Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/davwdr60

THE IMPACT OF AUTOIMMUNE ENDOCRINE DISORDERS ON PREGNANCY: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY AND CLINICAL OUTCOMES

Aiysha Gul[1*], Rizwanullah[2], Samah Badr Hamad[3], Esraa Awad[4], Fardin Akbar Hyderi[5], Giftty E. Obadan[6], Karthiga Vasudevan[7]

[1*]Department of Obstetrics and Gynaecology, Mardan Medical Complex, Pakistan
[2]Department of Medicine, Hayatabad Medical Complex, Pakistan
[3]Department of Basic Medical Sciences, University of Khartoum, Sudan
[4]Department of Medicine, Zagazig University Hospitals, Egypt (Esraaawadmd@gmail.com)
[5]Department of Medicine, Bangladesh Medical College, Bangladesh
[6]Department of Medicine, Philadelphia College of Osteopathic Medicine, USA
[7]Department of Medicine, Yerevan state medical university, Armenia

***Corresponding Author:** Aiysha Gul
***Email address:** ayeshag0342@gmail.com

Abstract

Pregnancy is a transformative period characterized by extensive physiological, psychological, and immunological changes, which play a critical role in the health of both the mother and the fetus. The immune system undergoes significant modifications to tolerate the fetus, an entity resembling a temporary histoincompatible allograft, with sex hormones such as progesterone (P4) and estrogen (E) modulating these changes. This review explores the intersection of endocrine autoimmunity and pregnancy, focusing on the physiological adaptations and their clinical implications for autoimmune disorders.

The review highlights the unique role of progesterone in immune modulation, including its effects on Th1 and Th2 cell responses, and its influence on autoimmune disease activity. During pregnancy, hormonal shifts lead to immune system adaptations that often result in the remission of some autoimmune disorders but can exacerbate others postpartum. Autoimmune endocrine disorders, particularly thyroid disorders, are prevalent in women of reproductive age and significantly impact pregnancy outcomes. The review details the pathophysiology of autoimmune thyroid diseases, including Hashimoto's thyroiditis and Graves' disease, and their management in pregnant women. The risks associated with autoimmune thyroid disorders, such as miscarriage, preterm delivery, and postpartum thyroiditis, are discussed, along with guidelines for monitoring and treatment.

The review also covers autoimmune primary adrenal insufficiency (Addison's disease) and its implications during pregnancy, including management strategies and associated risks. Additionally, it addresses the challenges of managing type 1 diabetes in pregnant women, emphasizing the importance of preconception care and ongoing management throughout pregnancy to optimize maternal and fetal outcomes.

In summary, this article provides a comprehensive overview of the interplay between endocrine autoimmunity and pregnancy, offering insights into the physiological, pathophysiological, and clinical aspects of managing autoimmune endocrine disorders during this critical period.

Keywords: Pregnancy, immunological adaptation, autoimmune diseases, endocrine autoimmunity, progesterone, thyroid disorders, Hashimoto's disease, Graves' disease, postpartum thyroiditis, adrenal insufficiency, Type 1 diabetes

Introduction:

Pregnancy is a unique and transformative time in a woman's life, marked by significant psychological, social, and physiological changes within a relatively short gestational period. From an immunological standpoint, the fetus is akin to a temporary histoincompatible allograft, capable of triggering a strong immune reaction. To ensure a successful pregnancy, the maternal body must adapt to these changes and suppress immune responses directed against the fetus. Sex hormones play a dual role in this process by supporting reproductive functions and modulating the immune system to protect the developing embryo (1).

Due to these adjustments in the immune system, pregnancy can alter the clinical manifestation and progression of autoimmune diseases. Conversely, autoimmune disorders, particularly those affecting the endocrine system, can have a significant impact on the course of pregnancy (2). In this article, we aim to explore the physiological, pathophysiological, and clinical aspects of endocrine autoimmunity during pregnancy, as well as discuss specific considerations for pregnant women.

Review

Immune Modifications in Pregnancy and the Unique Role of Progesterone

During human pregnancy, numerous physiological changes occur, especially with the development of the placenta, which functions as a temporary but highly active endocrine organ (3). The placenta produces several hormones, including placental growth hormone (pGH), insulin-like growth factor-1 (IGF-1), human placental lactogen (HPL), growth-hormone-releasing hormone (GHRH), adrenocorticotropin (ACTH), estradiol, and progesterone (P4). Pregnancy involves a complex interaction of various placental and non-placental hormones, notably estrogens (E) and P4, with P4 playing a vital role in sustaining a healthy pregnancy. The immune adaptations that occur during pregnancy influence not only the fetus's health but also the mother's entire immune profile, balancing T helper type 1 (Th1) and T helper type 2 (Th2) cells. P4 and E modulate the immune system through multiple systemic adaptations, which coincidentally affect the clinical course of pre-existing autoimmune disorders. Sex steroids promote a Th2-specific response and suppress Th1/Th17 responses, leading to worsening Th2-type disorders and improvement in Th1/Th17-type disorders (4-6).

