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Brigitte K. Budenhofer, Nina Ditsch, Udo Jeschke, Roland Gärtner, Bettina Toth

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Thyroid (dys-)function in normal and disturbed pregnancy

Brigitte K. Budenhofer · Nina Ditsch · Udo Jeschke · Roland Gärtner · Bettina Toth

Abstract
Introduction During pregnancy, physiologic changes in maternal thyroid function take place especially due to hormonal as well as metabolic processes. Human chorionic gonadotropin activates the maternal thyroid gland leading to increased thyroid hormone production. A sufficient availability of maternal thyroid hormones is essential for fetal development, especially during the first trimester of pregnancy, when the fetal thyroid gland is not yet functional.
Materials and Methods Current knowledge of thyroid dysfunction including thyroid autoimmunity, hypothyroidism or hyperthyroidism is summarized with special focus on miscarriage and pregnancy disorders. Therefore, a Medline research as well as an analysis of current guidelines on thyroid function and pregnancy was performed.
Results A study focusing on TSH levels in normal and disturbed pregnancies, the risk of miscarriage in association with thyroid autoantibodies, and (subclinical) hypothyroidism in infertile and fertile women were included.
Conclusion Maternal thyroid dysfunction negatively affects pregnancy outcome. Besides a routine iodine supplementation in pregnant women and treatment of hypo as well as hyperthyroidism, TSH levels should routinely be measured in women during childbearing years and adjusted to concentrations <2.5 mIU/l in order to optimize maternal health and fetal development.

Keywords Pregnancy · Miscarriage · Thyroid dysfunction · Hypothyroidism · Hyperthyroidism · Thyroid autoimmunity · Hashimoto's thyroiditis

B. K. Budenhofer · U. Jeschke
Department of Obstetrics and Gynecology, Ludwig-Maximilians University, Maistraße 11, 80337 Munich, Germany

N. Ditsch
Department of Obstetrics and Gynecology, Ludwig-Maximilians University, Großhadern, Marchioninistraße 15, 81377 Munich, Germany

R. Gärtner
Department of Endocrinology, Ludwig-Maximilians University, Ziemsenstraße 1, 80336 Munich, Germany

B. Toth
Department of Gynecological Endocrinology and Fertility Disorders, Ruprechts-Karls University Heidelberg, Voßstraße 9, 69115 Heidelberg, Germany
e-mail: bettina.toth@med.uni-heidelberg.de

Introduction

The thyroid gland interferes with the female reproductive tract in the non-pregnant as well as in the pregnant state and proper thyroid function is required for reproductive processes. In women affected by thyroid dysfunction, menstrual irregularities to the point of infertility can be observed more frequently than in euthyroid women. Impaired thyroid function, such as hypothyroidism or thyroid autoimmune diseases, can have detrimental consequences to embryonic and fetal development and result in an increased risk of miscarriage. In fact, thyroid autoantibodies are associated with a higher rate of both, spontaneous and recurrent miscarriages. Therefore, diagnosing and treating maternal thyroid dysfunction even before conception is of major importance. To date, thyroid function tests are only performed in women at risk for thyroid disorders, whereas we recommend routine screening before and during pregnancy.

This review focuses on the (patho-)physiologic changes of the maternal thyroid function during pregnancy and possible effects on fetal development. Additionally, the

