8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) as a Cause of Autoimmune Thyroid Diseases (AITD) During Pregnancy?

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The thyroid is not necessary to sustain life. However, thyroid hormones (TH) strongly affect the human body. Functioning of the thyroid gland affects the reproductive capabilities of women and men, as well as fertilization and maintaining a pregnancy. For the synthesis of TH, hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) is necessary. From the chemical point of view, TH is a reactive oxygen species (ROS) and serves as an oxidative stress (OS) promoter. H\textsubscript{2}O\textsubscript{2} concentration in the thyroid gland is much higher than in other tissues. Therefore, the thyroid is highly exposed to OS. 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) are DNA lesions resulting from ROS action onto guanine moiety. Due to their abundance, they are recognized as biomarkers of OS. As thyroid function is correlated with the level of OS, 8-oxodG and 8-OHdG has been taken under consideration. Studies correlate the oxidative DNA damage with various thyroid diseases (TD) such as Hashimoto’s thyroiditis (HT), Graves’ disease (GD), and thyroid cancer. Human sexual function and fertility are also affected by OS and TD. Hypothyroidism and hyperthyroidism diagnosed in pregnant women have a negative effect on pregnancy as it may increase the risk of miscarriage or fetus mortality. In the case of TD in the mother, fetal health is also at risk – neurodevelopment and cognitive function of the child may be impaired in its future life. This review presents thyroid function in the context of TD during pregnancy. The authors introduce OS and describe oxidative DNA lesions as a crucial marker of thyroid pathologies.

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Abbreviations: 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AES, American Endocrine Society; AITD, autoimmune thyroid diseases; ATA, American Thyroid Association; BER, base excision repair system; CAT, catalase; DIO2, iodothyronine deiodinase type 2; DIO3, iodothyronine deiodinase type 3; DIIT, diiodothyronine; ETA, European Thyroid Association; ETC, electron transport chain; G, guanine; dG, 2′-deoxyguanosine; GD, Graves’ disease; GPX, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; H\textsubscript{2}O\textsubscript{2}, hydrogen peroxide; hCG, chorionic gonadotropin; HO\textsubscript{2}•, hydroperoxyl radical; HT, Hashimoto’s thyroiditis; I\textsuperscript{−}, iodine; I\textsuperscript{131}, iodine-131; ID, iodine deficiency; MIT, moniodothyronine; MUTYH, MutY DNA glycosylase; NO\textsuperscript{•}, nitric oxide; NOS, nitric oxide synthase; O\textsubscript{2}•−, superoxide anion radical; O\textsuperscript{2−}, singlet oxygen; OGG1, oxoguanine glycosylase 1; OH, hydroxyl radical; ONOO\textsuperscript{−}, peroxinitrite; OS, oxidative stress; OXPHOS, oxidative phosphorylation; PRX, peroxiredoxin; ROS, reactive oxygen species; RTH, Refetoff syndrome, thyroid hormone resistance; SOD, superoxide dismutase; T2, diiodothyronine, 3,3′-diiodothyronine; T3, triiodothyronine, 3,5,3′-triiodothyronine; rT3, reverse triiodothyronine; T4, thyroxine, 3,5,3′,5′-tetraiodothyronine; T3G, thyroxine-binding globulin; TD, thyroid diseases; TG, thyroglobulin; TH, thyroid hormones; TPO, thyroid peroxidase; TR, thyroid hormone receptor; TRH, thyrotropin-releasing hormone; TRX, thioredoxin; TSH, thyrotropin, thyroid-stimulating hormone; TRHR, TSH receptor; Tyr, tyrosine.

Keywords: thyroid diseases, oxidative stress, pregnancy, deoxyguanosine, DNA damage, thyroid hormones
INTRODUCTION

Over the past decade, increase in the incidence of TD, including thyroid cancer, has been noted [1]. TD along with gestational diabetes are the most frequently diagnosed endocrinopathies during pregnancy [2]. World Health Organization’s research (1994-2006) estimated that about 31% of the world population has insufficient iodine (I-) intake [3]. Iodine deficiency (ID) is a common problem in many regions of the world where it concerns a significant part of the population (30% in Southeast Asia, 42% in Africa, 47.2% in the East Mediterranean region and 52% in Europe) [4]. The situation is different in the US. The estimated average I- intake (138-353 mcg/day) fulfills demand for I- in the US population [5]. Insufficient I- level causes e.g. hypothyroidism – a condition in which not enough TH is produced for maintaining optimal body function [6]. The incidence of diagnosed hypothyroidism reaches 5.3% in the European population, while in the US it is 0.3% for clinical hypothyroidism and about 4% for subclinical form [7,8]. Incidence of overt hyperthyroidism in the US and Europe is 0.5% and 0.7%, respectively. However, data show that 1 in 20 people in US, including 1 in 8 women, will develop TD [9].

