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Review
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Review

Thyroid hormones and female reproduction†

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Abstract

Thyroid hormones are vital for the proper functioning of the female reproductive system, since they modulate the metabolism and development of ovarian, uterine, and placental tissues. Therefore, hypo- and hyperthyroidism may result in subfertility or infertility in both women and animals. Other well-documented sequelae of maternal thyroid dysfunctions include menstrual/estral irregularity, anovulation, abortion, preterm delivery, preeclampsia, intrauterine growth restriction, postpartum thyroiditis, and mental retardation in children. Several studies have been carried out involving prospective and retrospective studies of women with thyroid dysfunction, as well as in vivo and in vitro assays of hypo- and hyperthyroidism using experimental animal models and/or ovarian, uterine, and placental cell culture. These studies have sought to elucidate the mechanisms by which thyroid hormones influence reproduction to better understand the physiology of the reproductive system and to provide better therapeutic tools for reproductive dysfunctions that originate from thyroid dysfunctions. Therefore, this review aims to summarize and update the available information related to the role of thyroid hormones in the morphophysiology of the ovary, uterus, and placenta in women and animals and the effects of hypo- and hyperthyroidism on the female reproductive system.

Summary Sentence

Thyroid dysfunctions are associated with several morphophysiological and behavioral alterations, including reproductive disorders in women and animals. Thus, the objective of this review was to summarize the role of thyroid hormones in ovarian, uterine and placental morphophysiology.

Key words: thyroxine, triiodothyronine, reproduction, female, disease.

Introduction

Thyroid hormones (THs) are vital for the normal reproductive function of humans and animals. L-thyroxine (3,5,3',5'-tetraiodothyronine, T4) and L-triiodothyronine (3,5,3'-triiodothyronine, T3) act directly on ovarian, uterine, and placental tissues via specific nuclear receptors that modulate the development and metabolism of these organs [1–5]. In addition, they act indirectly through multiple interactions with other hormones and growth factors, such as estrogen, prolactin (PRL), and insulin-like growth factor (IGF), and by influencing the release of gonadotrophin-releasing hormone (GnRH) in the hypothalamic-pituitary-gonadal axis [6, 7]. Therefore, changes in the serum levels of THs, such as hypo- and hyperthyroidism, may result in subfertility or infertility in both women and animals [8–11].

Thyroid dysfunction is usually acquired and can occur at any time in life. The prevalence of clinical and subclinical hypothyroidism in women of reproductive age and during pregnancy is 0.3% and 4.3%, respectively [12, 13]. In domestic animal species, such as goats, dogs, and equines, hypothyroidism is also considered one of the main endocrinopathies [14–16]. Hypothyroidism usually results from autoimmune thyroiditis, in which the body's own antibodies react against key thyroid proteins, such as thyroperoxidase (TPO) and/or thyroglobulin (Tg), resulting in destruction and the loss of gland function [17]. The occurrence of hypothyroidism in women and animals is associated with reproductive disorders, such as delayed onset of puberty [18], anovulation, ovarian cysts, menstrual/estral irregularity [7, 19], infertility, increased frequency of spontaneous abortions [20], and the birth of preterm infants with low birth weight and congenital anomalies [20–22]. In addition, research has recently shown that these gestational changes also result from compromised placental development, with reduced proliferation and increased apoptosis of trophoblastic cells and a failure of intrauterine migration associated with alterations in the endocrine, immune, and angiogenic profiles at the maternal–fetal interface [9, 23, 24].

The prevalence of hyperthyroidism in women of reproductive age is 1.3%, and the disease usually occurs as a result of an increase in antibodies against the thyroid-stimulating hormone (TSH) receptor, which is known as Graves' disease. Data supporting the association of hyperthyroidism with infertility are still sparse and sometimes conflicting [11], but retrospective and prospective studies suggest that 5.8% and 2.1% of women with hyperthyroidism have primary and secondary infertility, respectively [25, 26]. Although its prevalence is lower than that of hypothyroidism, the occurrence of hyperthyroidism is also associated with menstrual irregularity, increased follicular atresia, and ovarian cysts [12, 27–30]. In rats, hyperthyroidism also alters placental morphogenesis and increases the proliferative activity of trophoblasts [31] and is believed to affect the oxidative state of the endometrium, as it influences the activity of superoxide dismutase, catalase, and glutathione peroxidase [32].

Thus, because thyroid dysfunction is associated with several morphological, physiological, and behavioral alterations, including reproductive disorders in women and animals, the objective of this review was to summarize the role of THs in ovarian, uterine, and placental morphophysiology. Additionally, this review aimed to provide an update on the effects of hypo- and hyperthyroidism on the female reproductive system in humans and animals. It is important to emphasize that previous reviews of this subject are scarce, and the only review in the literature on this subject was published almost two decades ago [33]. According to the review criteria, all original articles and review articles that focused on thyroid physiology and/or hypo- or hyperthyroidism in association with female reproduction were searched on PubMed or Scielo. We used the search terms "thyroid," "reproduction," "female," "fertility," "infertility," "hypothyroidism," "hyperthyroidism," "pregnancy," and "disease." Most of the papers identified were English-language, full-text articles.

Hypothalamic-pituitary-thyroid axis

The mechanisms regulating the synthesis and release of T3 and T4 are similar in humans and animals [33], and the control of the serum concentrations of these hormones is regulated by a negative feedback loop that involves the hypothalamus, the pituitary and the thyroid. Thyroid-stimulating hormone, which is also known as thyrotropin, is secreted by thyrotrophic cells of the anterior pituitary, regulates the synthesis and secretion of T3 and T4 by the thyroid, and is a physiological marker of the action of THs [34]. In addition, thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus and regulates the secretion of pituitary TSH. TSH, TRH, and THs form the hypothalamic-pituitary-thyroid axis (HPT) [35]. In general, elevated blood levels of THs inhibit the release of TRH and TSH, whereas the opposite effect occurs when serum TH levels decrease [33].

T3 and T4 are composed of two tyrosyl residues, which are linked by an ether bond, and substituted by three and four iodine residues, respectively. For the biosynthesis of these hormones by the thyroid, iodide entry into the thyroid follicle is required, which is dependent on the activity of two transmembrane glycoproteins present in the thyroid, sodium-iodide symporter (NIS) and pendrin [36] (Figure 1). After its entry into the thyroid follicle, iodide is oxidized by TPO and incorporated into Tg to form monoiodothyronine (T1) and diiodothyronine (T2), with the subsequent formation of T3 and T4 [37]. The expression of NIS and pendrin, as well as TPO and Tg, is dependent on the expression of the transcription factor Pax8, which is vital for the development and proper functioning of the thyroid [38].