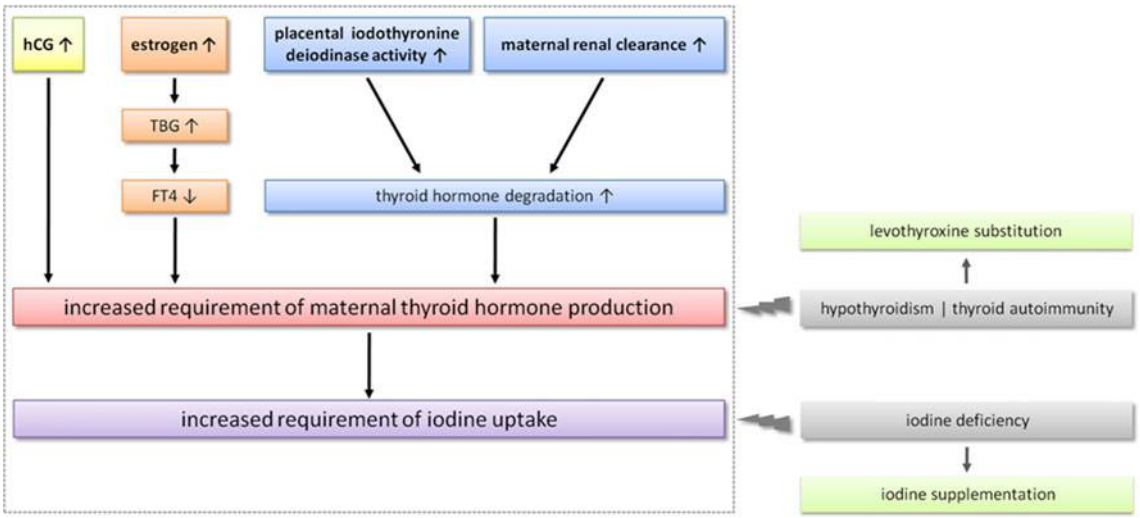

Fig. 1 Physiologic changes of the maternal thyroid function during pregnancy. Several factors contribute to an increased requirement of thyroid hormone production in pregnancy. First, hormonal changes such as raised hCG levels and increased estrogen concentrations result in a stimulation of the thyroid hormone production. Second, metabolic changes leading to a reinforced thyroid hormone degradation induce an increase in thyroid hormone output. If the capacity of thyroid function is restricted in patients with hypothyroidism or thyroid autoimmunity, levothyroxine has to be substituted for insuring a sufficient thyroid hormone status. For a larger amount of thyroid hormones being produced, the iodine uptake has to be increased. Therefore, in case of iodine deficiency, iodine has to be supplemented. *hCG* human chorionic gonadotropin, *TBG* thyroxine-binding globulin, *FT4* free thyroxine

management of thyroid dysfunction during pregnancy as well as iodine substitution is reviewed.

Physiologic processes of thyroid function during normal pregnancy (Fig. 1)

The maternal thyroid gland is stimulated by human chorionic gonadotropin (hCG) [1]. As a significant homology exists between the structure of hCG and thyroxine stimulating hormone (TSH), hCG has a weak thyrotropic activity [2]. This results in reinforced thyroid hormonal release [2] as well as in an increment of thyroid size [1]. With the thyroid hormone secretion being boosted, TSH levels are suppressed [3, 4].

The magnitude of nausea and vomiting corresponds to the extent of TSH level suppression as well as to the increase in hCG and free thyroxine (fT4) [5]. Later in pregnancy, decreasing hCG levels may lead to a reduced thyroid hormone release and in higher TSH concentrations, mainly in the second half of gestation [1, 6].

Raised estrogen concentrations lead to a reduced clearance of thyroxine-binding globulin (TBG) by the liver [1, 3, 7–10], to the point that TBG levels duplicate and the quantity of T4 binding sites increases. Consequently, the concentration of free thyroid hormones (fT4, fT3) decreases. This decrement in fT4 concentration causes, in turn, an elevated requirement of thyroid hormone output [8]. Finally, estrogen-related increases in TBG levels lead to a further demand of intensified thyroid hormone secretion.

Increased concentrations of type 3 iodothyronine deiodinases in the developing placenta lead to a higher peripheral degradation of thyroid hormones. Deiodinating the inner ring of T4 and T3, the type 3 deiodinase inactivates thyroid hormones especially during the second half of gestation and therefore protects the fetal organism from excessive thyroxine and triiodothyronine concentrations [11, 12]. Consequently, the maternal thyroid gland has to compensate the increased deprivation of hormones by a fortified production.

Furthermore, an association between pregnancy and glomerular filtration of thyroid hormones does exist. Renal blood flow and therefore the glomerular filtration are increased, so that the clearance of thyroid hormones shows higher values during pregnancy [11].

In sum, thyroid hormones are increased during pregnancy [13] with the overall serum T4 concentrations being 1.5 times higher than those found in non-pregnant women [9]. Therefore, sufficient iodine availability is a precondition. An impaired maternal thyroid function even before conception is not able to meet the demands of a reinforced hormonal output, resulting in a deficiency of thyroid hormones and probably in disturbed fetal development [6, 8].