I- is used by the thyroid to synthesize TH. Its deficiency may result in the hypothyroidism and negative effects on reproductive functions, pregnancy, lactation, and may impact the fetus. The American Thyroid Association (ATA), American Endocrine Society (AES), and European Thyroid Association (ETA) recommended thyrotropin (TSH) ranges for pregnant women (Table 1). The guidelines are similar for the US and Europe. However, clinical trials from China and India show that ethnicity has an impact on reference values, which are higher than Western guidelines [10-13].

In the case of maternal TD, developmental disorders of the nervous system in the child may occur and cognitive functions may be weakened (e.g. congenital ID syndrome) during the offspring’s life. In addition, there is a higher risk of miscarriage, stillbirth, mortality, and impaired somatic development [14,15]. The negative effects of TD on the fetus have been confirmed in China in over 1000 pregnant women and their children [16]. The study shows that maternal hypo- or hyperthyroxinemia increases risk of fetal loss, congenital circulation system malformations, poor vision development, and neurodevelopmental delay. Therefore, it is important to control I- levels, especially in pregnant and lactating women [17]. Table 2 presents recommended I- intake for US and Europe [18,19].

TD are divided according to its underactive and overactive physiological status [20]. The two most common autoimmune thyroid diseases (AITD) are HT, a thyroid-degrading inflammation associated with hypothyroidism, and GD, associated with hyperthyroidism and gland enlargement [21]. AITD are associated with an increase of OS level. 8-oxodG and 8-OHdG are markers of OS due to its frequent formation. Therefore, they are worth considering as diagnostic markers in the field of TD [22-24].

Proper thyroid function is also important for female and male fertility. In women, hypothyroidism causes changes in menstrual cycle length and bleeding, reduces the likelihood of conception, and negatively affects the miscarriage rate [25]. The topic of female fertility is discussed further in the text. As for men, AITD can cause a decrease in semen quality, sexual behavior, and impotence disorders. Studies indicate that sperm density, morphology, and motility were unsatisfactory in patients with hyperthyroidism [26]. Hyperthyroidism is also associated with a decrease in testosterone/estradiol ratio which contributes to libido disorders [27]. Moreover, hypothyroidism appears to be correlated with fewer spermatozoa and their reduced motility, which can significantly affect fertility as the female body may even reject impaired semen [25,28-30]. AITD are also associated with male sexual dysfunctions – sexual coldness, erectile dysfunction, or premature ejaculation. According to a study from 2008, 84% of patients diagnosed with hypothyroidism have problems with sexual function [25,26,31].

Clearly, poor quality of sperm may affect the success of conception and possibility of pregnancy. Furthermore, it is worth considering that DNA damage such as 8-oxodG (which form more often in AITD) may be present also in sperm’s genetic material. It impairs the quality of sperm and carries the potential of passing on mutated DNA onto a child.

In the first part of this review, we present the thyroid gland, its hormones and autoimmune diseases. Next, we describe alterations in thyroid functions during pregnancy and its influence on fertility. The second part focuses on introducing the concept of OS, oxidative DNA damage and its correlation with TH in order to discuss the influence of OS biomarkers (8-oxodG and 8-OHdG) on the TD in pregnant women and to discuss other environmental factors that may impact rate of repair of those lesions in DNA.

THYROID AND ITS HORMONES

Thyroid Gland Development

The thyroid is the earliest developing gland in the fetus. It appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue in the embryo (weeks 3-4 of gestation) [32]. Next, it migrates to the base of the neck. During migration, the thyroid remains connected to the tongue by a narrow canal (thyroglossal duct). At the
end of week 5, the thyroglossal duct degenerates. Over the following 2 weeks the detached thyroid reaches its final location. Although not much is known about the pathways of the proper thyroid development, defects at this stage lead to complex health problems (e.g. thyroid dysgenesis or reduced TH sensitivity) [32]. The thyroid gland is not crucial for survival, but its absence or hypothyroidism during fetal and neonatal life can cause severe intellectual disabilities and dwarfism in the child [33].

Thyroid Hormones

TH affect functioning of the reproductive system and conception in humans – especially in women. TH modulate the action of other hormones such as estrogen, prolactin, and gonadotropin-releasing hormone, which impact women’s fertility and the possibility of fertilization or termination of pregnancy [34]. TH are small molecules formed by the linkage of two threonine molecules on the surface of thyroglobulin (TG). After iodination they obtain tri- or tetra-iodo versions of the hormone [35]. Triiodothyronine (T3) and thyroxine (T4) regulate metabolism and act through receptors located in the placenta, uterus, and ovaries. Approximate secretion of TH is: T4 – 80 mcg/day, T3 – 4 mcg/day, rT3 – 2 mcg/ day [33].