Progesterone (P4) is produced in the adrenal glands and is significantly elevated by the corpus luteum during the luteal phase of the menstrual cycle. However, the production of P4 by the ovaries and placenta during pregnancy is substantially higher than in non-pregnant women. Recent research has demonstrated that P4 is essential not only for preparing the uterine lining for implantation and maintaining the cervix's structure but also, importantly, for modulating the maternal immune response to pregnancy by directly and indirectly inhibiting Th1 cell response and by blocking cytotoxic T cell and natural killer (NK) cell activity and proliferation (7-9). High levels of P4 stimulate the production of progesterone-induced binding factor (PIBF) (10). Consequently, elevated PIBF levels promote the differentiation of CD4+ lymphocytes into Th2 cells, which produce anti-inflammatory cytokines such as interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 10 (IL-10) (8). Recent studies show that P4 directly affects CD4+ T cell activation through altered transcription factor activity (11).

During a normal pregnancy, a decline in Th1 action is accompanied by reduced production of pro-inflammatory cytokines, such as interleukin 2 (IL-2), interferon gamma (IFN-γ), and tumor necrosis

factor alpha (TNF-α) (10). The balance between Th1 and Th2 cells promotes pregnancy by reducing the immune response and appears to be maintained primarily through CD4+CD25+ regulatory T cells (Tregs) (10). Treg expansion throughout pregnancy occurs due to fetal antigen presentation to immune cells and estrogen-stimulated expression of various chemokines, which is further enhanced by high estrogen levels (10). After delivery, the number of Tregs rapidly decreases, allowing Th1 cells to become the dominant subgroup again, resulting in the release of pro-inflammatory cytokines and exacerbation of autoimmune diseases. P4 also suppresses the humoral response by inhibiting post-translational glycosylation of active immunoglobulins (11).

Thus, the shift in the hormonal profile of pregnant women, particularly the significant increase in P4 levels, triggers a multi-level modification of immune activity. In practice, this can be observed in pregnant women with a history of autoimmune diseases. Diseases such as rheumatoid arthritis, multiple sclerosis, or systemic lupus erythematosus often go into remission during pregnancy but may flare up again after delivery (12). In addition to these broad adaptations, other changes occur, such as thymic involution, altered levels of complement factors and regulatory proteins, and modifications in the function of virtually all immune cell subtypes (13, 14). However, as this article focuses on the clinical aspects of endocrine autoimmunity during pregnancy, further discussion of these topics will be omitted.

The most common autoimmune endocrine disorders in women of reproductive age are thyroid disorders, specifically Hashimoto's disease and Graves' disease, with women being at a significantly higher risk than men (15). After childbirth, postpartum thyroiditis may develop. Although primary adrenal insufficiency is less common, it can cause several complications. Large epidemiological studies have confirmed the link between thyroid disorders and various complications that can threaten the health of mothers, fetuses, and newborns (16). Thyroid dysfunction is associated with an increased risk of spontaneous abortion, preterm delivery, preeclampsia, and gestational diabetes mellitus (17).

The pathogenesis of autoimmune thyroid disorders is driven by the activation of CD4+ lymphocytes, which can stimulate B lymphocytes to produce anti-thyroid antibodies (18). Autoimmune thyroid disorders (AITDs) are believed to result from Treg dysfunction, direct cytotoxicity, and cytokine-induced apoptosis of thyroid cells. The clinical presentation of AITDs can vary among patients, and thyroiditis can be associated with symptoms of either hypothyroidism or hyperthyroidism. These differences arise from the type of recognized antigens, the presence of stimulating or blocking antithyroid antibodies, the degree of glandular infiltration and destruction, and the extent of fibrotic changes within the thyroid.