Possible effects of thyroid dysfunction on fetal outcome

Hypothyroidism

Overt and subclinical hypothyroidism (SCH) is one of the most frequent endocrine dysfunctions in pregnancy with a

prevalence of 2.5 % (overt hypothyroidism) and 2–5 % (SCH) [14] The main causes of hypothyroidism are Hashimoto's thyroiditis and iodine deficiency, both resulting in a diminished thyroid hormone production. However, SCH remains unknown in 25 % of all pregnancies [15].

Hypothyroidism influences the female reproductive tract in general. First, it can disturb the menstrual cycle and lead to bleeding irregularities (whereas the extent corresponds to the increase of serum TSH levels) or menorrhagia (due to a decreased production of certain coagulation factors) [16]. Second, hypothyroidism can alter the function of the oocytes, as normal thyroid hormone levels seem to be essential for oocyte maturation. Third, hypothyroidism reduces the concentration of sex hormone-binding globulin [8, 17]. An association between infertility and SCH does exist and the prevalence of SCH seems to be higher in infertile patients than in fertile controls (Table 1).

In addition, spontaneous as well as recurrent miscarriages, anemia, gestational hypertension, placental abruption, postpartum hemorrhage, intrauterine fetal demise and preeclampsia are more frequent in hypothyroid women [18]. Furthermore, the offspring born to a hypothyroid mother can be affected by fetal death [15, 19], congenital malformations, low birth weight [10, 15, 19], premature birth [17, 19, 20] and psychoneurological restrictions [9, 19, 21]. SCH may lead to an increase in miscarriage rate and to a reduplication of premature delivery rates [11].

Hyperthyroidism

Hyperthyroidism appears less frequently [15] during pregnancy than hypothyroidism with a prevalence of 0.2 % [15] and is associated with an increased risk of stillbirth, preterm delivery, preeclampsia, heart failure, neonatal hyperthyroidism, growth restriction [22], maternal hypertension and thyroid storm [23]. Furthermore, the risk for miscarriage is raised in women who are thyrotoxic at conception [24].

Thyroid autoimmunity (Hashimoto's thyroiditis and Graves disease)

The prevalence of autoimmune thyroiditis (AIT) is around 5–10 % in females in child bearing age. Autoantibodies like thyreoglobulin autoantibodies (TG) and especially thyroperoxidase (TPO) are associated with an inflammation of the thyroid gland. In patients with Graves disease, autoantibodies bind to the TSH receptor and exert stimulatory effects on the thyroid. The prevalence is 0.01–0.02 % in pregnant patients [25]. Patients with Graves disease who are not treated and thus remain thyrotoxic during the second half of gestation, are more frequently affected by obstetric and neonatal complications, such as congestive heart failure, preeclampsia and atrial fibrillation [26, 27]. The risk of adverse fetal outcome is increased ninefold in hyperthyroid mothers who are not treated compared to mothers with euthyroid function because not only the thyroid hormones but also the TSH-stimulating antibodies (TRAb) cross the placenta and might induce Graves disease in the fetus [10, 29]. In fact, therapy can decrease the risk of adverse pregnancy outcomes to values which correspond almost to those of healthy women, indicating the importance of treatment and control of Graves disease [28].

Antithyroid drugs can pass the placenta and finally block the fetal thyroid gland in a higher degree than the maternal [29], which can possibly lead to neonatal goiter [10]. Therefore, antithyroid drugs should be maintained as low as possible [15]. Furthermore, 1–2 % of children born to mothers with Graves disease are affected by neonatal thyrotoxicosis [10]. By developing Graves disease itself and producing a vast quantity of thyroid hormones, the fetus is exposed to a threatening amount of thyroxine. This metabolic state is described as "neonatal thyrotoxicosis".

Thyroid autoimmunity, especially Hashimoto's thyroiditis seems to be associated with infertility as thyroid autoimmunity can be diagnosed more frequently in infertile than in fertile women even with still normal thyroid

Table 1 Studies focusing on the prevalence of subclinical hypothyroidism in infertile women as compared to fertile controls

Study	Study design	Number of patients (*n*)	Prevalence of SCH in infertile patients (%)	Prevalence of SCH in fertile patients	Definition of SCH
Arojoki et al. [49]	Retrospective	299	1.3	2–3 %	Basal TSH >5.5 mIU/l
Grassi et al. [50]	Prospective	129	4.6	No controls	Basal TSH >4.5 mIU/l
Poppe et al. [51]	Prospective	438	0.9	<1 %	Basal TSH >4.2 mIU/l
Raber et al. [52]	Prospective	283	34.0	No controls	Basal TSH >4 mIU/l or peak TSH >15 mIU/l
Abalovich et al. [53]	Retrospective	244	10.2	1.9 %	Basal TSH >5 mIU/l

