Thyroid Disorders and Hormonal Contraceptives

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Abstract

Thyroid dysfunction are common endocrine disorders among reproductive-aged women, the groups of women who most commonly use effective hormonal contraceptives (HCs) for both spacing and limiting births. However, HCs including either combined estrogen-progestin or progestin-only contraceptives and thyroid hormones have profound interactions to each other. Although, women with no thyroid disease adapt quickly to thyroid hormonal alteration induced by those agents, but those small alteration may be clinically important for women who suffer from thyroid disorders. Similarly, there are limited studies suggest that thyroid hormones may affect the action of estrogen and subsequently can affect the efficacy and safety of HCs. This chapter focuses on the various aspects of interaction between thyroid hormones and HCs in order to present the clinical guide for daily practice.

Introduction

Contraception is the intentional prevention of conception through the use of various devices, sexual practices, chemicals, drugs or surgical procedures. An effective contraception allows a physical relationship without fear of an unwanted pregnancy and ensures freedom to have children when desired.

The hormonal contraceptives (HCs), which contain a combination of the hormones estrogen and progestin or progestin only contraceptives, are one of the most popular form of contraception around the world (table1) (1). They are highly effective for both spacing and limiting births (2), when used perfectly (3).

Table 1. Female hormonal contraceptives choice

Hormonal contraceptives		**Drug formulations**		**Instruction for use**
Combined hormonal contraceptives		Estrogen	Progestin	
Oral				
Conventional	Low dose	Ethinylestradiol, (35 µg or less)	One progestin: - Ethynodiol diacetate (1 mg) - Norethindrone (1 mg) - Norethindrone (0.5 mg) - Norethindrone (0.4 mg) - Norgestimate (0.25 mg) - Desogestrel (0.15 mg) - Drospirenone (3 µg) - Levonorgestrel (0.15 mg) - Norethindrone acetate (1.5 mg) - Norgestrel (0.3 mg)	The package contains 21-days of active pills and 7-days off
	High dose	Ethinylestradiol, (50 µg)	One progestin: - Norethindrone (1 mg) - Norgestrel (0.5 mg) - Ethynodiol diacetate (1 mg)	The package contains 21-days of active pills and 7-days off
	Triphasic (day: 1-7, 8-14, 15-21)	Ethinylestradiol, (30, 40, 30 µg) (35, 35, 35 µg) (20, 30, 35 µg)	One progestin: - Levonorgestrel (0.05, 0.075, 0.125 mg) - Norgestimate (0.18, 0.215, 0.25 mg) - Desogestrel (1.1, 0.125, 0.150 mg) - Norethindrone (1, 1, 1 mg) - Norethindrone (0.5, 0.75, 0.125 mg) - Norethindrone (0.5, 1, 0. 5 mg)	The package contains 21-days of active pills and 7-days off
Continuous dosing or extended cycle		Ethinylestradiol, (35 µg)	Levonorgestrel (0.15 mg)	3-month pack contains 84-days of active pills and 7-days off
Progesterone only contraceptives				
Oral, (mini-pill)		-	One progestin: - norethindrone (0.35 mg) - norgestrel (0.075 mg) - levonorgestrel (0.030 mg) - lynestrenol (0.50 mg) - ethynodiol diacetate (0.50 mg) - desogestrel (0.075 mg)	The package contains 28-daily of active pills without interruption
Injectable		-	Depot medroxyprogesterone (DMPA) - 150mg/mL - 400mg/mL	One shot either once every month or once every three months
Implant		-	Ethylene vinyl acetate (68 mg etonogestrel in each implant) (release rate: 35- 45 µg/day in first year, 30-40 µg/day in second year, in 25-30 µg/day third year)	Inserted beneath the skin of the upper arm up to 3-years
Hormonal Intra uterine devise		-	Levonorgestrel - 13.5 mg/device (Skyla), release rate: 14 µg/day) - 19.5 mg/device (Kyleena), release rate: 17.5 µg/day) - 52 mg/device (Liletta, Mirena), (release rate: 20 µg/day)	Inserted in the uterine up to 5-years

