone receptor (TSHR) mediates several effects on thyroid hormone metabolism, including among others iodide trapping, iodotyrosine synthesis, thyroglobulin synthesis, hormone release, and thyroid cell growth. TSH has a circadian rhythm with peak concentrations just prior to onset of sleep (10 PM to midnight).

Under normal circumstances, the thyroid secretes approximately 80% T_4 and 20% T_3 and also secretes thyroglobulin. Thyroid hormones are carried in the blood by three proteins; thyroxine binding globulin (TBG), transhyretin (TTR) and albumin. TBG has the highest affinity for T_4 and T_3, but is present in the lowest concentration. Despite its low concentration, TBG carries the majority of T_4 in serum (75%), followed by TTR (15%) and albumin (10%). Estrogen decrease clearance of TBG and increase its levels during pregnancy. Thyroid hormone synthesis is primarily regulated by the availability of iodine in the environment and by pituitary thyrotropin (TSH) that acts on its receptor (the TSHR) to stimulate the proliferation, differentiation, and function of the thyroid follicular cells. Negative feedback of the thyroid hormones on TSH secretion regulates thyroid hormone production and serum concentration, that is, the higher the serum levels of these hormones, the lower TSH release and vice versa. The negative feedback occurs at the pituitary anterior lobe and at the hypothalamus, principally, through T_4 taken from the circulation and converted into T_3 by outer-ring deiodinases. The major effects of the thyroid hormones are mediated through the nuclear T_3 receptors, with T_3 having the highest affinity. Both T_4 and T_3 can exert a negative feedback on TRH and this action is mediated through thyroid receptor-β (TRβ).