In most of the above-mentioned studies, the prevalence of SCH in infertile patients is increased as compared to fertile controls

SCH subclinical hypothyroidism

function [17]. One possible explanation for this phenomenon is the association between endometriosis and thyroid autoimmunity [17]. Autoantibodies to endometrial antigens are speculated to react also against thyroidal tissue and to provoke thyroid autoimmunity [17]. Furthermore, AIT leads to an increase in miscarriage rate [8, 13, 17, 20, 30, 31], especially in the first trimester [8, 17]. Table 2 resumes studies on the risk of miscarriage associated with the presence of thyroid autoantibodies and shows that the miscarriage rate in thyroid antibody-positive women is increased up to 54 % as compared to antibody-negative women [32, 33]. Miscarriages in women affected by thyroid autoimmunity mainly take place in the first trimester [34] and the incidence of AIT was rather high in patients with RM [35, 36]. Even subclinical hypothyroidism can lead to an increase in and to a reduplication of premature delivery rates [11] (Table 3).

Therefore, treatment of subclinical hypothyroidism is mandatory in order to minimize miscarriage rates in patients with thyroid autoimmunity. However, clinical studies must be implemented to analyse possible benefits of additional treatment options like selenium supplementation or aspirin.

Management of hypothyroidism during pregnancy

In accordance with the Endocrine Society Guidelines, hypothyroidism in pregnant women is indicated to be treated with levothyroxine, even if subclinical [18, 37]. The supplementation should be started with 1.5 µg/kg BW and has to be adjusted every 4 weeks. Women who are already treated with levothyroxine should receive a dosage increase by approximately 30 % as soon as pregnancy is confirmed and have their TSH and free T4 levels checked every 8 weeks with a target TSH level of <2.5 mIU/l. After delivery, TSH should be controlled 6–8 weeks postpartum and the levothyroxine dosage mainly returned to the preconceptional dose. Although levothyroxine is excreted in breast milk, breastfeeding is not contraindicated, as the levels are too low to impair neonatal thyroid function [38, 39].

A benefit of levothyroxine administration in pregnant women was demonstrated by several studies as it reduced rates of miscarriage and premature delivery in thyroid antibody-positive women to values similar to those of controls with euthyroid function [40]. The incidence of adverse obstetric outcome is decreased when euthyroidism is achieved and maintained [15, 18]. However, an improvement of fertility by levothyroxine administration in (subclinical) hypothyroidism has not yet been finally proven [37] (Table 4).

Management of hyperthyroidism during pregnancy

Hyperthyroidism is treated with thionamides, with propylthiouracil (PTU) being the drug of choice at a dose of 100–150 mg/8 h [41]. Free T4 levels are recommended to be measured monthly. If thionamides are contraindicated, beta blockers like propanolol can be administered at a dose of 20–40 mg 2–3 times/day to minimize possible adrenergic symptoms like tachycardia. Breastfeeding is not contraindicated when hyperthyroidism is treated with thionamides [24, 42].

Table 2 Studies focusing on the risk of miscarriage associated with the presence of thyroid autoantibodies

Study	Number of patients, *n* (TAI %)	Thyroid antibodies evaluated	Miscarriage rate in thyroid antibody-positive patients (%)	Miscarriage rate in thyroid antibody-negative controls (%)	*p* value ($p < 0.05$ = significant)
Stagnaro-Green et al. [32]	552 (19.6)	TPO, TG	17.0	8.4	0.001
Glinoer et al. [33]	726 (6.2)	TPO	13.3	3.3	<0.005
Lejeune et al. [34]	363 (6.3)	TPO, TG	22.0	5.0	<0.005
Bussen and Steck [35]	66 (17.0)	TPO, TG	36.0	7.0	<0.03
Iijima et al. [54]	1,179 (10.6)	Antimicrosomal	10.4	5.5	<0.05
Kutteh et al. [55]	900 (20.8)	TPO, TG, microsomal	22.5	14.5	0.01
Bussen et al. [35]	48 (30.6)	TPO, TG	54.2	8.3	0.002
Bagis et al. [56]	876 (12.3)	TPO, TG	50.0	14.1	<0.0001
Poppe et al. [57]	234 (14.0)	TPO	53.0	23.0	<0.016
Negro et al. [58]	484 (15.0)	TPO	52.0	26.0	<0.034
Negro et al. [59]	984 (11.7)	TPO	13.8	2.4	<0.05