TG, which is crucial for the synthesis of TH, accounts for approximately 50% of the protein content of the thyroid gland and contains up to 1% of I [36]. Moreover, it is a storage of the inactive forms of TH and I within the follicular lumen of a thyrocyte [37]. About 70% of I binds to Tyr residues in TG which results in inactive precursors formation (monoiiodothyronine (MIT) and diiodothyronine (DIT)) (Figure 1) [38]. MIT and DIT are subsequently coupled to form T3 [39]. Each TG molecule forms approximately 10 molecules of TH.

T4 is deiodinated by iodothyronine deiodinases type 1-3 (DIO1-DIO3) [40-42]. DIO3, present in placenta and neurons, deactivates TH through conversion of T4 to reverse triiodothyronine (rT3) and T3 to diiodothyronine (T2) [43,44]. Secretion of TH is regulated by TSH, which is regulated by thyrotropin-releasing hormone (TRH) [45]. It binds to its receptor (TRHR) at the basolateral membrane of the follicular cells, which results in stimulation of cell growth and TH synthesis [38]. RT3 is associated with elevated activity of DIO3 or impaired detoxication mechanisms. Increased level of rT3 occurs

Table 1. Reference values for TSH level in pregnant women depending on the trimester.

| Trimester | ATAa [10] | ETAb [11] | China [12] | India [13] |
|-----------|-----------|-----------|------------|------------|
| I         | < 2.50 mU/L | < 2.50 mU/L | < 4.51 mIU/L | < 5.00 μiu/mL |
| II        | < 3.00 mU/L | < 3.00 mU/L | < 4.50 mIU/L | < 5.78 μiu/mL |
| III       | < 3.00 mU/L | < 3.50 mU/L | < 4.54 mIU/L | < 5.70 μiu/mL |

*aAmerican Thyroid Association, *European Thyroid Association

Table 2. I intake recommendation for US and Europe.

| Age          | US (mcg/day) | Europe (mcg/day) |
|--------------|--------------|------------------|
| 0-6 months   | 110 (AI)     | -                |
| 7-11 months  | -            | 70 (AI)          |
| 7-12 months  | 130 (AI)     | -                |
| 1-3 years    | 90 (RDA)     | 90 (AI)          |
| 4-6 years    | -            | 90 (AI)          |
| 4-8 years    | 90 (RDA)     | -                |
| 7-10 years   | -            | 90 (AI)          |
| 9-13 years   | 120 (RDA)    | -                |
| 11-14 years  | -            | 120 (AI)         |
| 13-18 years  | 150 (RDA)    | -                |
| 15-17 years  | -            | 130 (AI)         |
| Adult (18+ years) | 150 (RDA) | 150 (AI)        |
| Pregnancy (all ages) | 220 (RDA) | 200 (AI)        |
| Lactation (all ages) | 290 (RDA) | 200 (AI)        |

*aadequate intake, *recommended dietary allowances
in e.g. euthyroid sick syndrome, heart failures, and liver cirrhosis [44,46].

Most TH are bound to thyroxine-binding globulin (TBG, 70%), thyroxin-binding prealbumin, (TBPA, 10%) and thyroxine-binding albumin (TBA, 15%), which prevent their urinary loss [47]. Hormones bind to intracellular thyroid hormone receptors (TR-α1, TR-α2, TR-β1, and TR-β2), modulate DNA transcription, and interact with enzymes within the cell membrane or cytoplasm [48]. To some extent, the thyroid gland produces T3 directly. In the follicular lumen, Tyr residues become iodinated, which requires $\text{H}_2\text{O}_2$. At high TSH levels, the TRHR couples Gq/11 protein, activating the phospholipase C-dependent inositol phosphate Ca$^{2+}$/diacylglycerol pathway. It causes overgeneration of $\text{H}_2\text{O}_2$ and subsequent TG iodination [38,49].

The fetal hypothalamus and pituitary start to secrete TRH and TSH at week 11. By weeks 18-20, T4 reaches a clinically significant level [50]. Fetal T3 remains low (<15 ng/dL) until week 30 and increases at full-term (50 ng/dL). The fetus needs proper level of TH in order to avoid neurodevelopmental disorders which arise due to maternal hypothyroidism. One of the factors limiting the synthesis of TH is I$^-$ level, which is also essential for healthy neurodevelopment [51]. For proper I$^-$ supply, the T4:T3 ratio in TG is 7:1 [36]. The optimal I$^-$ intake for adults is 150 mcg/day – it ensures proper TH synthesis (Table 2) [52].

