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Review

Fetal thyroid disorders: Pathophysiology, diagnosis and therapeutic approaches

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ABSTRACT

Fetal thyroid disorders while uncommon in general, have significant morbidity and profound effects in the neonate. Pregnancy provides the opportunity not only for the diagnosis of these conditions but also for therapeutic interventions. In careful balance, these disorders range from hypothyroidism to hyperthyroidism, both may manifest with fetal thyroid goiters as well. The intrauterine therapeutic approach of these must also weight the balance in this range as well as the maternal well being which may also express thyroid dysfunction. In this review we explore the different fetal manifestations of thyroid disease, describe the pathophysiology and therapeutic approaches both in practice and in development.

Contents

Introduction: biosynthesis and development

Thyroid hormone function, synthesis and secretion are dependent on the coordinator and function of a number of developmental processes. Dysfunction can occur at any step along this process. The thyroid gland itself must undergo cell migration, differentiation and maturation. From the systemic-endocrine aspect, the hypothalamic-pituitary-thyroid axis must properly develop as well as maturity of the thyroid gland must occur for functional thyroid hormone production [1].

Maturity of the fetal thyroid gland occurs approximately at 11–12 weeks gestation, but secretion of function thyroid hormone does not being until mid-second trimester, around 16–17 weeks gestation [2]. Prior to this period, an adequate source of maternal thyroid hormone is essential for appropriate development of the fetal central nervous system (CNS), since CNS development occurs during the first trimester [3]. A number of animal studies have shown this transfer of maternal thyroid hormones across the placental barrier; in addition, the placenta contains deiodinases, which can convert T4 to T3 [4]. In populations with profound maternal hypothyroidism, the effect of low thyroid hormone levels during fetal development is evident as cretinism, presenting with deaf-mutism, mental retardation and spasticity [5].

Iodine is an essential element for the synthesis of thyroid hormones. Maternal iodine requirements increase during pregnancy [6]. Recent data suggests maternal sources of iodine may directly affect fetal thyroid development and intellectual development [7].

Fetal goiter

Goiters are the clinical manifestation of thyroid gland dysfunction of the fetus. The incidence of fetal thyroid goiter is reported to be between 1:30,000 to 1:50,000 live births [8]. There are two types of Thyroid Receptor Antibodies (TRAbs), Thyroid stimulating antibody (TSAb) and Thyroid Stimulating Blocking

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Antibody (TSBAb). TSAb causes hyperthyroidism and TSBAb results in hypothyroidism. TSBAb is less likely to cause fetal thyroid goiters [9].

The overall effects of fetal thyroid goiters are recognized to be both mechanical (mass effect) and biochemical. Due to the general size and location of the mass, possible (although rare) complications include esophageal and tracheal compression resulting in polyhydramnios or asphyxia as well as dystocia at time of delivery. The biochemical effects of thyroid goiters depend on the etiology of the goiter. In the case of hyperthyroidism, cardiac failure, growth restriction and mental retardation are encountered. In the case of hypothyroidism, delays in milestones associated with motor and mental function are noted as well as deafism. These will both be detailed later.

Fetal thyroid goiters are initially diagnosed by ultrasonography. This is best achieved in the second or third trimester. Mothers with known thyroid disorders should be carefully screened. Nomograms based on gestational age have been developed to aid in diagnosis [10].

Hypothyroidism

Congenital hypothyroidism may result in cretinism, characterized by severely stunted physical growth and mental disabilities. Congenital hypothyroidism may result from absence of the thyroid gland (dysgenesis), reduction in thyroid volume (hypoplastic thyroid), pituitary dysfunction (central hypothyroidism) or normal thyroid tissue with dysfunctional thyroid hormone production (dyshormonogenesis) [11].

In addition, congenital hypothyroidism may represent a manifestation of a syndromic condition such as Pendred syndrome [12], Bamforth-Lazarus syndrome [13] or brain-lung-thyroid syndrome [14]. Pendred syndrome is an autosomal recessive condition resulting from mutations of the *SLC26A4* (pendrin) gene on chromosome 7. Pendrin is a cellular ion transport protein and loss of function results in hearing loss and reduced thyroid iodine incorporation. Bamforth-Lazarus syndrome results from loss of function of the *FOXE1* gene, which encodes the thyroid transcription factor 2 (TTF2). Loss of TTF2 results in aberrant thyroid morphogenesis. Lastly, Brain-lung-thyroid syndrome results from a mutation of the *NKX2-1* gene, which codes the homeobox protein Nkx-2. Homeobox proteins such as Nkx-2 are crucial for embryogenesis, thus, loss of function results in dysmorphogenesis of various organs.