Transport and bioavailability of thyroid hormones

T3 is the biologically active hormone, while T4, which is the major hormone secreted by the thyroid, is considered a precursor of T3 or a prohormone. T3 is approximately four times more potent than T4, but its circulating concentration and plasma half-life are much lower than T4. The deiodination of T4 in peripheral tissues (e.g. in the liver) by the action of deiodinases (D1, D2, and D3) leads to the production of T3 and/or reverse T3 (rT3). Reverse T3 has no known genomic effects [33], while T3 performs its action by binding to four specific nuclear receptors, TRα1, TRα2, TRβ1, and TRβ2, resulting in the gene expression of THRα and THRβ. The expression of each of these receptors varies according to the target tissue [39].

Deiodinase type 1 (D1) is responsible for most of the circulating T3, while D2 controls the generation of intracellular T3. D1 is also able to inactivate T4 by converting it to rT3 [10, 40]. A third deiodinase, D3, is also present in tissues and is responsible for inactivating THs by converting T4 and T3 into rT3 and T2, respectively [41]. It is also important to emphasize that in addition to the action of the deiodinases, the bioavailability of THs is influenced by sulfation, and 80% of the T4 produced by the thyroid is metabolized to inactive sulfated biological molecules, such as T4S, T3S, and rT3S [42].

Less than 0.1% of the total amount of circulating TH (T3 or T4) is in its free form, not bound to plasma proteins, and can be transported into cells by specific carrier-mediated mechanisms [43]. When released into the bloodstream, T3 and T4 bind reversibly to three different transporter proteins that are primarily produced in the liver: thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin [44]. All three proteins can carry T3 and T4, although T4 has a higher affinity for the three proteins [45]. Lipoproteins can also bind to a small fraction of THs. However, the major carrier protein in humans is TBG because of its greater affinity for THs [44, 46]. In rodents, in contrast, the major carrier protein is albumin, since although TBG has a higher affinity for T3 and T4, its plasma concentration is small in these species [47].

T3 and T4 enter the target cell by diffusion or by carrier-mediated transport involving membrane transporters, such as MCT8, MCT10, and Oatp1a2. Within the target cell, THs perform their function directly by activating their nuclear receptors, stimulating or repressing

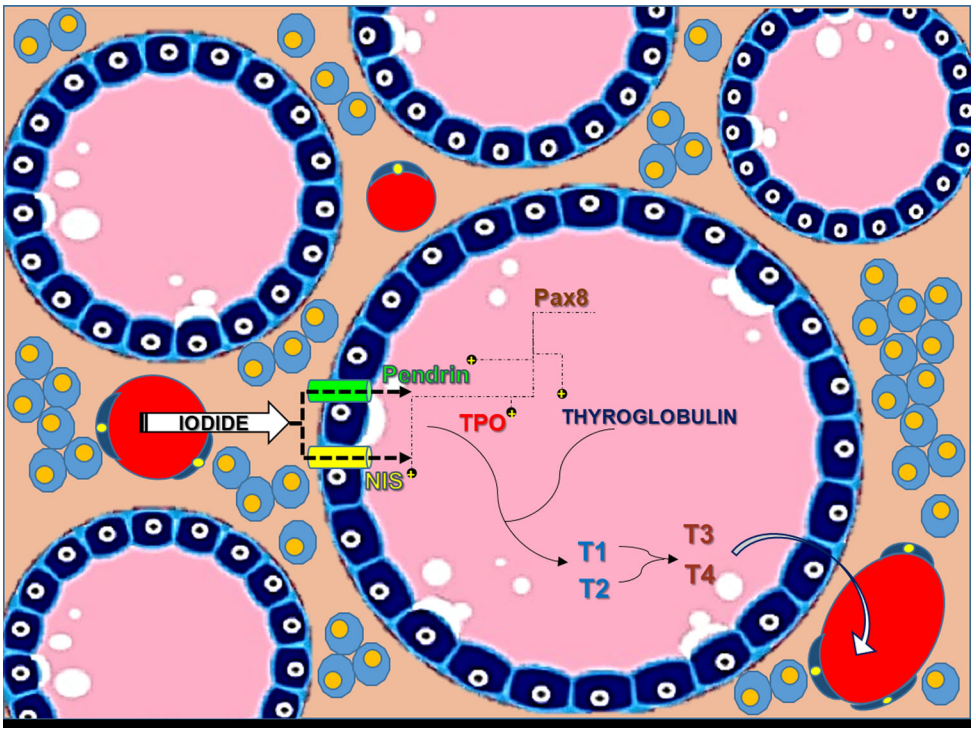

Figure 1. Biosynthesis of thyroid hormones by the thyroid. Iodide moves across the basolateral plasma membrane of thyrocytes and enters into the thyroid follicle through two transmembrane glycoproteins: sodium-iodide symporter (NIS) and pendrin. After its entry into the thyroid follicle, iodide is oxidized by thyroperoxidase (TPO) and incorporated into thyroglobulin to form monoiodothyronine (T1) and diiodothyronine (T2), with the subsequent formation of T3 and T4. The expression of NIS, pendrin, TPO, and thyroglobulin is dependent on the expression of the transcription factor Pax8.

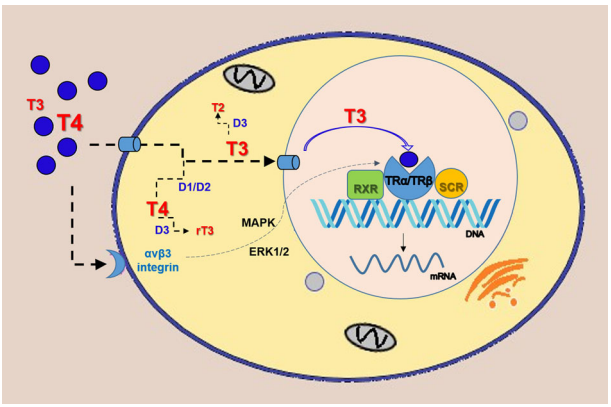

Figure 2. Mechanism of action of thyroid hormones on target cells. THs, mostly T4, enter the target cell by diffusion or by carrier-mediated transport. Within the target cell, T4 is converted to T3 by deiodinases of type 1 (D1) and type 2 (D2). Deiodinase type 3 (D3) is responsible for inactivating THs by converting T4 and T3 into rT3 and T2, respectively. T3 enters the cell nucleus and activates its nuclear receptors in the DNA, stimulating or repressing the expression of transcriptional genes that are dependent on retinoic acid X receptor (RXR) dimerization and/or the recruitment of coactivators, such as steroid receptor coactivator (SRC). In addition to nuclear receptors, THs can also act by binding to $\alpha v\beta 3$ integrin, which is present in the cell membrane and activates a signal transduction cascade via MAPK and ERK1/2 to regulate the transcription and phosphorylation of its nuclear receptors.

the expression of transcription genes that are dependent on retinoic acid X receptor dimerization (RXR) and/or the recruitment of coactivators, such as steroid receptor coactivator (SRC) (Figure 2) [48, 49]. In addition to nuclear receptors, THs can act indirectly by binding to a membrane protein, $\alpha v\beta 3$ integrin, which activates a signal transduction cascade via MAPK and ERK1/2 to regulate the transcription and phosphorylation of its nuclear receptors [50].