**Thyroid Diseases**

There are three major groups of TD [7,53]. Two of them are associated with hyper-/hypothyroidism and the third group is parathyroid disorders. AITD are mostly defined by HT and GD, especially due to their connections to genetic alterations [54]. AITD are separated into two clinical categories: (1) if goiters are present, it is understood as HT, (2) if the thyroid is atrophic, and does not present goiters, it is atrophic thyroiditis and also refers to GD [55]. Moreover, postpartum thyroiditis may be diagnosed within the first year after giving birth.
ALTERATIONS IN THYROID FUNCTIONS DURING PREGNANCY

Thyroid gland function influences conception and pregnancy. Changes in the physiology of a woman’s body during gestation have an impact on the morphology and function of the thyroid gland. Therefore, daily I- requirements (Table 2) are higher during and after pregnancy due to increased renal I- excretion, increased TH production, significant I- requirement of a fetus, and I- secretion into breast milk [57]. Pregnancy impacts thyroid secretory functions so diagnostic standards for healthy adults do not apply to pregnant women.

The estrogen and chorionic gonadotropin (hCG) interact with iodothyronines and TSH secretion. HCG is secreted by the placenta from the first weeks of pregnancy. Due to the structural similarity to TSH, hCG influences thyroid activity – increases T4 and decreases TSH secretion. Hence, a spike of T3 and T4 levels occurs. The concentration of hCG in the blood peaks at about weeks 8-11 of pregnancy, then decreases and reaches a plateau around week 20.

During pregnancy production of TH increases. TBG, a TH binding protein, is the main repository for TH and regulates the total level of thyroid hormones and the level of free TH – not bound to proteins. TBG level increases from the first weeks of pregnancy about 2-3-fold and reaches a plateau about halfway through gestation. Estrogen levels in the blood are positively correlated with TBG [58]. Increased TBG levels contribute to a drop of free TH and increase of the overall level of TH in the blood [58]. The increase in TBG is gradual and stops during the second trimester. At the same time TH show an increase of approximately 50%. Moreover, hCG causes an increase of free T3 and T4 levels, which induces TSH decrease. The action of placental DIOs contributes to the increased demand for TH. DIO3 is involved in the transformation of T4 to rT3 and T3 to T2. It protects the fetus from overexposure to maternal TH by inhibiting T4 activation and T3 deactivation. DIO2 catalyzes the transformation of T4 to T3 and provides the optimal level of T3 for fetal development. Both enzymes are produced from the beginning of pregnancy and their activity decreases with time.

At the beginning of the second trimester, the secretory activity of the placenta decreases and settles at a certain level. The level of free TH decreases, while TSH concentration increases [58]. The secretory functions of the thyroid gland change significantly as pregnancy progresses (Table 3). Due to these fluctuations the reference values of hormones differ from the values for healthy adults [28,59].

The fetal thyroid begins to work between weeks 12-20 of pregnancy. Until then, TH must come from the mother and I- must be transported from the mother throughout pregnancy [60]. TH levels differ on the maternal and fetal side of the placenta. T3 is lower (4.34 ng/g in fetus and 5.93 ng/g in mother) and T4 is higher (67.72 ng/g in fetus and 44.96 ng/g in mother) on the fetal side [61]. I- levels on the fetal side of the placenta are lower than on the mother’s side (0.45 μg/g and 1.38 μg/g, respectively). In pregnant women, the I- level in placenta and urine is associated, however this is not observed for fetal I- placental level [61].
In the case of GD, alleviation of the course of hyperthyroidism is observed after the first trimester. The attack of the immune system on thyroid antigens is weakened and the disease stabilizes. However, after delivery, the immune processes regain activity, which may cause the AITD relapse [64].

After birth, the immunosuppressive effect of pregnancy subsides and the incidence of hyperthyroidism increases due to the rebound of the immune system [63,65]. The occurrence of hyperthyroidism is the highest within 7-9 months after delivery (more than 5 times higher than before delivery and 10 times higher than during the third trimester). Similar study confirms the reduction in the incidence of illness during pregnancy with a minimum in the third trimester (3 times lower than in the period before pregnancy), and a maximum in

Pregnancy Immunosuppression and its Effect on the Thyroid Gland

Antigenic compatibility between the mother and the fetus is is rarely 100%. To prevent rejection of pregnancy, the functions of the immune system change in women – immune responses are suppressed. It was shown already in 1997 in clinical studies where the number of immune cells in pregnant women have decreased, but postpartum it has risen even above pre-pregnancy level [62]. This phenomenon is called pregnancy immunosuppression and its effect on the course of AITD is confirmed [63]. Over 400,000 Danish women were tested during the year before and two years after pregnancy. Results show that the incidence of hyperthyroidism in the first trimester increased (compared to before pregnancy) and then decreased to its lowest in the third trimester [63].