The miscarriage rate in thyroid antibody-positive patients is significantly higher than in thyroid antibody-negative patients

TAI thyroid autoimmunity, *TPO* thyroperoxidase antibodies, *TG* thyroglobulin antibodies

Table 3 Studies focusing on TSH levels in normal and disturbed pregnancy

Study	Study design	Number of patients (n)	Study group	Controls	p value ($p < 0.05$ = significant)
Benhadi et al. [41]	Cohort study	2,497	Mean TSH levels in women with child loss ($n = 27$)	Mean TSH levels in controls	<0.05
			1.48 mU/l	1.11 mU/l	
Negro et al. [60]	Prospective	4,123	Rate of pregnancy loss in women with TSH levels below 2.5 mU/l	Rate of pregnancy loss in women with TSH levels between 2.5 and 5 mU/l	0.006
			3.6 %	6.1 %	
Rao et al. [42]	Prospective	323	Mean TSH levels in hypothyroid women with recurrent pregnancy loss	Mean TSH levels in hypothyroid controls	<0.005
			29.89 μlU/ml	11.38 μlU/ml	
			Mean TSH levels in euthyroid women with recurrent pregnancy loss	Mean TSH levels in euthyroid controls	<0.005
			2.67 μlU/ml	2.29 μlU/ml	

The studies show significantly higher TSH levels in women with pregnancy loss and a higher rate of pregnancy loss in women with TSH levels above 2.5 mU/l

Table 4 Overview on the management of thyroid disease during and after pregnancy

Thyroid disorder	Management
Hypothyroidism due to iodine deficiency	• Iodine supplementation with 150–200 μg, starting preconceptionally • Breast feeding women should receive 250 μg iodine daily
Autoimmune thyroid disease	• Adjustment of TSH levels <2.5 mU/l
Hyperthyroidism	• Treatment with Propylthiouracil, e.g. 100–150 mg/8 h in the first trimester, second and third trimester with Methimazol • Control of maternal antibodies before 22 weeks gestation in Graves disease or history of Graves disease
Hypothyroidism	• Treatment with levothyroxine, initial dosage of 0.10–0.15 mg/day • In case of preconceptional levothyroxine treatment, dosage should be increased by approximately 30 %

Management of thyroid dysfunction during and after pregnancy; modified according to [61]

Iodine substitution during pregnancy

Iodine deficiency is defined as urinary iodine excretion below 100 μg/l and over two billion people are affected worldwide [43]. The increased requirement of thyroid hormone secretion and an increased glomerular filtration and clearance of iodide demand an augmented availability of iodine during pregnancy. In fact, iodine intake has to be doubled to insure sufficient thyroid hormone synthesis by both the maternal and the fetal thyroid gland [3]. Iodine supplementation depends on the iodine deprivation before pregnancy. Preferentially, iodine availability in women of childbearing age should be sufficient prior to conception [7, 44] by a daily iodine intake of 150 μg [7].

Nevertheless, excess iodine can exert harmful effects on the human organism as well [45] and may trigger autoimmune thyroid disease and secondary hypothyroidism. A reinforced lymphocyte infiltration of the thyroid gland by high iodine intake and the suppressive effect of large amounts of iodine on thyroid hormone production seem to be the trigger [46]. On the other hand, the low risks of excess iodine intake are outweighed by the substantial danger of iodine deficiency [47].

Conclusions

Maternal thyroid dysfunction, especially hypothyroidism and thyroid autoimmunity, negatively affects fetal development and leads to first trimester miscarriages as well as gestational disorders. So far, a routine screening for thyroid (dys-)function in women during childbearing years does not exist and should be established not only by gynecologists, but also by general practitioners [48]. Iodine supplementation of 250 μg per day and TSH adjustment in

hypothyroid women to values <2.5 mIU/l are strongly recommended to improve pregnancy outcomes.

Conflict of interest None.

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