After activating their receptors, THs perform their function of regulating the metabolism of carbohydrates, proteins, and lipids in all cells, as well as regulating cell differentiation and proliferation [51, 52]. Thus, changes in the plasma levels of THs may affect all organs and organ systems, including adverse effects on the reproductive system [8–10, 23, 31, 45, 53, 54].

Bioavailability of thyroid hormones during pregnancy

The transfer of THs from mother to fetus during pregnancy varies between women and animals. This process is dependent on the type of placenta, which will influence the expression of transporter molecules, binding proteins, and D3 activity. D3 has high expression in the uterus, placenta, and amniotic membrane, where it plays an important role as an enzymatic barrier to the excessive transfer of maternal THs to the developing fetus [55]. Mice in which D3 has been knocked out have thyrotoxicosis and perinatal lethality [56]. In addition, D2 is expressed in the hemochorial placenta, brain, pituitary gland, and brown adipose tissue and generates local concentrations of T3 that are essential for normal tissue development and function, rather than contributing significantly to the circulating pool of T3. It is known that T3 levels in the amniotic and celomatic fluid and in the fetal bloodstream are consistently low during gestation, and fetal T3 is mainly locally produced by D1 and D2 activity, as the production of T3 in the fetus by hepatic D1 is considered to be the major endocrine source of circulating T3 [57]. In ovine, caprine,

equine, and swine species, the placenta is epitheliochorial and appears to be impermeable to the maternal–fetal transfer of THs [55]. The placental transfer of iodide is mediated by NIS and pendrin, which are necessary for adequate iodine transfer from the mother to the growing fetus [58, 59]. In addition, the placenta is freely permeable to TRH but not to TSH. It is assumed that maternal TRH transferred to the fetus may play an important role in the control of fetal thyroid function before full maturation of the fetal HPT (16th to 18th week of gestation in humans, 17th day of gestation in rats and 5th to 6th week of gestation in sheep) [55, 60, 61].

It has been shown that the thyroid receptor isoforms TRα1, TRα2, and TRβ1 are present in the placenta, and their expression increases with fetal age [62, 63]; in humans, these receptors are present in both the interstitial trophoblast and the extravillous trophoblast, with strong expression mainly in the latter [64]. In humans, at the end of the first trimester of gestation, the maternal serum

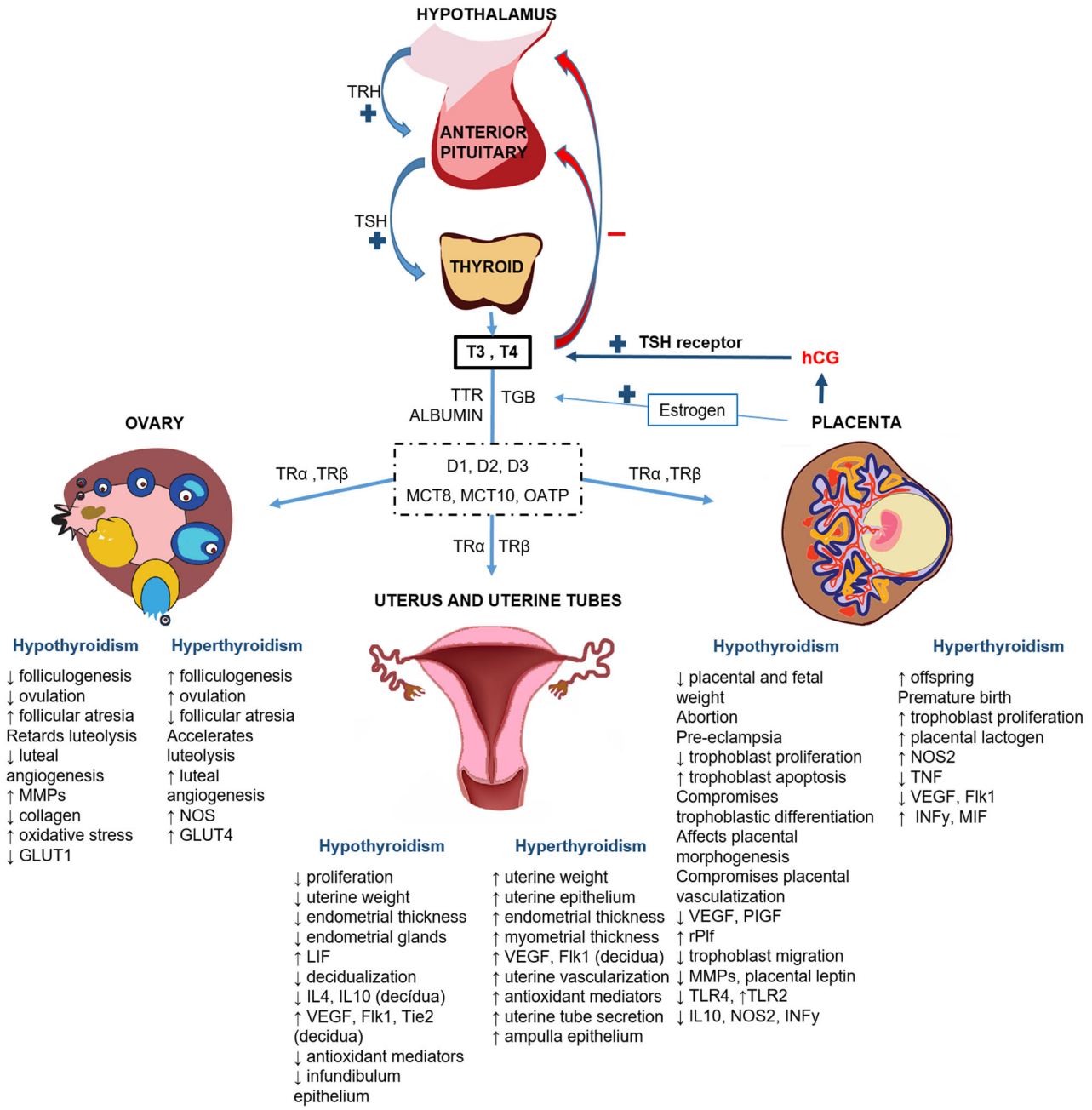

Figure 3. Hypothalamic-pituitary-thyroid axis and effects of hypo- and hyperthyroidism on the morphophysiology of the ovary, uterine tube, uterus, and placenta. Low blood levels of THs are detected by the hypothalamus and the pituitary. Thyrotropin-releasing hormone (TRH) is released by the hypothalamus, stimulating the pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to produce THs, returning the level of THs in the blood to normal. In contrast, elevated blood levels of THs inhibit the release of TRH and TSH. During pregnancy, human chorionic gonadotrophin (hCG), produced by the placenta, binds to the TSH receptor and activates the maternal HPT axis, stimulating TH synthesis. Increased levels of estrogen during gestation also stimulate the expression of TBG by the liver, increasing the total TH serum concentrations. T4, L-thyroxine. T3, L-triiodothyronine. TBG, thyroxine-binding globulin. TTR, transthyretin. D, deiodinase. MCT8, MCT10, and Oatp1a2 are membrane transport proteins. TRα and TRβ are thyroid nuclear receptors.