Thyroid Gland Autoimmune Disorders

Thyroid antibodies, even in the absence of overt thyroid disorders, can negatively impact pregnancy. Antibodies such as anti-thyroperoxidase (ATPO) and anti-thyroglobulin (ATG) are detected in approximately 5-14% and 3-18% of pregnant women, respectively (1). Studies show that euthyroid women with these antibodies have a higher risk of spontaneous miscarriage, preterm delivery, progression to hypothyroidism, and postpartum thyroiditis (18–22). Although the precise mechanisms are not entirely understood, several theories have been proposed. One suggests that the presence of antithyroid antibodies may indicate a broader autoimmune response, which could contribute to obstetric complications (19). This is supported by data showing increased levels of CD5+CD20+ B lymphocytes—key players in autoimmunity—in women who have experienced miscarriages (1). Another theory points to elevated thyrotropin (TSH) levels in women with positive antithyroid antibodies, suggesting that these women may have insufficient thyroid hormone levels to meet the increased demands of pregnancy. A third hypothesis links these antibodies with reduced fertility, particularly in older women (20). Additionally, ATPO has been found to enhance IL-2 production and natural killer (NK) cell activation. The discovery of thyroid peroxidase in the endometrium and placenta also provides a possible explanation for the increased miscarriage risk associated with ATPO positivity (21).

Despite research showing a decrease in antithyroid antibody levels during pregnancy, women with autoimmune thyroiditis still tend to have higher TSH levels compared to those without antibodies (22). Although ATG and ATPO can cross the placenta, they do not cause thyroid disorders in the fetus. Many changes seen during pregnancy can be attributed to altered regulatory T cell (Treg) activity, which increases during pregnancy and decreases postpartum (5, 8, 15).

Given the increased risk of pregnancy complications associated with antithyroid antibodies, there has been debate over whether early thyroid hormone supplementation in euthyroid women with these antibodies might be beneficial. Recent studies suggest that administering low-dose levothyroxine (LT4) (50 mg daily) to euthyroid pregnant women with confirmed autoimmune thyroid disease (AITD) does not improve outcomes related to infertility or miscarriage (23).

Current guidelines recommend that women with a history of autoimmune thyroid disease who become pregnant should have their thyroid function closely monitored. Pregnant women with positive antithyroid antibodies should have their TSH levels checked every four weeks until mid-pregnancy and once more around the 30th week, due to the increased risk of developing hypothyroidism (23).

Positive ATPO status is a known risk factor for postpartum thyroiditis and subsequent persistent hypothyroidism, with postpartum thyroiditis affecting up to 30-50% of patients with circulating ATPOs (15). Therefore, thyroid function should be assessed 6-8 weeks after delivery in women with confirmed ATPO positivity (24).

Hypothyroidism (Hashimoto’s Thyroiditis)

Hashimoto's disease is the leading cause of hypothyroidism in young women when there is no iodine deficiency in the region. During pregnancy, the demand for thyroid hormones significantly increases, up to 50% above baseline levels. This heightened requirement raises the likelihood of developing hypothyroidism in women with positive anti-thyroid peroxidase (ATPO) and/or anti-thyroglobulin (ATG) antibodies; even if the antibody levels spontaneously decrease. Due to increased estrogen levels during pregnancy, the liver produces more thyroxine-binding globulin (TBG), and there is a change in deiodinase activity (15, 23). Consequently, pregnant women with autoimmune thyroid conditions can develop subclinical or overt hypothyroidism.

Subclinical hypothyroidism, characterized by elevated thyroid-stimulating hormone (TSH) levels while free thyroxine (fT4) remains within normal ranges, is the most prevalent thyroid disorder in pregnancy, affecting 2.5% of pregnant women. Up to 60% of women with subclinical hypothyroidism have positive antithyroid antibodies. In contrast, overt hypothyroidism, defined by elevated TSH and reduced fT4 levels, is less common, occurring in 0.2-0.5% of pregnancies (25). Hypothyroidism during pregnancy is associated with numerous maternal and fetal complications, including miscarriage, preterm delivery, gestational hypertension, preeclampsia, low birth weight, placental abruption, and postpartum hemorrhage (26). If left untreated, overt hypothyroidism in mothers can lead to lower intelligence quotient in their children. Although subclinical hypothyroidism may increase the risk of adverse pregnancy outcomes, the available data is not consistent (27, 28).

Symptoms of hypothyroidism are often subtle and may be masked by pregnancy. The most frequent symptoms include fatigue, drowsiness, constipation, weight gain, cold intolerance, and dry skin. Diagnosing hypothyroidism in pregnant women is based on elevated TSH and reduced fT4 levels, adjusted for gestational age and population-specific reference ranges (29).