Combined oral contraceptives (OCs), including estrogen and a progesterone, are the most common form of HCs worldwide (4). A dose of 35 µg ethinylestradiol (EE), a derivative of 17 beta-estradiol, has been the predominant estrogen in combined contraceptive pills because of its high oral bioavailability. As such, levonorgestrel or norethisterone have been used as the main progestin in those pills. These combination is considered the 'gold standard' in OCs in relation to their safety profile (5). Newer progestogens such as gestodene and desogestrel are structurally related to progesterone, but have greater specificity for progesterone receptors than the older progestogens. They reduce the potential for androgenic, estrogenic and glucocorticoid effects. Drospirenone is a

spironolactone analogue and has a mild diuretic effect (6). Cyproterone has anti-androgenic effects which may be beneficial in women with hyperandrogenic symptoms (7).

Generally, hormonal contraceptive could influence the hypothalamo-pituitary-ovarian axis and reduce the ovarian production of sex steroids. Combined hormonal contraceptives act primarily by preventing ovulation through the suppression of ovulation by inhibition of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and the mid-cycle LH surge (8). This effect is mediated by both the progestin and estrogen component of the COs working synergistically, but estrogen suppression of FSH, which in turn prevents folliculogenesis, is likely the most important mechanism. Additionally, the estrogen component stabilizes the endometrium to maintain a regular withdrawal bleeding pattern (9). The progestin component also renders the cervical mucus relatively impenetrable to sperm and reduces the receptivity of the endometrium to implantation (10).

It is well documented that HCs have profound interactions with thyroid function (11). Those interaction are particularly important in women who suffer from thyroid disorders, since those diseases are very common in women of reproductive age (12-14).

This chapter focuses on the various aspects of interaction between thyroid hormones and hormonal contraceptives in order to present the clinical guide for daily practice.

Physiological consideration

Thyroid hormones have been shown to exert a modulatory influence on female reproductive function (15). It was reported that thyroid hormone receptors (TRs) are present in human ovarian surface epithelium and act on ovarian follicles and shows some slight localization in granulosa cells of ovarian follicles (16). As such, ovarian hormones could influence thyroid function. As such, thyroid function could be modulated by gonadal or sex steroids, primarily by altering the clearance of thyroxine-binding globulin (TBG) (17) , and peripheral deiodination of thyroxine (18).

Estrogen has a well-known direct and indirect effect on thyroid economy. States of estrogen excess, either endogenous or exogenous, are associated with a rise in serum TBG concentrations (19). This occurs through the increased sialylation of TBG, thereby slowing its clearance from the circulation by the liver and increasing its half-life (20, 21). However, same mechanism leads to increase the levels of similar glycoproteins, mainly sex hormone binding globulin (SHBG) (22, 23). Whether estrogen increases biosynthesis of TBG remains controversial (17).

These effects are modulated by the chemical structure of the steroid being used, its dose and the route of administration. In this respect it is reported that, in the same therapeutic effects, transdermal administration of estradiol causes minimal changes in serum TBG concentrations, but oral administration could lead to a 50–70% increase in serum TBG (24). Moreover, since ethinyl estradiol undergo limited liver metabolism and remains longer in the liver, therefore it is more potent to increase the serum concentration of binding proteins compared to estradiol or other chemical forms of estrogens (17, 25).

A rise of TBG results in a reduced clearance of thyroxine (T4) and triiodothyronine (T3) and, hence, result in a new thyroid hormone equilibrium characterized by an increase in total T3 and T4 by 20–40% and a reduced resin triiodothyronine (T3 uptake) level (26). However, the free or bioactive fractions of thyroid hormones remain normal or only slightly affected if the patient is euthyroid, because this is the function of the circulating hormone regulated by the feedback "axis" (27-29). In this respect, serum-free T4 may transiently decrease inducing a response from the pituitary to increase TSH secretion, which, in turn, will stimulate the thyroid to produce more T4. A new steady state is reached between free and bound T4 and TSH levels remain normal (27, 30).