concentration of human chorionic gonadotrophin (hCG), which is produced by the placenta, is sufficient to bind to the TSH receptor and partially stimulate maternal HPT activity (Figure 3). Activation of the receptor for TSH by hCG stimulates T4 synthesis, decreases serum TSH levels, and increases free T4 levels, an effect that is intensified by twin pregnancies [33, 65]. It is important to note that in some situations, excessive stimulation of the TSH receptor by hCG may result in maternal thyrotoxicosis [66]. Increased levels of estrogen during gestation also stimulate the expression of TBG by the liver, which nearly doubles its serum concentration, allowing a concomitant increase in total T3 and T4 serum concentrations [67]. This effect explains the increased levels of TGB in humans and rats during gestation, in contrast to the observation in mice that TBG levels decrease [33]. It is important to emphasize that during pregnancy, the placenta complements maternal hepatic function, as it produces TTR, α1 antitrypsin, and β1-acid glycoprotein, proteins that locally modulate TH transport at the maternal–fetal interface [68, 69]. It is suggested that TTR protects against the deiodination of THs, mainly by D3, in the placental tissue, allowing greater passage of those hormones to the fetal circulation [55, 70, 71]. This passage is dependent on membrane transporters, including MCT8, MCT10, and Oatp1a2 [72, 73]. Catalano et al. [74] also demonstrated that TPO and Tg are expressed by the endometrium and may be responsible for the local production of TH at the maternal–fetal interface.

Role of thyroid hormones in the female reproductive system

The effect of THs on fertility and fetal development has been extensively investigated by assessing adverse outcomes in individuals with thyroid dysfunctions and by experimental induction of these dysfunctions in laboratory animals or in domestic animals, such as dogs, cattle, sheep, and pigs [8, 10, 19, 20, 23, 31, 45, 65, 75–80]; the results obtained in these studies are shown in Figure 3. Based on these investigations, plasma levels of THs in women and animals are known to influence molecular mechanisms that affect menstrual/estrous cycle control, sexual maturation and behavior, ovulation, maternal ability, pregnancy maintenance, postnatal and fetal growth, and lactation [22, 31, 78, 81–83]. These effects are due to both the direct action of THs in the reproductive organs and the action of THs on the bioavailability of other hormones and growth factors that are also necessary for the proper functioning of the female reproductive system [55, 84].

Effect of thyroid hormones on other hormones and growth factors

Sex steroids

Disorders of reproductive behavior and cycling in females caused by thyroid dysfunctions are associated with changes in the bioavailability and metabolism of other hormones, such as sex steroids and their transport proteins [84]. It is known that the blood transport of sex steroids (testosterone, dihydrotestosterone, and estradiol) occurs through the action of sex hormone-binding globulin (SHBG) and that THs affect the production of this transporter protein by altering the production of hepatic SHBG via hepatocyte nuclear factor-4α (HNF4α) [21, 85]. Under hypothyroid conditions, the serum level of SHBG is lower, causing a reduction of total circulating steroid levels and an increase in the free fraction. In contrast, under hyperthyroid conditions, increased SHBG increases the total circulating steroid levels, with a normal or reduced free fraction [86]. The rate of metabolic clearance of sexual steroids is also reduced in both hypo- and hyperthyroidism [86]. However, not only the transport and elimination rate but also the synthesis of sex steroids are affected by THs, so thyroid hyperfunction is associated with increased plasma levels of estrogen, androstenedione, and testosterone caused by increased synthesis of androstenedione and testosterone, decreased clearance of 17β-estradiol, and increased metabolism of androstenedione to estrone and testosterone to estradiol [21, 87].

These changes in serum steroid levels resulting from thyroid dysfunctions are capable of affecting sexual behavior in women and animals, although the results in the literature are conflicting. Some research shows that hyperthyroidism in women before puberty causes delayed menstruation and an increased incidence of oligomenorrhea or amenorrhea [21]. Hypothyroidism has also been shown to cause a delay in sexual maturity. However, in some cases, it has been reported that hypothyroidism may be associated with precocious puberty and galactorrhea [21]. In animals, T3 is required for the transition from the estrous phase to the anestrous state in species that reproduce seasonally [88]. In sheep, for example, T3 must be present at the end of the breeding season to start anestrous. However, this hormone plays no role in the maintenance or duration of anestrous [81, 89].

Leptin, corticosterone, growth hormone, insulin-like growth factor 1, and prolactin

In addition to decreased serum levels of total sexual steroids, hypothyroid rats also show increased circulating leptin levels and reduced levels of corticosterone, growth hormone (GH), and insulin-like growth factor 1 (IGF-I). Alterations in the serum levels of these hormones and growth factors are associated with prolonged periods of diestrus (pseudogestation) in hypothyroid rats [90–92]. In rats and mice, PRL is a luteotropic hormone that stimulates progesterone synthesis by the corpus luteum [93], and hypothyroid rats develop pseudopregnancy because there is an increase in serum concentrations of progesterone and PRL [90–92].

Some studies have shown that hypothyroidism increases the levels of PRL in women, rats, mice, and female dogs [94–99], as does the administration of TRH to lactating sows [77]. The elevation of PRL serum levels has been observed in 22% to 57% of women with clinical or subclinical hypothyroidism, and these levels normalize after treatment with L-thyroxine [98]. The PRL increase under hypothyroid conditions is related to TRH stimulation, as lactotropic cells, analogous to thyrotropic cells, express membrane receptors for this releasing hormone. Thus, hyperprolactinemia is typically reversed when euthyroidism is restored after treatment with L-thyroxine [100]. In addition, the hypothyroidism-induced increase in PRL is also due to an increase in pituitary vasoactive intestinal peptide, which affects PRL secretion by acting as a paracrine or autocrine regulator [101]. It is important to emphasize that hyperprolactinemia in women, similar to hypothyroidism, is also associated with the occurrence of hypogonadotrophic anovulation, amenorrhea, and decreased fertility, and treatment with dopaminergic agonists is able to reduce PRL secretion and restore fertility [102]. These reproductive changes result from the inhibition of the pulsatile secretion of LH caused by excess PRL that inhibits the activity of GnRH neurons [97, 103]. As hypothyroidism is also associated with failures in the occurrence of LH preovulatory peaks and a reduction of GnRH biosynthesis [6], it is believed that most of the reproductive dysfunctions observed in women and animals with hypothyroidism may also be due to hyperprolactinemia.