Current guidelines recommend immediate levothyroxine (LT4) replacement for all cases of overt hypothyroidism during pregnancy. Pregnant women with subclinical hypothyroidism and an autoimmune thyroid disorder should also begin thyroid hormone therapy; the diagnosis should be based on reference ranges appropriate for the specific population (30). Women who were being treated for hypothyroidism before becoming pregnant typically require a 30-50% increase in LT4 dosage, depending on the extent of thyroid damage and the duration of their condition. The target TSH level should be between the lower limit of the assay’s reference range and 2.5 mU/ml (29, 33).

Women on LT4 therapy should have their TSH levels checked every four weeks until mid-pregnancy and at least once around the 30th week (30).

Hyperthyroidism (Graves' Disease)

Graves' disease (GD) is the leading cause of autoimmune hyperthyroidism in pregnant women, accounting for approximately 85% of cases (1). The disease results from the production of autoantibodies that stimulate thyroid-stimulating hormone (TSH) receptors, known as TSH receptor antibodies (TSAbs). These antibodies cause the thyroid follicular cells to grow and become overactive, leading to excessive thyroid hormone production (19). GD-related hyperthyroidism is present in about 0.2% of all pregnancies (31). When hyperthyroidism occurs during pregnancy, it can lead to complications such as high blood pressure, heart failure, premature labor, preeclampsia, and a hypermetabolic state around the time of delivery (32). This condition also poses risks to the fetus, including low birth weight, congenital anomalies, increased perinatal mortality, and fetal hyperthyroidism if TSAbs cross the placenta. As a result, women diagnosed with GD are advised to delay pregnancy until their thyroid levels are normalized (33).

The likelihood of hyperthyroidism recurrence is higher in patients with persistently low TSH levels despite antithyroid treatment, those who received antithyroid medications for less than six months, those needing more than 5-10 mg of thiamazole daily, those with symptoms of thyroid eye disease, those with large goiters, and those with elevated TSAb levels. For patients at high risk of disease recurrence, antithyroid medication should be continued throughout the first trimester of pregnancy (34).

Some common signs and symptoms of hyperthyroidism, such as weight loss or failure to gain weight, goiter, eye disease related to thyroid, palpitations, and diarrhea, can resemble typical pregnancy symptoms (32). Hyperthyroidism associated with GD often intensifies in the first trimester, likely due to high TSAb levels early in pregnancy. Additionally, human chorionic gonadotropin (hCG) can stimulate thyroid hormone production until about 16-18 weeks of gestation. As pregnancy advances and the immune system adjusts, TSAb levels typically decrease, leading to a milder course of hyperthyroidism. These allow for a reduction in the dosage of antithyroid medications or even complete discontinuation in the latter half of pregnancy. However, hyperthyroidism can return after childbirth, affecting around 40% of women with GD (35).

If TSH levels are low during pregnancy, testing for total thyroxine (TT4), free thyroxine (fT4), and triiodothyronine is necessary (22). Hyperthyroidism in pregnant women is diagnosed biochemically through the characteristic pattern of suppressed TSH and elevated thyroid hormones. All test results should be interpreted with consideration of the specific population being tested. For a definitive diagnosis of GD, the presence of TSAbs must be confirmed. Determining the TSAb titer is essential because it not only establishes the cause of hyperthyroidism but also helps assess the risk of fetal hyperthyroidism, as these antibodies can cross the placental barrier. Fetal hyperthyroidism due to maternal TSAbs typically develops after the 20th week of pregnancy. Women with positive TSAbs early in pregnancy should have follow-up testing between 18-22 weeks of gestation to evaluate the risk of fetal hyperthyroidism and again between 30-34 weeks to assess the risk of neonatal hyperthyroidism.

Subclinical hyperthyroidism does not require immediate initiation of antithyroid medications. However, many women with GD may eventually develop overt hyperthyroidism and need appropriate treatment. Propylthiouracil (PTU) is the preferred medication during the first trimester of pregnancy (30, 34). After fetal organogenesis is complete at around 16 weeks of gestation, PTU can be switched to thiamazole. The treatment goal should be to use the lowest effective dose of antithyroid medications, targeting TT4/fT4 levels at the upper limit of the normal range for pregnant women. Initially, thyroid function in pregnant women with hyperthyroidism should be monitored every 2-4 weeks. Once target hormone levels are achieved, monitoring can be reduced to every 4-6 weeks. Antithyroid treatment can often be discontinued entirely in about 20-30% of patients by the third trimester or when they enter remission (36).