There have been limited studies assessed the effect of progestins on thyroid function, mostly have not demonstrated any effect of progestins on TBG concentrations (27). Cyproterone acetate, a progestin with anti-androgenic effects, was not observed to have any effect on TBG concentrations (26, 30).

As well, there are limited studies have been published on the effects of long acting drugs containing only progesterone on thyroid function. It is reported that depot medroxyprogesterone acetate (DMPA) could significantly increase FT4 levels after the 12-month follow-up (31). Accordingly, a randomized placebo-controlled 12-week trial found that oral micronized progesterone at the daily dose of 300 mg could decrease TSH, increase FT4 and did not have any effect on FT3 serum levels, compared to placebo (32). This evidence suggests a greater role for progestins in influencing thyroid function.

It should be noted that these effects are generally transient and partly reversed in the hormone-free interval of 1-8 weeks; also, maximal levels of SHBG are reached at the end of the third cycle and no further rise occurs during the following cycles (32, 33).

Guide for clinical practice

Thyroid dysfunction is one of the most common endocrine disorders among reproductive aged women (34), the groups of women who most commonly use effective hormonal contraception (35, 36). Although, women with no thyroid disease adapt quickly to thyroid hormonal alteration induced by gonadal steroids, but those small alteration

may be clinically important for women who suffer from thyroid disorders and may cause significant biochemical and clinical alterations requiring changes in the doses of thyroid medications. Likewise, there are limited studies suggest that thyroid hormones may affect the action of estrogen and subsequently can affect the efficacy and safety of hormonal contraceptives (11, 37). This suggests that euthyroidism is important for the effectiveness of OCs.

Meanwhile, since thyroid disorders are not contraindications to pregnancy, if pregnancy does occur, untreated thyroid dysfunctions are widely associated increased risk of feto- maternal and neonatal morbidity among pregnant women (38-41), Therefore, it is advisable to treat the problem first and begin contraception, when pregnancy is requested. However, side effects caused by those HCs, such as weight changes, emotional lability, or changes in energy level could be similar to symptoms of hypothyroidism, hyperthyroidism, and other types of thyroid dysfunction, and might unmask thyroid illness in previously undiagnosed subjects.

Here we provided the a guide for using the hormonal contraceptives among women with thyroid dysfunction for clinical practice. However, in a the holistic approach, the steps suggested here are intended to be general guidelines that would never substitute for clinical judgement. Each patient's total clinical and psychosocial circumstances must be considered, since the physician should treat the patient and not the disease.

Hypothyroidism

In contrast to the findings in thyroid subjects, estrogen component of HCs causes clinically significant alterations in thyroid function leading to increased levothyroxine requirements in women with hypothyroidism (26). In hypothyroid subjects, estrogen leads to an increase in serum TBG levels quantitatively similar to that observed in those with normal thyroid function (3). This alteration in those patients leads to slow the entry of thyroxine into cells, including pituitary cells, thereby reducing thyroid hormone action in tissue. Alternatively, estrogen might lower the serum free thyroxine concentration by increasing the clearance of thyroxine. Therefore, the serum concentrations of both serum TSH levels and free thyroxine (14) decrease in those patients and cannot stimulate by thyroid gland to produce more T4. Although those alteration are small but potentially clinically important and may need to in an increased need for thyroxine replacement. It should be noted that this effect is dose dependent and is usually observed within 6 weeks after HCs containing estrogen initiation and reaches its peak at 12 weeks (33).