Kisspeptin

It has been shown that kisspeptin is a key neuropeptide in the control of reproduction in both humans and animals because it regulates the pulsatile secretion of GnRH [104]. As kisspeptin neurons have receptors for PRL, it is believed that this is the pathway by which PRL influences the activity of GnRH neurons, since these neurons have receptors for kisspeptin [105]. Although the role of THs in the neuroendocrine regulation of kisspeptin is poorly understood, some studies have shown that there is an interrelation between THs and kisspeptin. Recently, Tomori et al. [106] demonstrated that the expression of kisspeptin in the hypothalamus is reduced in rats with thyroid hypofunction, suggesting that the dysregulation of reproductive function observed in hypothyroidism is caused by the inhibition of kisspeptin neurons in the hypothalamus. Ogawa et al. [107] also observed that T3 stimulates the gene expression of *Kiss2* and *Gnrh1* in male tilapia (*Oreochromis niloticus*), which are analogous to the *Kiss1* and *Gnrh* genes in mammals, and that the expression of *Kiss2* and *Gnrh1* is reduced in tilapia with hypothyroidism. Treatment of hamsters with T3 is also capable of modulating the hypothalamic expression of kisspeptin [108].

Thus, because kisspeptin, sex steroids, and PRL all affect the release of gonadotrophins and THs influence the expression of these hormonal mediators, it seemed likely that T3 and T4 may also affect the development and maturation of the reproductive system in humans and animals, during both intrauterine and postnatal life. However, it is now known that THs in human fetuses have little or no effect on the development of the female reproductive system, contrary to what is observed in rodents, which show impaired intrauterine development of the reproductive system in hypothyroid conditions [33]. Previously, it was believed that THs had a greater impact on ovarian function than on other reproductive tissues [109, 110]. However, in recent research, it has been observed that uterine and placental morphophysiology is also strongly influenced by serum TH levels, which are responsible for several pathologies, such as spontaneous abortion, intrauterine growth restriction, preeclampsia, and preterm labor, in the setting of thyroid dysfunction [111, 112].

Effect of thyroid hormones on ovarian morphophysiology

Folliculogenesis and ovulation

Female fertility depends on adequate development of the gonads, oocyte maturation, the proliferation and differentiation of granulosa cells, and the interaction between various hormones and growth factors that coordinate cyclic ovary changes during folliculogenesis [113]. Thus, at each stage of follicular development, factors of autocrine, endocrine, and/or paracrine origin act directly or indirectly in follicular cells to guide their differentiation, either for follicular growth or atresia [114]. Among these factors are T3 and T4, which have been identified in follicular fluid of human ovarian follicles [115].

Oocytes and granulosa, ovarian stromal, and cumulus cells express receptors for THs [115–117], demonstrating that T3 and T4 act directly on ovarian tissue. By means of in vitro studies, it was verified that the growth of preantral follicles of rats and the ovulatory rate are stimulated by THs. In addition, in combination with FSH, T3 is capable of enhancing proliferation and reducing apoptosis in granulosa cells [118, 119]. The interaction between T3 and gonadotropic hormones also inhibits the excessive production of androgens by theca cells and stimulates aromatization, with estrogen production by granulosa cells [120]. The THs are physiologically involved not only in the maturation of preovulatory follicles and mouse cumulus oophorus cells [121] via ERK1/2 signaling but also in the meiotic maturation of bovine and swine oocytes [122, 123]. However, in domestic cats, Wongbandue et al. [124] observed no beneficial effect of T4 on the in vitro growth of antral follicles, the follicular diameter, or the development and number of viable follicles.

Regarding the effects of thyroid dysfunctions on ovarian activity, research results are conflicting, possibly due to differences in the protocol and time for hypo- and hyperthyroidism induction and/or the methodology employed in the evaluation of the results. As an example, Hapon et al. [125] observed that there is no change in the preovulatory secretion pattern of LH and FSH in hypothyroid rats receiving propylthiouracil (PTU), an antithyroid drug, which differed from the results of Tamura et al. [96] and Hatsuta et al. [126], who showed a reduction of the preovulatory LH and FSH surges in PTU-treated and thyroidectomized rats, respectively. In relation to LH, this reduction was caused by the inhibition of the action of GnRH [96]. Tohei [127] observed that PTU-treated rats present a reduction in LH concentration during diestrus and proestrus, without altering the preovulatory LH peak. Mattheij et al. [6], on the other hand, reported an increase in preovulatory LH levels in rats after destruction of the thyroid with radioactive ^{137}I.

Dijkstra et al. [128] and Silva et al. [129] observed in rats that PTU-induced chronic hypothyroidism significantly reduced ovarian weight and the number of secondary and tertiary follicles and corpora lutea but did not alter the percentage of atretic follicles or the number of primary and preovulatory follicles. Meng et al. [130] showed similar results using a chronic diet-induced hypothyroidism model. However, those authors also observed a reduction in the number of primordial and primary follicles and an increase in follicular atresia. It is important to emphasize that hypothyroidism induced by Meng et al. [130] was started during the fetal period and lasted 4 months. However, rabbits and cattle with hypothyroidism induced by methimazole and PTU, respectively, do not present alterations in folliculogenesis [131, 132], although rabbits with hypothyroidism have smaller follicles [132]. Hapon et al. [125] also observed that hypothyroid rats receiving short-term treatment with PTU do not present reduced ovulation rates or a reduced number of corpora lutea, as was also suggested by Panciera et al. [20] in female dogs with induced hypothyroidism. In hyperthyroidism, in contrast, the number of secondary and tertiary follicles and corpora lutea is greater, with a reduction of follicular atresia [28]. Treatment of hypothyroid rats with T4 also increases the number of viable antral follicles and reduces the number of large atretic antral follicles [133]. Zheng et al. [117], on the other hand, reported a reduction of the number of primordial and antral follicles in hypo- and hyperthyroid prepubertal rats, respectively, after a short treatment period with methimazole or L-thyroxine. Bovines with induced hyperthyroidism also present no alterations in follicular growth waves or follicular diameter. However, they may present an abnormal estrous cycle length and anestrus [131].

Research has shown that hypothyroidism reduces proliferation of granulosa cells from preantral follicles of rats, with a reduction in the number of nucleolar organizing regions [129]. However, no change in cell proliferation was observed in the granulosa of antral follicles [128]. This finding demonstrates that the effect of hypothyroidism on granulosa cell proliferation is dependent on the stage of follicular development. In addition, changes in folliculogenesis in rats with hypothyroidism seems to be related to oxidative stress in the ovary, since there is a compromise of the antioxidant defense

system in ovarian cells due to reduced expression of antioxidant enzymes, such as catalase, peroxiredoxin 3, thioredoxin reductase 1, and nitric oxide synthase (NOS), and increased expression of superoxide dismutase 1 (SOD1) [30, 130]. This oxidative stress can be caused by a reduced ability of ovarian cells to receive glucose, since the expression of Glut1, a glucose transporter protein, is reduced in the ovaries of rats with hypothyroidism. In rats with hyperthyroidism, in contrast, there is an increase in Glut4 expression in the ovary [134].