Postpartum Thyroiditis

Postpartum thyroiditis (PPT) is defined by temporary disruptions in thyroid function that begin within the first year following childbirth, miscarriage, or an induced abortion. This condition often develops in women who already have an autoimmune thyroid disorder. PPT is observed in up to 33-50% of women who test positive for anti-thyroid peroxidase antibodies (ATPO) (37). PPT can occur in women who were euthyroid before pregnancy and had never been treated with levothyroxine (LT4), as well as in those with hypothyroidism who were receiving LT4 for subclinical or overt hypothyroidism. However, PPT is ten times more likely in women who were euthyroid before conception (36). Furthermore, euthyroid women at the start of their pregnancy, regardless of LT4 supplementation status, have a fourfold increased risk of developing PPT compared to women whose TSH levels were above the normal range (37).

PPT is primarily an inflammatory condition that causes the thyroid gland to release excessive hormones due to cell damage. The progression of PPT is typically triphasic, beginning with a hyperthyroid phase, followed by a hypothyroid phase, and eventually leading to a return to normal thyroid function (euthyroidism). In some cases, the thyroid dysfunction may present in just two phases: an initial hyperthyroid or hypothyroid phase followed by euthyroidism. The hyperthyroid phase usually appears between 2 and 6 months after childbirth. It may be completely asymptomatic or present with mild symptoms such as fatigue, irritability, heart palpitations, and weight loss. The hypothyroid phase generally develops between 3 and 13 months postpartum and is often more noticeable, with symptoms including dry skin, cold intolerance, and difficulty concentrating. PPT progresses to permanent hypothyroidism in about 10-20% of cases (37).

It's essential to distinguish the hyperthyroid phase of PPT from a recurrence of hyperthyroidism due to Graves' disease (GD). Unlike GD-related hyperthyroidism, the hyperthyroid phase of PPT does not require treatment with antithyroid medications; beta-blockers can effectively manage the symptoms. TSH levels should be monitored every 6-8 weeks to detect the onset of the hypothyroid phase. If symptoms of hypothyroidism develop, LT4 supplementation may be necessary, with thyroid function being reassessed every 4-8 weeks until it stabilizes. The need for continued LT4 treatment should be reconsidered after 12 weeks of therapy.

Primary adrenal insufficiency

Autoimmune primary adrenal insufficiency, commonly referred to as Addison's disease (AD), predominantly affects women of childbearing age. The occurrence of AD among pregnant women appears to be increasing. A cohort study examining 7.7 million births in the United States reported an initial incidence rate of AD in pregnant women of about 5.5 per 100,000, which rose to 9.6 per 100,000 over the following nine years (38). While adequately managed AD does not typically impair fertility, it is frequently associated with other autoimmune conditions, such as type 1 diabetes or autoimmune thyroiditis, which can negatively impact maternal health, fertility, and pregnancy outcomes (39). AD presents significant risks for the mother, including the potential for a life-threatening adrenal crisis. Additionally, a review of perinatal complications in women with AD compared to healthy women indicated a higher frequency of premature delivery, cesarean sections, delayed wound healing, infections, thromboembolic events, blood transfusions, and extended hospital stays (37).

AD generally progresses slowly over several years, with a gradual onset. The presence of anti-21-hydroxylase antibodies in a patient’s blood can serve as an early indicator of developing AD, detectable even before clinical symptoms manifest. The autoimmune aspect of AD is linked to autoreactive CD8+ T cells targeting peptides of the 21-hydroxylase enzyme (40).

It is uncommon for AD to first present during pregnancy; the condition is typically diagnosed earlier, allowing for proper management that supports conception. Diagnosing AD during pregnancy is challenging due to the overlap of its symptoms with those of a normal pregnancy. Common symptoms include nausea, vomiting, fainting (due to low blood pressure), and hyperpigmentation of the nipples, areolas, and skin. Signs particularly indicative of low

glucocorticoid levels include insufficient weight gain relative to pregnancy, abdominal pain, orthostatic hypotension, rapid heart rate, low sodium levels, low blood sugar, increased lymphocytes, and elevated eosinophils. Pregnancy naturally leads to increased circulating cortisol and adrenocorticotropic hormone (ACTH), complicating standard endocrine diagnostics. A morning cortisol level below 3 mg/dl confirms AD, while a level above 19 mg/dl rules it out. In uncertain cases, a synthetic ACTH stimulation test, commonly used in the general population, may be conducted as a follow-up (41).