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occurs in more than 52% of patients with the diagnosis of GD and 47% with HT [25,67]. Infertility is caused mainly by hormonal imbalance e.g. increased prolactin level. It impacts gonadotropin release and subsequently leads to decreased capacity of corpus luteum. Problems with fertilization may also result in ovulation disorders [69]. Furthermore, recent clinical studies show that untreated hypothyroidism (with TSH >4 mIU/L) increases the risk of miscarriage [70,71]. Interestingly, after bringing women to the state of euthyrosis, birth rates improve [72,73].

Impact of Thyroid Dysfunction on Female Fertility

Hyperthyroidism affects the level of sex hormones in women. In patients with thyroxicosis, estrogen levels may increase up to 3-fold. Levels of testosterone, androstenedione, and luteinizing hormone also increase. Moreover, menstruation disorders are the most common symptom of hyperthyroidism. They are associated with elevated total T4 levels and diagnosed 2.5 times more often than in healthy women. In patients with hypothyroidism, the concentration of total testosterone and estradiol in the blood decreases, while their unbound fractions increase. Disorders of blood coagulation factors and platelet function may also occur, with changes in the length of the cycle and the intensity of bleeding. Menstrual cycle disorders are the most common symptom in hypothyroidism [25,67,68].

In addition, TH may directly impact conception and pregnancy. Quintino-Moro et al. show that infertility occurs in more than 52% of patients with the diagnosis of GD and 47% with HT [25,67]. Infertility is caused mainly by hormonal imbalance e.g. increased prolactin level. It impacts gonadotropin release and subsequently leads to decreased capacity of corpus luteum. Problems with fertilization may also result in ovulation disorders [69]. Furthermore, recent clinical studies show that untreated hypothyroidism (with TSH >4 mIU/L) increases the risk of miscarriage [70,71]. Interestingly, after bringing women to the state of euthyrosis, birth rates improve [72,73].

Obviously, decreased function of women’s reproductive systems, such as menstrual disorders, impedes conception rate. In the context of human reproduction, it is of high importance that women have healthy thyroids or properly managed AITD in order to successfully plan and start a family. Therefore, in the next section we focus on the interesting aspect connected to thyroid function – oxidative stress and its markers. It is believed that this perspective may improve early diagnosis options and maybe even contribute to new therapeutic approaches.
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Lesions are 8-oxodG and 8-OHdG [84,85]. They are generated through interaction between 1O2 or •OH and G or 2′-deoxyguanosine (dG) (Figure 3). 8-oxodG is one of the most abundant lesions, which occurs 105 times per day/per cell [83,86]. Those lesions are corrected by the base excision repair (BER) system. The standard process consists of: recognition and excision of damaged base by glycosylases, filling in the nucleotide gap by polymerases, and strand ligation [87]. From glycosylases described in mammals, oxoguanine glycosylase 1 (OGG1) and formamidopyrimidine DNA glycosylase (Fpg) excise oxidative G lesions [88]. OGG1 is a primary BER bifunctional glycosylase, which removes 8-oxodG. However, OGG1 is susceptible to polymorphisms and may not always detect a damaged base. Therefore, 8-oxodG may form mispairs with adenine (A) leading to transversion (G::C → T::A) or transition (G::C → A::T) mutations. It makes G lesions highly mutagenic, especially when such mutations accumulate in the DNA strands in close proximity to one another [89]. MutY DNA glycosylase (MUTYH) is able to recognize and remove A opposite 8-oxodG and G [88,90]. OGG1 and MUTYH play crucial roles in normal cell functioning under OS and prevent development of pathological states [90].

INFLUENCE OF OXIDATIVE STRESS ON THYROID

Oxidative Stress and Oxidative DNA Damage Formation

In a healthy cell, there is an oxidative balance between ROS production and their neutralization by the cell (redox homeostasis), which, when disrupted generates OS [74]. ROS include: superoxide anion radical (O2•−), hydroperoxyl radical (HO2•), hydroxyl radical (•OH), singlet oxygen (O3), ozone (O3), H2O2, nitric oxide (NO•), and peroxinitrite (ONOO−), where •OH is the most reactive and interacts with proteins, lipids and nucleic acids [75,76]. About 90% of ROS is derived from mitochondrial oxidative phosphorylation (OXPHOS) activity through electron leakage in electron transport chain (ETC) [77-79]. In ETC, about 5% of O2 is transformed to H2O2 (Figure 2) [76].