Importantly, follicular development is also dependent on adequate remodeling of the collagenous tissue in the ovarian stroma to follicles that can grow and undergo maturation [135, 136]. Saha et al. [135] showed that ovarian collagen synthesis is decreased in hypothyroidism, and the Pitx-2 transcription factor may be involved in this dysfunction, since its expression in the ovary of hypothyroid rats is reduced, and it is an important factor for ovarian collagen synthesis [137]. In addition, in rats with hypothyroidism, there is increased expression of matrix metalloproteinases (MMPs) 2, 3, and 14 in the ovary [135]. MMPs are responsible not only for extracellular matrix degradation in different tissues and organs, including ovarian tissue during follicular development, but also for oocyte release at the time of ovulation and the formation of the corpus luteum [135, 138].

Thus, all results in the literature show that thyroid dysfunctions affect the ovarian activity of women and animals, and in rats, thyroid dysfunctions affect the ovaries of not only prepubertal and pubertal animals but also pregnant animals. However, in rats, maternal thyroid dysfunction may also affect the postnatal ovarian development of the offspring. Fedail et al. [30] demonstrated that both maternal hypo- and hyperthyroidism reduce postnatal follicular development in the ovaries of neonatal and prepubertal rats, with a reduction in the number of primordial, primary, secondary, and antral follicles. This same group found that maternal thyroid dysfunctions also affect the expression and activity of NOS in the ovary during postnatal development of the offspring, with increased NOS activity in hyperthyroidism and decreased NOS activity in hypothyroidism. Zheng et al. [117], on the other hand, demonstrated a reduction of NOS activity in prepubertal rats treated for a short period (10 days) with L-thyroxine, with no effect on hypothyroid rats. These results reaffirm that the effects of hypo- and hyperthyroidism on the ovary are dependent on the age of the animal and the protocol used to induce thyroid dysfunction.

Luteogenesis

The duration of the menstrual and estrous cycles in women and animals, respectively, as well as the duration of gestation, is dependent on the production of progesterone by the corpus luteum. Mattheij et al. [6] observed that rats with hypothyroidism present a prolonged luteal phase, which results from a decrease in the synthesis of 20 alpha-hydroxysteroid dehydrogenase (HSD) in the ovary, an enzyme responsible for the catabolism of progesterone in the corpus luteum to the inactive form, 20 alpha-hydroxyprogesterone. The elevation of progesterone levels negatively affects the secretion of gonadotropins by the hypothalamus and pituitary, promoting, together with high levels of PRL, decreased basal gonadotropin (LH and FSH) levels [97, 139]. The reduction of estradiol levels in rats with hypothyroidism [30] may be due to decreased responsiveness of ovary granulosa cells to FSH [140] or inhibition of FSH secretion induced by elevated levels of progesterone [126]. However, Hapon et al. [125] observed in hypothyroid rats increased circulating levels of estradiol and increased levels of the ERβ receptor and the cyp19A1 aromatase in the ovary during estrus. Those authors suggested that the increased estradiol may have been a consequence of the increase in the number of luteal receptors for LH caused by hyperprolactinemia. This increase in the number of receptors allows a greater effect of LH in the corpus luteum, stimulating the conversion of progesterone to androstenedione and estradiol [141].

Pregnant rats treated with PTU also present delayed parturition and a reduced number of pups [8, 91]. The delay in parturition results from decreased synthesis of PGF2α and HSD by the corpus luteum, in addition to increased PGE2, so a prolongation of the luteal phase is induced by the suppression of progesterone catabolism [91]. Silva et al. [53, 54] also observed reduced apoptosis and delayed gene and/or protein expression of COX-2 by the corpus luteum in cyclic and hypothyroid pregnant rats, as well as a reduction of luteal, endothelial and pericyte cell proliferation, and expression of angiogenic factors, such as vascular endothelial growth factor (VEGF) and its receptor, Flk1. Hyperthyroid pregnant rats, on the other hand, present premature labor caused by premature luteolysis [142, 143]. Cyclic and hyperthyroid pregnant rats present increased apoptosis and expression of COX-2, PGF2α, and HSD by the corpus luteum, a reduction of luteotropic factors, such as PGE2 and ERβ, and higher luteal expression of VEGF and Flk1 [53, 144, 145]. In addition, there is an increase in the proliferative activity of endothelial cells and pericytes [53, 144, 145]. All these data demonstrate that thyroid dysfunctions affect not only luteolysis in cyclic and pregnant rats but also luteal vascularization.

Thyroid dysfunction and ovarian cysts

The occurrence of ovarian cysts in women and animals with severe hypothyroidism may be related to changes in circulating LH concentrations and the preovulatory secretion of LH and FSH [96, 126, 127], especially during gestation [146–148], since the formation of large ovarian cysts is favored by the presence of equine or human chorionic gonadotropin [146]. According to the literature, cases of hypothyroidism causing ovarian hyperstimulation are underdiagnosed in women, especially in nonpregnant women, since they generally do not present the clinical symptoms of ovarian hyperstimulation, such as abdominal distension, hemoconcentration, and ascites or pleural effusion [148]. Despite this finding, it has been suggested that the occurrence of ovarian cysts in hypothyroidism may be associated with elevated levels of TSH that can activate FSH receptors in the ovary, since TSH and FSH are structurally related [149]. Another possibility is related to the hyperprolactinemia that occurs in hypothyroidism, as previously mentioned, which affects the secretion of LH through the inhibition of GnRH [97]. It is also suspected that mutations in the FSH receptor amplify the activation caused by hCG or TSH, since mutations in these receptors were observed in pregnant women with spontaneous ovarian hyperstimulation syndrome [150, 151]. However, although there are many possibilities, the exact mechanism by which severe hypothyroidism can cause ovarian cysts is unknown [148].

Effect of thyroid hormones on the uterus and uterine tube

Thyroid hormones act in the uterus and the uterine tube through their intracellular receptors, and they regulate the responsiveness of these organs to estrogen [152]. The expression of the T3 and T4 receptors in the uterine epithelium peaks in the middle of the

secretory phase, whereas the expression of deiodinases decreases in the secretory phase and is inversely proportional to the increase in progesterone [10, 74, 153]. Thus, it is plausible that changes in T3 and T4 serum levels affect uterine and uterine tube morphophysiology by not properly activating their receptors throughout the estrous or menstrual cycle, as well as by influencing plasma concentrations of sex steroids, affecting the trophic action of these hormones on the genital tract [21, 86].