Management of AD requires immediate and continuous supplementation with glucocorticoids and mineralocorticoids. Hydrocortisone is the preferred glucocorticoid because it does not cross the placenta and does not suppress the fetal adrenal glands. During the first and second trimesters, hydrocortisone replacement can typically be maintained at the usual dose (15-30 mg daily, divided into two or three doses). After the 24th week of pregnancy, doses are often adjusted and increased by 20-40% to account for the natural rise in cortisol seen in healthy pregnancies (42). Fludrocortisone, a synthetic mineralocorticoid, can be administered in the same manner as in the general population, at 0.05-0.2 mg daily, with careful monitoring of blood pressure and serum electrolytes. Both vaginal delivery and cesarean section in patients with AD require increased glucocorticoid supplementation. A dose of 100 mg of intravenous hydrocortisone should be given promptly during labor, and if a cesarean section is performed, an additional 100 mg should be administered intravenously every 6 hours. The increased need for hydrocortisone generally persists for up to two days postpartum, after which doses can be gradually reduced to the standard maintenance level (43, 44).

Type 1 Diabetes and Pregnancy

The global prevalence of diabetes mellitus, including all its forms, is on the rise. Diabetes is a frequent metabolic disorder that complicates pregnancies. Historically, pregnancies complicated by type 1 diabetes were associated with particularly poor outcomes. While there have been significant improvements over the last 20 years, there is still much progress to be made. The number of pregnant women with pre-existing diabetes is increasing, primarily due to a rise in type 2 diabetes cases, but type 1 diabetes cases are also increasing. Generally, type 1 diabetes represents about 5% to 10% of all diabetes cases outside of pregnancy, and when combined with type 2 diabetes, it accounts for around 10% of diabetic pregnancies (45). Managing diabetes in pregnancy is a complex process that ideally starts before conception. Different stages of pregnancy require specific attention when managing diabetic pregnancies. Diabetes, especially type 1, presents unique challenges during pregnancy. However, with proper education, vigilant monitoring, and advanced therapeutic approaches, women with diabetes can achieve healthy pregnancies. Ensuring a successful pregnancy for women with diabetes involves careful attention to diet, blood sugar control, managing metabolic stresses, and early detection and monitoring of potential complications (46).

Conclusion

In conclusion, the intricate interplay between pregnancy and autoimmune endocrine disorders underscores the necessity for vigilant management and tailored care throughout gestation. The physiological changes accompanying pregnancy—marked by significant hormonal shifts and immune adaptations—can markedly influence the course and outcomes of autoimmune endocrine conditions such as thyroid disorders, adrenal insufficiency, and type 1 diabetes. Understanding these dynamic interactions is crucial for optimizing maternal and fetal health. Early diagnosis, close monitoring, and appropriate therapeutic interventions can mitigate risks and improve outcomes for both mother and child. As our knowledge of these interactions evolves, continued research and individualized care strategies will be essential to address the complex needs of pregnant women with autoimmune endocrine disorders, ensuring better health outcomes and quality of life