The effects of ROS include modifications within the genome [80]. Oxidative DNA lesions induced by ROS manifest as nucleobases and/or sugar fragments modification, single and double strand breaks, apurinic/apyrimidinic sites, modified purine/pyrimidine/sugars, structurally mutated bases, deleted and/or translocated chromosome fragments, and DNA-protein cross-links [81]. About 100 oxidative DNA lesions are now identified, which constitute the largest group of all lesion types [82].

Due to the lowest redox potential, the most susceptible to OS is guanine (G) [83]. The most frequent lesions are 8-oxodG and 8-OHdG [84,85]. They are generated through interaction between O2 or •OH and G or 2′-deoxyguanosine (dG) (Figure 3). 8-oxodG is one of the most abundant lesions, which occurs 105 times per day/per cell [83,86].

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Oxidative Stress and Oxidative DNA Damage in Thyroid Diseases

Redox homeostasis is important in the thyroid
gland. H₂O₂, a redox signaling molecule, is produced in large amounts in thyrocytes due to its relevance in TH synthesis (Figure 4). Thyroid remains highly susceptible for oxidative damage in the case of any imbalance. Thus, it is crucial that thyroid cells maintain oxidative balance in order to prevent malignancies and disease development.

TH regulate mitochondrial function and thus, the rate of oxygen metabolism. TH affect the speed of mitochondrial activity and the systemic production of ROS [79]. T3 controls the proinflammatory reactions (through induction of GPX and SOD) and reduces ROS production in mitochondria by activating the mitochondrial ATP-dependent potassium channel. Moreover, T3 stimulates autophagy, mitochondrial DNA repair, and creation of new mitochondria [91,92].

H₂O₂ is necessary for TH production, but at the same time it increases OS levels in the thyroid gland [93]. GPX, a major enzyme catalyzing the reduction of H₂O₂, protects thyrocytes from ROS action and modulates TH synthesis [94]. The present data are inconclusive – GPX level may be decreased or increased in patients with HT [95].

OS is considered one of the most important causes of DNA damage formation – in particular 8-oxodG and 8-OHdG [78]. While ID impairs TH synthesis, excess of I- in the body may induce OS and HT. Higher I- levels were confirmed in patients with newly diagnosed HT, but the mechanism is not clear [95]. It is assumed that H₂O₂ overproduction may result from NADPH oxidase overexpression and I-/Tyr interaction in TG [95].

ROS accumulation and OS levels are directly related to AITD. In HT, a positive correlation between OS markers and disease progression was demonstrated [96]. ROS accumulation appears to favor TG fragmentation, which indirectly stimulates the immune system to thyroid auto-aggression [91]. In GD, OS also increases. The NF-κB pathway, which is activated by OS, seems to play a significant role in GD’s autoimmunity [97]. The level of OS and accumulated lesions such as 8-oxodG and 8-OHdG is related to the occurrence of thyroid cancers. Therefore, intensification of O₂ metabolism and decrease in DNA damage systems efficiency may have an effect on carcinogenesis.

**8-oxodG AND 8-OHdG AS A POTENTIAL STIMULANT OF AITD DEVELOPMENT DURING PREGNANCY**

**DNA Oxidative Damage in Pregnancy**

Sedentary lifestyle and exposure to toxins predispose to increased OS and might affect ova, sperm, and embryo development [98]. During uncomplicated gestation, OS is mainly stimulated by the mitochondria-rich placenta and purines metabolism. However, cells correctly neutralize or reduce the negative effects/products of ROS and maintain their concentration at the safe level.

ROS seem to play a pivotal role in right placenta development. Study on mice shows that 4-5 days after fertilization, the developing blastocyst produces O₂⁺ (>8 nmol/embryo h⁻¹) and H₂O₂ (ca. 4 nmol/embryo h⁻¹). Moreover, cytochemical evidence of H₂O₂ entails the appearance of •OH [99,100]. In the first trimester, level of placental O₂ is low – the embryo is protected from ROS which favors its development, placental angiogenesis, and cell proliferation. At the end of the first trimester, O₂ levels increase due to stabilization of maternal intraplacental circulation. The possibility of normal fetal development is ensured by modulation of hypoxia-inducible factor 1α (HIF-1α) and antioxidant defense systems [101]. A study by Hung et al. shows that among healthy pregnant women, the urinary level of 8-oxodG increases in the third trimester and returns to physiological level after delivery. Moreover, other biomarkers of OS also increase (GPX and SOD) [102]. A subsequent study by Hung et al. presents that increased level of OS among pregnant women may implicate pregnancy complications [103]. Excessive OS may induce polycystic ovary syndrome, endometriosis, preeclampsia, idiopathic infertility, premature birth, recurrent pregnancy loss, and intrauterine growth restriction [104]. OS plays a role in the course of pregnancy and thyroid disorders, therefore it is interesting to explore the scenario where both conditions are present simultaneously. Hence, the next sections attempt to explore this connection of oxidative stress and thyroid disease in pregnant women and also discuss factors which influence their incidence such as diet (e.g. antioxidant intake).