A common physical manifestation of hypothyroidism (with normal thyroid tissue present) is a fetal thyroid goiter secondary to persistent stimulation from a lack of thyroid hormone negative feedback. In addition to dyshormonogenesis, this may present secondary to maternal use (and transplacental passage) of antithyroid medications such as propylthiouracil (PTU) or methimazole (MMI) often used for the treatment of Grave's disease [15]. Transplacental passage of anti-thyroid antibodies may also result in fetal hypothyroidism [16]. The presence of the thyroid goiter not only reflects severity of the fetal disease, but also presents mass-effect on fetal/neonatal physiology (pharyngeal occlusion and airway obstruction) and dystocia at time of vaginal delivery as well as impeding the cardinal movements of fetal descent [17].

Treatment of secondary fetal hypothyroidism (and resultant goiter formation) is cessation of the offending maternal medication in the case of PTU and MMI. Alternatively, is cessation is not medically feasible, intra-amniotic levothyroxine therapy has been implemented with varying results. The proposed mechanism of action is fetal swallowing of the intra-amniotic levothyroxine with conversion to T3.

In these regards, many different protocols and dosages have been reported, optimal pharmacokinetics of amniotic uptake and conversion are currently unknown [18]. The gestational age to initiate therapy is also uncertain with some beginning therapy as soon as the diagnosis is made while others, citing the risk of infection, delay therapy closer to the third trimester [19]. Therapeutic monitoring is often achieved by different methods: often, serial ultrasounds of goiter volume are implemented, cordocentesis allows for direct measurement of fetal hormones and amniotic fluid allows for indirect measurement of these [20]. Success rates have been reports as high as 70% after intra-amniotic therapy [21]. When failure to note goiter shrinkage is noted, careful consideration should be given to inefficiency of dosage vs. normal physiologic growth relative to the gestational age [22]. Also, if swallowing is impaired by goiter-mass effect, fetal intramuscular or umbilical cord injections may be an alternative [23].

Hyperthyroidism

Fetal hyperthyroidism is far less common than fetal hypothyroidism. Fetal hyperthyroidism occurs as a result of transplacental passage of thyroid-stimulating antibodies, most commonly in the setting of maternal Grave's disease. Although a life-threatening disease, fulminant neonatal hyperthyroidism, is a rare occasion (<1% of mothers with Grave's disease). Passage of these antibodies result in dysregulated activation of the fetal thyroid. Circulating (thus transplacental) anti-thyroid antibodies persist after maternal definitive therapy such as radioablation or thyroidectomy [24]. Alternatively, TSH receptor mutations have been described which result in neonatal and familial graves disease [25].

While subclinical hyperthyroidism is not associated with poor fetal outcomes, fetal overt hyperthyroidism may result in intrauterine growth restriction (IUGR), goiter formation, tachycardia and heart failure [26]. Screening and diagnosis for fetal findings of hyperthyroidism are recommended for patients with uncontrolled hyperthyroidism and TRAb levels three times the normal value. Ultrasound screening includes growth assessment, brain/heart/skeletal development, amniotic fluid volumes and presence of thyroid goiters. In addition, prenatal care should be coordinated with experienced perinatologists.

Therapeutic approach to fetal hyperthyroidism is a careful balance of maternal and fetal well-being. PTU may be given to the mother with careful monitoring, as to not cause iatrogenic hypothyroidism described before. PTU is also associated with hepatotoxicity and leukocytosis [27]. Once euthyroidism is achieved, add back therapy with levothyroxine is not

Table 1
Summary and recommendations.

Condition	Fetal Manifestations	Screening	Treatment
Hypothyroidism	Most are asymptomatic until birth. May present with goiter.	Newborn screening at birth.	If iatrogenic, discontinuation of maternal medication
Hyperthyroidism	IUGR, goiter formation, tachycardia, heart failure	Maternal TRAb levels, if >3 times normal, serial ultrasonography.	Maternal PTU. If fetal tachycardia present, consider beta blockage

Table 1 Summary and recommendations for both fetal hypo- and hyperthyroidism.

recommended given the additional side effect profile and difficulty to discern causative agent of side effects [28]. PTU is preferred over MMI given reports of teratogenicity such as choanal atresia, aplasia cutis and hearing loss [29]. Yet, in the case of mothers with definitive Grave's disease treatment, maternal levothyroxine supplementation is required [30]. In the setting of fetal tachycardia secondary to hyperthyroidism, beta blockage has been used but carries the additional risk of fetal growth restriction and variable efficiency [31].

Conclusion

Fetal thyroid disorders may have varying manifestations but result in chronic long-term conditions, which affect neonatal development and health. Current recommendations and guidelines are summarized as Table 1. The uterine environment presents a unique opportunity for the diagnosis as well as early treatment of these conditions. As medicine has advanced we have developed ultrasound-guided methods of intra-amniotic therapy as well as manipulation of transplacental pharmacokinetics. Yet much work is needed to elucidate the mechanisms and optimization of therapy to benefit both mother and developing fetus.

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