References

1. Hussain T, Murtaza G, Kalhoro DH, Kalhoro MS, Yin Y, Chughtai MI, et al. Understanding the immune system in fetal protection and maternal infections during pregnancy. *J Immunol Res*. 2022; 2022:7567708. doi: 10.1155/2022/7567708.
2. Lazarus JH. Thyroid function in pregnancy. *Br Med Bull*. 2011; 97:137–48. doi: 10.1093/BMB/LDQ039.
3. Stern C, Schwarz S, Moser G, Cvitic S, Jantscher-Krenn E, Gauster M, et al. Placental endocrine activity: adaptation and disruption of maternal glucose metabolism in pregnancy and the influence of fetal sex. *Int J Mol Sci*. 2021; 22(23):12722. doi: 10.3390/ijms222312722.
4. Lichiardopol C, Mota M. The thyroid and autoimmunity. *Romanian J Intern Med*. 2009; 47:207–15. doi: 10.1177/003693306000501207.
5. Stern C, Schwarz S, Moser G, Cvitic S, Jantscher-Krenn E, Gauster M, et al. Placental endocrine activity: adaptation and disruption of maternal glucose metabolism in pregnancy and the influence of fetal sex. *Int J Mol Sci*. 2021; 22(23):12722. doi: 10.3390/ijms222312722.
6. Piccinni MP, Lombardelli L, Logiodice F, Kullolli O, Parronchi P, Romagnani S. How pregnancy can affect autoimmune diseases progression? *Clin Mol Allergy*. 2016; 14:11. doi: 10.1186/S12948-016-0048-X.
7. Bomba-Opon D, Czajkowski K, Karowicz-Bilinska A, Kotarski J, Nowak-Markwitz E, Oszukowski P, et al. Recommendations of the Polish Gynecological Society concerning application of progesterone in obstetrics and gynecology. *Ginekol Pol*. 2015; 86:234–8. doi: 10.17772/GP/2068.
8. Kumar P, Magon N. Hormones in pregnancy. *Niger Med J*. 2012; 53(4):179–83. doi: 10.4103/0300-1652.107549.
9. Hellberg S, Raffetseder J, Rundquist O, Magnusson R, Papapavlou G, Jenmalm MC, et al. Progesterone dampens immune responses in in vitro activated CD4+ T cells and affects genes associated with autoimmune diseases that improve during pregnancy. *Front Immunol*. 2021;12:672168. doi: 10.3389/FIMMU.2021.672168.
10. Rafiee M, Rezaei A, Alipour R, Sereshki N, Motamedi N, Naseri M. Progesterone-induced blocking factor (PIBF) influences the expression of membrane progesterone receptors (mPRs) on peripheral CD4+ T lymphocyte cells in normal fertile females. *Hormones (Athens)*. 2021;20(3):507-514. doi: 10.1007/s42000-021-00291-5.
11. Kokubo K, Onodera A, Kiuchi M, Tsuji K, Hirahara K, Nakayama T. Conventional and pathogenic Th2 cells in inflammation, tissue repair, and fibrosis. *Front Immunol*. 2022;13:945063. doi: 10.3389/fimmu.2022.945063.
12. Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal immunological adaptation during normal pregnancy. *Front Immunol*. 2020;11:575197. doi: 10.3389/fimmu.2020.575197.
13. Luppi P. How immune mechanisms are affected by pregnancy. *Vaccine*. 2003;21:3352–7. doi: 10.1016/S0264-410X(03)00331-1.
14. PA M, JM G, IR M. Sexual dimorphism in autoimmune disease. *Curr Mol Med*. 2009;9:1058–79. doi: 10.2174/156652409789839116.
15. Mammen JSR, Cappola AR. Autoimmune thyroid disease in women. *JAMA*. 2021;325(23):2392–3. doi: 10.1001/jama.2020.22196.
16. Li M, He Y, Mao Y, Yang L, Chen L, Du J, et al. Preconception thyroid-stimulating hormone levels and adverse pregnancy outcomes. *Clin Endocrinol (Oxf)*. 2021. doi: 10.1111/cen.14668.
17. Vella K, Vella S, Savona-Ventura C, Vassallo J. Thyroid dysfunction in pregnancy - a retrospective observational analysis of a Maltese cohort. *BMC Pregnancy Childbirth*. 2022;22(1):941. doi: 10.1186/s12884-022-05266-x.
18. Rydzewska M, Jaromin M, Pasierowska IE, Stożek K, Bossowski A. Role of the T and B lymphocytes in pathogenesis of autoimmune thyroid diseases. *Thyroid Res*. 2018;11:2. doi: 10.1186/s13044-018-0046-9.

19. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. *Front Immunol*. 2017;8:521. doi: 10.3389/fimmu.2017.00521.
20. McNeil AR, Stanford PE. Reporting thyroid function tests in pregnancy. *Clin Biochem Rev*. 2015;36(4):109–26.
21. Balucan FS, Morshed SA, Davies TF. Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance. *J Thyroid Res*. 2013;2013:182472. doi: 10.1155/2013/182472.
22. Di Girolamo R, Liberati M, Silvi C, D'Antonio F. Levothyroxine supplementation in euthyroid pregnant women with positive autoantibodies: A systematic review and meta-analysis. *Front Endocrinol*. 2022;13:759064. doi: 10.3389/fendo.2022.759064.
23. Lee SY, Pearce EN. Assessment and treatment of thyroid disorders in pregnancy and the postpartum period. *Nat Rev Endocrinol*. 2022;18(3):158–71. doi: 10.1038/s41574-021-00604-z.
24. Moleti M, di Mauro M, Alibrandi A, Vita R, Benvenga S, Vermiglio F. Postpartum thyroiditis in women with euthyroid and hypothyroid Hashimoto's thyroiditis antedating pregnancy. *J Clin Endocrinol Metab*. 2020;105–8. doi: 10.1210/clinem/dgaa197.
25. Deshauer S, Wyne A. Subclinical hypothyroidism in pregnancy. *CMAJ*. 2017;189(28)doi: 10.1503/cmaj.161388.
26. Nazarpour S, Ramezani Tehrani F, Simbar M, Azizi F. Thyroid dysfunction and pregnancy outcomes. *Iran J Reprod Med*. 2015;13(7):387–96.
27. Lee SY, Pearce EN. Testing, monitoring, and treatment of thyroid dysfunction in pregnancy. *J Clin Endocrinol Metab*. 2021;106:883–92. doi: 10.1210/clinem/dgaa945.
28. de Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:2543–65. doi: 10.1210/jc.2011-2803.
29. Jansen HI, Boelen A, Heijboer AC, Bruinstroop E, Fliers E. Hypothyroidism: the difficulty in attributing symptoms to their underlying cause. *Front Endocrinol*. 2023;14:1130661. doi: 10.3389/fendo.2023.1130661.
30. Solha STG, Mattar R, Teixeira PFDS, Chiamolera MI, Maganha CA, Zaconeta ACM, Souza RT. Screening, diagnosis, and management of hypothyroidism in pregnancy. *Rev Bras Ginecol Obstet*. 2022;44(10):999–1010. doi: 10.1055/s-0042-1758490.
31. Nguyen CT, Sasso EB, Barton L, Mestman JH. Graves' hyperthyroidism in pregnancy: a clinical review. *Clin Diabetes Endocrinol*. 2018;4:4. doi: 10.1186/s40842-018-0054-7.
32. Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A, Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. *J Prenat Med*. 2012;6(4):64–71.
33. Moleti M, Di Mauro M, Sturniolo G, Russo M, Vermiglio F. Hyperthyroidism in the pregnant woman: Maternal and fetal aspects. *J Clin Transl Endocrinol*. 2019;16:100190. doi: 10.1016/j.jcte.2019.100190.
34. Jin M, Jang A, Kim CA, Kim TY, Kim WB, Shong YK, et al. Long-term follow-up result of antithyroid drug treatment of Graves' hyperthyroidism in a large cohort. *Eur Thyroid J*. 2023;12(2) doi: 10.1530/ETJ-22-0226.
35. Yap YW, Onyekwelu E, Alam U. Thyroid disease in pregnancy. *Clin Med (Lond)*. 2023;23(2):125–8. doi: 10.7861/clinmed.2023-0018.
36. Chung JH. Antithyroid drug treatment in Graves' disease. *Endocrinol Metab (Seoul)*. 2021;36(3):491–9. doi: 10.3803/EnM.2021.1070.
37. Fariduddin MM, Singh G. Thyroiditis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2023 Aug 8]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555975/.
38. Munir S, Quintanilla Rodriguez BS, Waseem M. Addison disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2024 Jan 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441994/.

39. Oliveira D, Lages A, Paiva S, Carrilho F. Treatment of Addison's disease during pregnancy. *Endocrinol Diabetes Metab Case Rep*. 2018;2018:17-0179. doi: 10.1530/EDM-17-0179.
40. Hellesen A, Aslaksen S, Breivik L, Røyrvik EC, Bruserud Ø, Edvardsen K, et al. 21-Hydroxylase-specific CD8+ T cells in autoimmune Addison's disease are restricted by HLA-A2 and HLA-C7 molecules. *Front Immunol*. 2021;12:742848. doi: 10.3389/fimmu.2021.742848.
41. Birtolo MF, Antonini S, Saladino A, Zampetti B, Lavezzi E, Chiodini I, et al. ACTH stimulation test for the diagnosis of secondary adrenal insufficiency: Light and shadow. *Biomedicines*. 2023;11(3):904. doi: 10.3390/biomedicines11030904.
42. Bothou C, Anand G, Li D, Kienitz T, Seejore K, Simeoli C, et al. Current management and outcome of pregnancies in women with adrenal insufficiency: Experience from a multicenter survey. *J Clin Endocrinol Metab*. 2020;105(8) e2863. doi: 10.1210/clinem/dgaa266.
43. National Guideline Alliance (UK). Evidence review for long-term systemic steroids: Intrapartum care for women with existing medical conditions or obstetric complications and their babies: Evidence review E. London: National Institute for Health and Care Excellence (NICE); 2019 Mar. (NICE Guideline, No. 121.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK576742/.
44. Pestana I, Guimarães H, Saraiva A, Veiga D, Machado H. Adrenal crisis during cesarean section in a patient with primary adrenal insufficiency. *Cureus*. 2023;15(12) doi: 10.7759/cureus.49964.
45. Bapayeva G, Terzic S, Dotlic J, Togyzbayeva K, Bugibaeva U, Mustafinova M, et al. Pregnancy outcomes in women with diabetes mellitus - the impact of diabetes type and treatment. *Przegl Menopauzalny*. 2022;21(1):37–46. doi: 10.5114/pm.2022.113781.
46. Alexopoulos AS, Blair R, Peters AL. Management of preexisting diabetes in pregnancy: A review. *JAMA*. 2019;321(18):1811–9. doi: 10.1001/jama.2019.4981.