**Oxidative Stress in Thyroid Disease and its Effect on Pregnancy**

AITD are common endocrine dysfunctions during gestation which affect about 1% of all pregnant women [105]. H₂O₂ is a ROS and OS inducer but is also essential for TH synthesis. Studies show that H₂O₂ production is dependent on I- and TSH levels [106]. AITD are associated with TSH secretion, caused by ID and affect the H₂O₂ production in the thyroid gland. H₂O₂ does not react directly with genetic material but is a precursor of highly reactive compounds: ¹O₂ and ‘OH [107]. AITD are correlated with OS and its markers – 8-oxodG and 8-OHdG. These lesions are formed directly in the reaction of G moiety with ‘OH and ¹O₂ and, in the case of AITD, their accumulation is observed [24]. Hyperthyroidism is linked with overproduction of OS markers while hypothyroidism is linked with reduced availability of antioxidants [23].

Connections between AITD and the DNA damage is studied worldwide but still needs more extensive
exploration. In 2013, studies assessed the level of 8-OHdG in people with TD. The results show that patients suffering from toxic multifollicular goiter, GD, and HT have a higher concentration of 8-OHdG in urine. For each disease, 8-OHdG is on average 22.26 ng/ml (5.11 ng/ml for the control) [108]. In addition, plasma 8-OHdG levels (1.23 ng/ml and 0.67 ng/ml in the study and control group, respectively) are useful markers of carcinogenic potential for multinodular goiter. Thyroid nodules occur in 68% of the general population (with 7-15% malignant) thus, testing 8-OHdG plasma levels may improve early diagnosis of thyroid cancer [24]. Impact of AITD in pregnant women on fetal OS is considered. A study from 2018 shows that subclinical form of hypothyroidism increases the level of OS in amniotic fluid – O₂⁻ level increased from 0.1 to 0.2 nmol/10⁶ cells. The authors suggest that diet and supplementation of antioxidants may counteract effects of OS [109]. A different study on pregnant women with clinical hypothyroidism shows that the level of O₂⁻ in the amniotic fluid doubles (from 3.5 to 8.0 nmol/mL). Additionally, it describes a positive correlation between O₂⁻ and a reduced body weight in women and reduced Apgar scores in newborns [110]. As suggested by those authors, environmental factors, such as diet and weight, impact the level of OS. In the case of pregnant women, diet and overall health is crucial for the mother and the fetus. However, not only as a mean to the well-nourished child and healthy women, but as it turns out also in terms of maintaining genetic integrity, preventing DNA damage formation, and DNA repair systems operation.

**Impact of Diet on DNA Repair Mechanisms**

DNA damage and its aftermath may cause cancer, neurodegenerative diseases, and others [111]. The accumulation of DNA lesions induce deregulation of cell functions e.g. DNA replication and transcription, proliferation, or immune response [112]. Fortunately, cells are equipped with several DNA repair mechanisms including direct repair, excision repairs, and recombination systems [113]. The fundamental mechanism for oxidative DNA damage repair is the BER system. Fragment of 1-20 nucleobases can be excised from DNA strand depending on the damage type [114].

The impact of a plant-rich diet on DNA repair mechanisms has been studied for over 20 years. While at first results were contradictory, currently it is known that a diet rich in vegetables and fruit has genoprotective properties and positive influence on DNA repair mechanisms, including BER. Clinical studies also stress the fact that poor dietary choices and subsequent problems, such as obesity, which induces ROS generation, are correlated with the thyroid and its disorders [115].

As diet provides antioxidants that restore the balance between the formation and removal of ROS it may reduce DNA damage level in the genome [116]. The most widely considered antioxidant is vitamin C. Its influence on oxidative lesions was identified for the first time in 1998 [117]. Subsequent years brought new results, where fruit and vegetable consumption and its influence on 8-oxodG, 8-OHdG, and in some cases DNA repair gene expression levels were examined [118-123]. Typically used in such studies are broccoli, kiwifruit, or vitamin C supplements. However, results were contradictory for a long time and hard to compare probably due to testing variable subject groups such as smokers, healthy people, or patients with different pathologies. However, subsequent years brought new insights and confirmed that diet rich in fruit and antioxidants protects from DNA damage and stimulates DNA repair [120,124-128]. Moreover, recent in vitro studies seem to confirm the beneficial properties of antioxidants on expression of proteins involved in DNA repair mechanisms (e.g. GPX, OGG1) [119,129-131]. Green tea is also widely considered as beneficial in the field of genome protection. *Camellia sinensis* increases OGG1 activity after only 7 days of regular intake. Moreover, DNA damage level decreases by 30% just after 1h from drinking the tea [129,132].