In 1981, Kirkland et al. [154] demonstrated that thyroid hypofunction decreases the proliferative rate of epithelial and stromal cells and of the uterine musculature by reducing the response of uterine cells to estrogen. This is the reason for the significant reduction of endometrial thickness and the smaller number of endometrial glands observed in hypothyroid rats [129, 155], as well as the reduction of the absolute volume and height of the uterine epithelium [156]. Inuwa and Williams [156] also reported that hypothyroid rats present a reduced nuclear volume of the uterine epithelium and thickening of the basement membrane, all of which were reversed by treatment with L-thyroxine.

In the uterine tube, similar to changes observed in the uterus, TH deficiency reduces the villus height of the infundibulum, as well as the number and size of villus-lining cells, significantly reducing the epithelial height of that segment [129]. All these alterations in the uterus and uterine tubes can compromise the fertilization, differentiation, nutrition, and implantation of the embryo, explaining the embryonic loss and reduced implantation rate observed in individuals with hypothyroidism [157].

In hyperthyroidism, in contrast to observations in hypothyroidism, there is an increase in the height of the epithelium of the ampulla in the uterine tube of pubertal rats, which is not observed in prepubertal rats [158]. Hyperthyroidism in rats also increases the secretory activity of the uterine tube and increases the thickness of the endometrium and myometrium, making the uterine wall thicker [158]. This alteration in the uterus that results from thyroid hyperfunction is observed in both pubertal and prepubertal rats [158], demonstrating that changes in the uterine tube in cases of hyperthyroidism are dependent on the sexual maturity of the rat, which does not occur in the uterus.

Effect of thyroid hormones on the uterus during gestation

It has also been shown that hypothyroidism increases serum levels of leukemia inhibitory factor, an important factor involved in the process of decidualization and implantation of the embryo [159], and that TSH increases the expression of this factor in cultures of endometrial stromal cells [153]. This finding corroborates the fact that not only THs but also TSH are important in the implantation and decidualization process.

The decidualization of the endometrium is vital for the implantation and survival of the embryo, as well as for anchoring and coordinating fetal-placental development [160]. Although research evaluating the role of THs in decidualization is still scarce, it is known that hypothyroidism impairs decidualization during implantation [4] and that women with hypothyroidism exhibit reduced expression of interleukin (IL)-4 and IL-10 by decidual cells [161]. The in vitro synthesis of inflammatory cytokines and angiogenic factors by human decidual cells is also responsive to triiodothyronine, and this effect is dependent on the gestational period [162]. Souza et al. [163] showed that hypothyroid rats have a reduced decidual area, as well as an increase in the expression of VEGF, Flk-1, and Tie-2 by decidual cells at mid-gestation, without effects on the number of blood vessels and the area occupied by blood vessels. In hyperthyroid rats, in contrast, there is not only an increase in the expression of VEGF and Flk-1 but also an increase in the number of blood vessels in the decidua [163], demonstrating that THs increase vascularization in the decidualized endometrium. Souza et al. [164] also showed that the administration of T4 to pregnant gilts increases uterine vascularization and the height of the luminal and glandular epithelium. Adequate vascularization of the endometrium during gestation is essential for avoiding oxidative stress at the maternal–fetal interface and subsequent obstetric complications. Kong et al. [32] demonstrated that the uterus of hyperthyroid pubertal rats shows increased nitric oxide expression and NOS activity, as well as glutathione peroxidase and catalase activity. All of these antioxidant mediators were reduced in the uterus of hypothyroid rats [32]. These results corroborate the importance of THs in the adequate establishment of the maternal–fetal interface.

Effect of thyroid hormones on placental morphophysiology

Maternal THs have a strong influence on pregnancy, particularly on the placenta [165], and they are involved in the proliferation, differentiation, survival, and invasive and endocrine functions of trophoblastic cells [45]. This involvement in the activity of trophoblast cells is mainly due to the direct action of THs on specific nuclear receptors that are present in the villous placenta of humans, specifically in the syncytiotrophoblast and villous cytotrophoblast, and in the rat and mouse placenta. Abortion, preterm delivery, preeclampsia, fetal death, and mental deficits in children are well-documented sequelae of maternal thyroid dysfunction in women [65, 166–170].

In relation to fetal-placental development, some studies have shown that hypothyroidism affects placental and/or fetal weight in both women and rats [8, 65], whereas in female dogs, there is not only a reduction of pup weight but also an increase in fetal mortality [20]. It is important to emphasize that some prospective studies failed to associate thyroid dysfunction in female dogs with infertility, perhaps because spontaneous hypothyroidism is underdiagnosed in female dogs with reproductive dysfunction [20, 171]. In contrast, pregnant rats with induced hypothyroidism present alterations in placental glycogen stores [172], reduced trophoblast proliferative activity [8], increased placental apoptosis [8], and changes in the expression of c-fos and c-jun by the placenta [173, 174]. Abnormal expression of c-fos and c-jun, which are associated with differentiation [173] and trophoblastic proliferation [174], respectively, may be related to placental dysfunction, since the expression of these factors is elevated in the placentas of women with preeclampsia or intrauterine growth restriction [175].

Rats with hypothyroidism present not only fetal and placental weight reductions but also a reduction of fetal vessels and dilatation of the maternal venous sinuses in the placental labyrinth [8]. According to our research group, these changes in the placental labyrinth may be due, at least in part, to reduced expression of pro-angiogenic factors, such as VEGF and placental growth factor, in the placentas of these animals, which is associated with increased proliferin-related protein (rPlf), a hormone with antiangiogenic effects [23]. On the other hand, Souza et al. [164] observed increased VEGF expression in the placenta of gilts treated with L-thyroxine, and Cabell and Esbenshade [77] demonstrated greater postnatal weight gain in pups from hyperthyroid sows. Changes in placental vascularity are

the main causes of abortion and fetal growth restriction in women and domestic animal species, as such changes compromise the transport of nutrients and metabolites and, consequently, fetal-placental development [112, 176, 177].

Silva et al. [22] also demonstrated that the placentas of rats with hypothyroidism present increases in the trophoblast giant cell layer and the glycogen cell population in the junctional zone, raising the suspicion that the migration of these cells towards the decidua fails. Based on this hypothesis, in 2014, Silva et al. [9] showed that the intrauterine migration of trophoblastic cells is reduced in rats with hypothyroidism, which may further compromise uterine vascularization, since invasive trophoblastic cells control vascular remodeling at the maternal–fetal interface [112]. The reduction of migration was caused not only by reduced expression of MMPs 2 and 9 and placental leptin in the placentas of these animals but also by the anti-inflammatory cytokine NOS2 [79], whose in vitro expression by trophoblasts influences trophoblast motility and cellular invasion capacity [178].

