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Review article

Maternal hypothyroidism: An overview of current experimental models

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ABSTRACT

Maternal hypothyroidism (MH) is the most common cause of transient congenital hypothyroidism. Different animal models are used for assessing developmental effects of MH in offspring. The severity and status of hypothyroidism in animal models must be a reflection of the actual conditions in humans. To obtain comparable results with different clinical conditions, which lead to MH in humans, several factors have been suggested for researchers to consider before designing the experimental models. Regarding development of fetal body systems during pregnancy, interference at different times provides different results and the appropriate time for induction of hypothyroidism should be selected based on accurate time of development of the system under assessment. Other factors that should be taken into consideration include, physiological and biochemical differences between humans and other species, thyroid hormone-independent effects of anti-thyroid drugs, circadian rhythms in TSH secretion, sex differences, physical and psychological stress. This review addresses essential guidelines for selecting and managing the optimal animal model for MH as well as discussing the pros and cons of currently used models.

1. Introduction

Hypothyroidism is one of the most common endocrine disorders during pregnancy [1]. Proper development of the fetus depends on its genetics [2] as well as the hormonal, metabolic, and nutritional environments provided by the mother [3]. Thyroid hormones (THs) are essential for metabolism, development, and normal growth of fetal organs [4]. Prior to the development of the fetal thyroid gland, maternal THs are the only source of THs during fetal life [5,6].

Over the years, many studies have examined developmental effects of TH deficiency on various systems in the fetus, using animal models and their results have provided better understanding of disease pathogenesis and also helped in treatment of TH insufficiency during fetal life [7–9]. As a general rule for all animal models, animal models of maternal hypothyroidism (MH) should be as close as possible to the human disease, emphasizing that researchers must consider the exact prerequisites before any experiment [10].

In this study, we focus on animal models of MH, as one of the main causes of congenital hypothyroidism [11]; in addition, the advantages and disadvantages of different models have been compared. Since almost 80% of animal experiments are mostly conducted on rodents, viz., in rats [12], in this review, MH has been mainly compared between humans and rats.

2. Hypothyroidism: definition and epidemiology

Hypothyroidism, defined as insufficient TH production by the thyroid gland [13,14], is the most common hormone deficiency [15]. Hypothyroidism is very common among women [15,16], i.e. a prevalence of 18 in 1000 women (compared to 1 in 1000 in men) for overt hypothyroidism and 75 in 1000 women (compared to 28 in 1000 in men) for subclinical hypothyroidism [16]. The National Health and Nutrition Examination Survey (NHANES III) reported that about 1 in 300 persons in the US have hypothyroidism [14] and prevalence of the disease is higher in whites than African-Americans and Hispanics (5.1% vs. 1.7%, and 4.1%, respectively) [15].

Hypothyroidism is classified based on the time of onset (congenital or acquired), severity (clinical or subclinical) and disorder origin (primary or secondary) [15]. Deficiency of THs at birth is considered as congenital hypothyroidism (CH), which is classified into two categories, the permanent and the transient [11]. Etiology of CH determines whether the hypothyroidism is permanent or transient [17]; permanent CH is mainly (85%) due to anomalies related to development of thyroid gland and migration and to a lesser extent (10–15%) is attributed to other factors including disorders in synthesis, metabolism, or transport of THs [11,17].

Transient CH is mainly attributed to maternal thyroid disorders [1,11]. The most common cause of transient CH is iodine deficiency [18], which is a public health problem in 118 countries [19]. Most of

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these countries are located in Latin America, Africa, Asia and large areas of Europe; in the mountainous parts of these areas such as the Himalaya, Andes and Alps where the soil is frequently eroded by floods, the mineral elements such as iodine content are severely reduced in the soil and agricultural products grown in these areas do not have enough iodine [19]. The incidence of transient CH is very rare in iodine-sufficient areas such as the United States and Canada, i.e. 1 in 50,000–1 in 40,000 [20] or can be very common in the iodine-deficient areas such as Europe (1 in 100) [11] and the central part of the Africa (1 in 10) [21].

Before implementation of the newborn screening (NBS) programs, the incidence of CH was reported to be approximately 1 in 7000 to 1 in 10,000 live births; after the NBS, this range increased to about 1 in 3000–1 in 4000 [11,22,23]. Incidence of CH in the United States has doubled during 1987–2002 from 1 in 3985 to 1 in 2273 and again during 2002–2005 to 1 in 1415, similar to a rise reported in New Zealand, representative of their Asian population, during 1993–2010 [22]. The prevalence of CH is 1 in 650 in Turkey, 1 in 800 in Greece, 1 in 1000 in France [24], 1 in 1608 in Iran [25], 1 in 2372 in America, and 1 in 2640 in India [24]. However, over the past two decades, the worldwide prevalence of CH has increased dramatically from 1 in 1600 to 1 in 2800 live births; this variability in prevalence is related to environmental factors, changes in the ethnicity, race, and the method of screening in the population studied [23].