According to Lalonde’s theory, who already in 1976 determined that the overall health status of humans depend, in more than 50% on environmental factors, diet seems to be a major factor influencing our well-being [133]. These facts are especially important for women, as proper dietary choices and healthy lifestyle are crucial before, during, and after pregnancy.

**CONCLUSIONS AND OUTLOOK**

AITD, as a growing health problem of developing countries, became widely investigated in relation to pregnancy and early fetus development as a crucial part of human procreation. Increasing numbers of studies indicate a connection between ROS overgeneration and the regulation of the immune system during pregnancy. During uncomplicated gestation ROS levels are higher, mainly due to mitochondria-rich placenta [99]. OS is an important factor in predicting complications during pregnancy. It may cause dysfunction in cells and lead to a generation of DNA lesions such as 8-oxodG and 8-OHdG [102]. Elevated level of these lesions during pregnancy may indicate pathological states e.g. AITD. These disorders may cause complications for mother and fetus. Current evidence shows that patients with GD and HT have elevated levels of 8-OHdG in urine samples [108]. Considering novel data level of urine 8-OHdG can be an important biomarker of pregnancy complications, including those concerning thyroid. Moreover, increased level of ROS during gestation stimulates dysfunction
of the endocrine system. This might induce doubling of O$_2^-$ levels in the amniotic fluid or provoke reduced body weight among mothers and reduced Apgar scores in newborns [110]. Further studies in the field of redox biology are highly demanded. ROS formation and identification of possible cut-off values cannot be yet precisely monitored. If possible, this would help to predict negative consequence of ROS generation and develop personalized treatments.

As 8-oxodG and 8-OHdG are connected with AITD, studies should continue to determine their levels in various pathologies. Oxidative lesions may also indicate the condition of pregnant women and fetuses, but more data is needed concerning correlation of newborn health and level of oxidative DNA damage in the mother. In order to improve the care of pregnant mothers, future studies should focus on deepening knowledge about endocrine system dysfunction during pregnancy and possible cut-off values of 8-OHdG and 8-oxodG for later clinical application. We believe it would help to better understand the etiology of AITD, select high-risk patients, and avoid passing on risk of health complications onto a child. Therefore, the oxidative DNA damage as a potential AITD biomarker are worth exploring in order to advance personalized treatment options and early diagnosis, especially for pregnant women.

Furthermore, AITD have a direct impact on human reproductive capacity [25,27]. Apart from sex hormone disorders, men experience sexual dysfunction, such as impotence or frigidity [26,31]. In women, AITD result mostly in menstrual disorders as well as limited fertility and/or ability to maintain pregnancy [67,70,71]. Information presented in this review allows us to assume that different kind of DNA lesions may be the missing link between AITD and complications of pregnancy, including miscarriages. Therefore, we believe that studies should be undertaken to examine how cellular systems of DNA damage control impact pregnant women with AITD and the condition of the fetus.

As mentioned in the previous section, nutrients and antioxidant intake influence to some extent oxidative DNA lesion levels and efficiency of BER mechanism, which in turn may impact all reproductive processes – female and male fertility, conception, pregnancy, and even proper development of the fetus. Recently, more studies confirm a connection between the diet and cellular capacity to prevent and/or repair DNA lesions, including 8-oxodG. Antioxidants present in e.g. broccoli or green tea, are important factors in maintaining cellular redox homeostasis, hence, increasing the defense capabilities of cells.

All species are not supposed to be immortal (long living). The main evolutionary goal is to sustain life, reproduce, and pass on the genetic material to ensure the survival of the entire species. In this context, DNA is the most important particle of life and any damage or impairment to its integrity may have severe consequences for the survival of the species. Therefore, it is of high importance that the genome remains intact or properly repaired by specialized systems, so the whole organism (human being) may serve its purpose in evolution.

Referring to Lalonde’s theory once more, if 50% of our health depends on environmental factors, and the major factor in everyday life is the diet, we have a vast possibility to influence our own well-being. Due to the fact that both pregnancy and AITD are related to increased DNA damage formation, a healthy plant-rich diet should be integral part of the strategy to protect our organism from destructive influence of OS and oxidative DNA damage. It especially concerns pregnant women with higher risk or already diagnosed AITD [134].

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