The influence of HCs containing estrogen in patients with subclinical hypothyroidism has not been clearly understood. But it might be possible that such patients become overtly hypothyroid following HCs containing estrogen usage. Based on current knowledge, there are no restrictions on the choice of HCs methods in women

with controlled hypothyroidism with the same guidelines that are used for healthy women. Moreover, in patients with levothyroxine treatment, it is recommend to consider up-titration of the levothyroxine dose in new HCs user. In this respect, TSH and FT4 should be measured 4–8weeks after the up-titration in order to check the adequacy of replacement. However, it is unnecessary to stop the use of hormonal contraceptive to evaluate thyroid function, but it would be prudent to assess thyroid function in those patients after withdrawal of HCs.

Hyperthyroidism

There are limited studies addressing the influence of HCs in patients with hyperthyroidism. The increase in TBG and the associated decrease in free thyroxine levels would explain the observed amelioration of Graves' hyperthyroidism with exogenous estrogen (42, 43). Based on current knowledge, generally, there are no restrictions on the choice of hormonal contraceptive methods in women with hyperthyroidism with the same guidelines that are used for healthy women. In patients with antithyroid medications therapy, it is recommend to consider antithyroid agents dosage in new hormonal contraceptives user. In this respect, TSH and FT4 could be measured 4–8 weeks after initiation of those contraceptives to show if your thyroid medication needs a dosage adjustment. Additionally, It is unnecessary to stop the use of HCs to evaluate thyroid function, but it would be prudent to assess thyroid function in those patients after withdrawal of HCs.

Autoimmunity

Sex hormones regulate molecular mechanisms in the innate and adaptive immune systems, and control immune responses in health (44). Hormonal contraceptives (HCs) are very potent hormones that have effects on the immune system (45). Estrogens, in general, are considered immune-stimulatory due to enhance cellular proliferation and antibody secretion by decreases the CD4+/CD8+ T cell ratio and TNF-α cytotoxicity in T cells and increases immunoglobulin secretion, B cell survival, and polyclonal activation of B cells as well as IgG and IgM production in peripheral blood mononuclear cells (46-48). In contrast, progestins clearly have immunomodulatory and immunosuppressive effects on the immune system, by inhibition of macrophage activation, nitric oxide production, and IFN-γ production by NK cells (44, 49) and therefore counteract the pathways affected by estrogen (44). Hormonal contraceptives also suppress pituitary gonadotropins, which have a number of additional immunomodulatory effects (50, 51). Thus, while a specific mechanism linking HCs to autoimmune disease pathogenesis has not been elucidated, it is speculate that the administration of HCs, either combined estrogen-progestin contraceptives or progestin-only contraceptives, would modulate the immune system and may affect the

predisposition of hormonal- contraceptive users to autoimmune diseases (45). Autoimmune thyroid diseases are usually accompanied by the presence of anti-thyroid peroxidase (TPO), anti-thyroglobulin (Tg), and anti-thyroid-stimulating hormone receptor (TSHR) antibodies (48). There are some evidence showed that sex hormones may play a role in thyroid autoimmunity. In this respect, it is showed that higher circulating estradiol is related to thyroid autoimmunity in males as reflected by positive TSH receptor antibody (TRAb) (52).

However, at current time there is the lack of literature supporting the effect of HCs on Autoimmune thyroid diseases. Therefore, based on indirect available evidence, generally, there are no restrictions on the choice of hormonal contraceptive methods in women with autoimmune thyroid diseases with the same guidelines that are used for healthy women. However, it is recommend to consider thyroid agents dosage in new hormonal contraceptives user. In this respect, TSH and FT4 could be measured 4–6 weeks after initiation of those contraceptives to show if your thyroid medication needs a dosage adjustment.

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Summary

Hormonal contraceptives (HCs) are able to impact the thyroid gland function. Although, women with no thyroid dysfunction can tolerate thyroid hormonal alteration induced by those agents, but those small alteration in thyroid hormones concentrations may be clinically important for women who suffer from thyroid disorders. In such cases, serum level of thyroid hormones should be measured at least 4–8weeks after initiation of HCs order to check the adequacy of thyroid medications.