3. Hypothyroidism in pregnancy

Depending on the diagnostic criteria and the pregnancy trimester, prevalence of hypothyroidism in pregnancy varies, and on an average ranges from 2 to 5% for clinical and 3–5% for subclinical hypothyroidism [1,6]. The main cause of MH during pregnancy is dietary iodine insufficiency [15,26,27]. In iodine-sufficient areas, the most common cause of MH is chronic autoimmune thyroiditis [1,28], with a prevalence of ~18% for positive thyroid peroxidase antibody (TPO-Ab$^+$) or thyroglobulin antibody (Tg-Ab$^+$) among pregnant women [29]. These antibodies can cross the placenta and can affect fetal thyroid function [30]. Data also show that 1–5% [31] of neonates whose hyperthyroid mothers had been treated with propylthiouracil (PTU), were born with suppressed THs [31–33]. Iodine excess during pregnancy is another reason for MH [1,34,35], e.g. taking amiodarone, an iodine-containing antiarrhythmic drug [11,16,34]. Other causes of MH during pregnancy include previous radioactive iodine therapy and total or subtotal thyroidectomy for treatment of hyperthyroidism, as in Graves' disease and thyroid cancer [1]; these women are euthyroid before pregnancy but are at risk for developing hypothyroidism during pregnancy [29]. Iron deficiency is another cause of hypothyroidism during pregnancy [1] as thyroid peroxidase, which is necessary for TH synthesis is a heme-containing enzyme [1,36]. Iron deficiency is a common disorder with a prevalence of ~18% in USA [37] and 4.3–21.5% among pregnant women in Iran [38].

3.1. Current clinical treatment for hypothyroidism during pregnancy

For diagnosis of hypothyroidism during pregnancy, serum levels of thyroid-stimulating hormone (TSH), free thyroxine (FT_4), total thyroxine (TT_4), and TPO-Ab are measured in early pregnancy [1]. Increased TSH levels along with decreased FT_4/TT_4 (according to trimester-specific reference ranges) or TSH > 10.0 mIU/L, regardless of FT_4 indicate overt hypothyroidism [1,29]. If trimester-specific reference ranges are not available, the following reference ranges can be used: first trimester, 0.1–2.5 mIU/L, second trimester, 0.2–3.0 mIU/L, and third trimester, 0.3–3.0 mIU/L [28,29]. Raised TSH in presence of normal FT_4/TT_4 is considered as subclinical hypothyroidism, which may be TPOAb$^+$ or TPO-Ab$^-$ [1]. Women with overt and TPO-Ab$^+$-subclinical hypothyroidism during pregnancy are treated with levothyroxine aiming at maintaining serum TSH levels in the above-mentioned reference ranges [1]. Thyroid function tests then should be measured every 4–6 weeks [1]. Women with TPO-Ab$^-$-subclinical hypothyroidism during pregnancy are followed by measuring thyroid function test every 4–6 weeks [1].

Elevated TSH and low thyroxine (T_4) in newborn screening tests are critically used to detect MH [39]. Regardless of the causes of CH, treatment of the newborn should be initiated promptly after birth [40], to maintain serum levels of FT_4 or TT_4 in the upper normal range during the first year of life [11]; NBS has provided promising results in preventing CH-related dysfunctions but unfortunately there is no established NBS program for 71% of babies currently born worldwide [22]. Since treatment of CH does not always prevent the irreversible disorders created by TH insufficiency during fetal period [41,42], it has been proposed that this screening must also be done during pregnancy [43].

4. Thyroid hormone functions during pregnancy in human

In humans, the maternal thyroid gland and its functions undergo significant changes during pregnancy. To provide the extra 50% required for iodine and production of THs during pregnancy, the thyroid gland enlarges by ~10% [29,44]. In very early pregnancy, high estrogen levels stimulate hepatic thyroxine binding globulin (TBG) synthesis [45] and increase circulating TBG approximately 2–3 fold [46]. Moreover the estrogen increases sialylation of TBG that increases the half-life of TBG from 15 min to 3 days [46]; enhancement of TBG is the main triggering factor for high concentrations of TT_4 and triiodothyronine (T_3) during pregnancy [46]. In addition, placental production of type III deiodinase [46,47], which converts T_4 to T_3 and T_3 to 3,5-diiodo-L-thyronine (T_2), increases the demand for T_4 and T_3 [48,49]. Human chorionic gonadotropin secretion of the placenta which has mild thyrotropic activity is another mechanism for further production of THs [46,50].

The fetal thyroid gland in humans is inactive until 10–16 weeks of pregnancy [4,51,52] and maternal THs are the only source of TH during the first trimester [43,52]; therefore, in humans, MH during this period leads to fetal hypothyroidism. After the first trimester, fetal TH secretion increases,thereby providing cooperation between maternal and fetal THs [4]. From the second trimester to birth, the embryo is still 20–50% dependent on maternal THs [4].

5. Thyroid hormone functions during pregnancy in rats

The basic mechanisms involved in the regulation and function of the hypothalamus-pituitary-thyroid axis are generally similar between rats and humans; there are however clear biochemical and physiological differences [53]. In humans, THs bind to TBG which has a high affinity, i.e. only 0.03% of T_4 is in the free form [53]. In rats, TBG is replaced with albumin (also in other species, including cats, rabbits, mice, guinea pigs) and transthyretin [10] as adult rats do not have TBG [54]. The binding affinity of albumin and transthyretin is about one-hundredth of TBG; therefore, compared to rats, FT_4 levels are lower in humans [10]. In addition, lack of TBG in adult rats causes much higher T_4 clearance compared to humans, which increases T_4 production and changes the morphology of the thyroid gland to small follicles, which are more active [53].

Total serum TH concentrations in adult male and female rats are different; the average values are shown in Table 1. Few studies have reported circulation TH levels during pregnancy in rats. Compared with nonpregnant rats, plasma T_4 and T_3 levels significantly decrease in the last days of pregnancy (days 17–22), but plasma TSH levels do not change significantly; in addition, TSH responses to THs and TRH are decreased and prolonged, respectively [55]. Decreased TH levels during pregnancy are also attributed to lack of TBG and chorionic gonadotropin in rats [53].

Bioavailability of THs is different between humans and some other