Unlike rats with hypothyroidism, hyperthyroid rats have a higher birth rate without exhibiting effects on fetal weight [179]. This finding may be related not only to the greater proliferative activity of the trophoblast in hyperthyroid rats [31] but also to the increased expression of placental lactogen 1 in the placentas of these animals [23], which is the major hormone involved in fetal metabolism and development [180]. Rats with hypothyroidism, unlike rats with hyperthyroidism, present reduced expression of placental lactogen 1 by the placenta [23], which likely contributes to the reduction of fetal weight [22].

It is important to emphasize that fetal-placental development is also dependent on the establishment of an appropriate anti-inflammatory environment (Th2) at the maternal–fetal interface during pregnancy, and a shift to a "Th1" state leads to abortion or pregnancy complications [181, 182]. Additionally, the processes of vascularization, trophoblastic migration, and fetal nutrition are influenced by inflammatory mediators produced by the placenta [183]. The establishment of an anti-inflammatory environment in the placenta of hypothyroid rats is compromised by the fact that there is a reduction of IL-10 and NOS2 expression in the placentas of these animals [79]. In contrast, rats treated with L-thyroxine present an increase in anti-inflammatory cytokines in the placenta in the middle of gestation, as well as a reduction of TNFα, a pro-inflammatory cytokine [9]. The release of these inflammatory cytokines at the maternal–fetal interface is dependent on the activation of Toll-like receptors (TLRs), the main receptors involved in the recognition of pathogenic microorganisms. Silva et al. [9] showed that placental TLR expression is affected by maternal thyroid dysfunction, since hypothyroid rats present reduced TLR4 expression and increased TLR2 expression in the placental disc.

However, physiologically, the profile of inflammatory cytokines and angiogenic factors in placental tissue changes throughout gestation. While the circulating levels of cytokines and chemokines decrease significantly during mid-pregnancy, the first trimester and the end of the pregnancy are characterized by a dominant proinflammatory profile. This profile not only determines embryo implantation but also promotes the initiation of childbirth [182, 184]. Silva et al. [9, 23] observed that rats with hyperthyroidism present increased inflammatory cytokines (MIF and INF-y) at the end of gestation, as well as reduced endovascular trophoblastic migration and expression of pro-angiogenic factors, such as VEGF and Flk-1. It is believed that these changes in the placenta of rats with hyperthyroidism are involved in premature labor in these animals [143, 179]. For the initiation of parturition, there is a reduction of angiogenic factors in the placenta, in addition to the establishment of an inflammatory environment at the maternal–fetal interface. In addition, the inflammatory environment is indispensable, among other functions, for the removal of the trophoblast cells present in the decidua and placental release [182, 185].

However, although thyroid dysfunctions affect fetal-placental development, the effects of these dysfunctions on the reproductive performance of women and animals will depend on the time of onset of endocrine dysfunction in relation to conception and on the severity of hypo- or hyperthyroidism [11, 45, 66, 186]. Thyroidectomy in rats before gestation has no effect on placental weight but delays fetal growth in moderate to severe hypothyroidism [174, 186, 187]. However, induction of moderate or severe maternal hypothyroidism shortly after conception permanently delays fetal growth and placental weight gain [188–191].

It is important to emphasize that both clinical hypo- and hyperthyroidism in women during pregnancy require treatment, unlike subclinical hypo- and hyperthyroidism [11, 45, 66]. Currently, there is little evidence concerning whether the treatment of subclinical maternal hypothyroidism is beneficial, and there is no scientific consensus regarding the need for treatment. However, the treatment of gestational subclinical hypothyroidism can be beneficial when it is due to autoimmune thyroid disease [192, 193]. Maternal subclinical hyperthyroidism is still an infrequent disease and does not require treatment during pregnancy [11, 45, 66].

Effects of thyroid hormones on trophoblastic cells in vitro

The results of in vivo investigations involving thyroid dysfunctions were corroborated by in vitro studies using human placental explants [194–198] and mouse ectoplacental cones [199]. Those studies demonstrated that T3 at physiological doses (10^{-7} or 10^{-8} M) stimulates the gene expression and/or secretion of endocrine factors, such as hPL, hCH, SHBG, progesterone, and 17β-estradiol, in human placental tissue, as well as the expression of genes involved in differentiation (*Tpbp*) and the immune (*Infy*), angiogenic (*Vegf*), and endocrine (*Pl1*) activity of mouse trophoblastic cells. In contrast, the absence or excess of T3 results in a negative effect on the expression of angiogenic, endocrine, and/or immunological factors in human and mouse trophoblastic cells [194, 199]. At physiological concentrations, T3 also suppresses the apoptosis of extravillous trophoblasts by inhibiting Fas/FasL expression and the cleavage of caspase 3 and poly(ADP-ribose) polymerase [197]. Using an in vitro invasion model in Matrigel, Oki et al. [198] also showed that T3 stimulates the invasion of extravillous trophoblasts and the expression of MMP2, MMP3, oncofetal fibronectin, and $\alpha5\beta1$ integrin, corroborating the in vivo results obtained by Silva et al. [79] in hypothyroid rats. All these in vitro results confirm that both TH deficiency and excess may compromise trophoblastic cell function. However, these effects depend on the gestational period since term placenta explants from women do not respond to treatment with THs in vitro, as occurs with the placenta during the first trimester of pregnancy [64, 200].

Concluding comments

Thyroid hormones are involved in the regulation of various physiological processes, and changes in their serum concentrations compromise the proper functioning of the whole organism,

particularly the reproductive system. Well-documented sequelae of maternal thyroid dysfunctions include subfertility or infertility, menstrual/estrous irregularity, anovulation, abortion, preterm delivery, intrauterine growth restriction, and mental retardation in children. Therefore, in recent years, several studies have been carried out involving prospective and retrospective studies of women with thyroid dysfunction, as well as in vivo and in vitro studies of hypo- and hyperthyroidism using animal models and/or ovarian, uterine, and placental cell cultures. The results from these studies have shown that folliculogenesis and ovulation are stimulated by THs, while hypothyroidism reduces the number of growing follicles and increases follicular atresia, and these effects are caused not only by changes in the GnRH/LH axis but also by changes in kisspeptin and sex steroid secretion and increased PRL levels. In addition, THs affect luteolysis, with prolongation of the luteal phase in hypothyroidism due to suppressed catabolism of progesterone and stimulation of luteal vascularization in the setting of hyperthyroidism. At the maternal–fetal interface, studies showed that THs modulate not only the responsiveness of the uterus to estradiol but also endometrial vascularization and decidualization. In relation to the placenta, THs influence the differentiation and migration of trophoblastic cells, as well as their endocrine, angiogenic, and immunological activity. It has been suggested that hypothyroidism is related not only to fetal-placental growth restriction but also to the occurrence of preeclampsia. It is important to note that all these effects of THs in the female reproductive system were observed mainly in women and rats with thyroid dysfunction, so the literature still lacks information on the influence of thyroid dysfunctions on the reproductive function of domestic animal species.

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