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Mini review article

THE MOST COMMON ENDOCRINE DISORDERS IN PREGNANCY

NAJČEŠĆI ENDOKRINI POREMEĆAJI U TRUDNOĆI

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Abstract

Pregnancy is a state of altered physiological mechanisms, affecting almost all systems of organs. Endocrine disorders that occur during pregnancy can significantly impact maternal and fetal health, necessitating a comprehensive understanding of their etiology, diagnosis, and management. If unrecognized or untreated, all these conditions can lead to poor pregnancy and maternal outcomes.

The most common endocrine disorders during pregnancy are gestational diabetes and thyroid gland dysfunctions. Diabetes during pregnancy carries a higher risk of complications, such as preeclampsia, preterm birth, macrosomia, and cesarean delivery. However, with careful management, numerous women with diabetes can have healthy pregnancies and deliver healthy babies. Hypothyroidism during pregnancy refers to an underactive thyroid gland function, where the thyroid gland doesn't produce enough thyroid hormones. This condition can have significant implications for the mother and the developing fetus. Unrecognized and untreated hypothyroidism may lead to severe complications, including intellectual and developmental issues in the child, preeclampsia, anemia, miscarriage, or preterm birth.

Endocrinological disorders during pregnancy represent a complex and critical area of concern for both maternal health and fetal development. Furthermore, they can have far-reaching implications that extend beyond the duration of pregnancy, having lifelong implications for the future mother and the offspring. Effective management of endocrinological disorders in pregnancy requires a multidisciplinary team approach involving obstetricians, endocrinologists, nutritionists, and other healthcare professionals. Timely interventions, personalized treatment plans, and close monitoring are at the core of optimal obstetric care for these patients. Lifestyle modifications, medication adjustments, and regular prenatal care play crucial roles in optimizing maternal health and birth outcomes.

Keywords:
pregnancy,
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Sažetak

Trudnoća je stanje intenzivnih fizioloških promena koje utiču na gotovo sve organe i sisteme. Endokrini poremećaji u trudnoći mogu značajno uticati na zdravlje majke i fetusa, što zahteva sveobuhvatno razumevanje njihove etiologije, dijagnostike i lečenja. Ukoliko se ne prepoznaju ili ne leče, ova stanja mogu dovesti do lošeg ishoda trudnoće.

Najčešći endokrini poremećaji u trudnoći su gestacijski dijabetes melitus i poremećaj funkcije štitaste žlezde. Gestacijski dijabetes je povezan sa povećanim rizikom od komplikacija, kao što su preeklampsija, prevremeni porođaj, makrozomija i porođaj carskim rezom. Međutim, uz pažljiv nadzor, trudnice sa dijabetesom mogu imati urednu trudnoću i roditi zdravo dete. Hipotireoza tokom trudnoće predstavlja smanjenje funkcije, zbog čega štitasta žlezda ne proizvodi dovoljno hormona. Ovo stanje značajno može da utiče na zdravlje majke i razvoj ploda. Neprepoznati i nelečeni hipotireoidizam može dovesti do ozbiljnih komplikacija, uključujući intelektualne i razvojne probleme deteta, preeklampsiju, anemiju, spontani pobačaj ili prevremeni porođaj. Pored ova dva najčešća endokrina poremećaja, na zdravlje majke i fetusa značajno mogu da utiču i drugi poremećaji endokrinih žlezda, kao što su disfunkcija paratireoidne, nadbubrežne žlezde i hipofize.

Endokrinološki poremećaji u trudnoći su veoma kompleksna i specifična stanja zbog uticaja na zdravlje majke i razvoj ploda. Štaviše, oni mogu imati dalekosežne implikacije na kvalitet života majke i njenog potomstva nakon završetka trudnoće. Efikasno lečenje endokrinih poremećaja u trudnoći zahteva multidisciplinarni timski pristup koji uključuje perinatologe, endokrinologe, nutricioniste i druge zdravstvene radnike. Pravovremene intervencije, personalizovana terapija i pažljivo praćenje suština su optimalnog tretmana ovih pacijenata. Promena načina života, adekvatna terapija i redovne prenatalne kontrole igraju ključnu ulogu u očuvanju zdravlja buduće majke i poboljšanju ishoda trudnoće.

Ključne reči:
trudnoća,
endokrini poremećaji,
dijabetes,
hipotireoidizam,
hipertireoidizam

Introduction

Pregnancy is a state of altered physiological mechanisms, affecting almost all systems and organs. In the setting of turbulent endocrine changes and adaptations during pregnancy, the maternal-fetal unit and the placenta appear to have the function of a temporary endocrine gland (1). Effects of pregnancy on specific hormones presented in **table 1**.

During the first trimester of pregnancy, the endocrine function of the fetus is completely dependent on maternal endocrine functions, as most glands begin hormone production during the second trimester. The development of fetal glands continues until delivery, so as pregnancy progresses, a fetus becomes less reliant on the hormone production of the mother (2-4). Most endocrine disorders during pregnancy may lead to serious maternal and fetal complications. Endocrinopathies can be chronic, diagnosed preconceptionally, or gestational, diagnosed during pregnancy. The most common endocrinological disorder diagnosed during pregnancy is diabetes mellitus. Raising incidences of functional abnormalities of the thyroid and parathyroid glands, as well as adrenal and pituitary disorders, have unfortunately become another significant concern for pregnant women and their healthcare providers. Treatment options for most of the endocrine disorders during pregnancy are usually effective and safe for both the mother and the fetus. Untreated endocrinological conditions during pregnancy are associated with major risk factors affecting maternal and fetal well-being and the offspring. Pharmacotherapeutic management of these conditions is often required, and therefore, clinicians need to be familiar with treatment options to prevent and avoid complications during pregnancy and the postpartum period. Furthermore, patients should always be informed about the potential risks associated with pharmacological treatment. From the third until the end of the tenth gestational week, during cellular differentiation and organogenesis, drugs may potentially display teratogenic effects and cause congenital anomalies. In the second and third trimesters of pregnancy, drugs may cause fetal toxicity, affecting primarily functions of the central nervous system (1, 5, 6).

Timely and accurate diagnosis of endocrinopathies during pregnancy can often be challenging, due to the significant overlap of symptoms usually accompanying pregnancy and those implying a specific endocrine disorder (7). For instance, hyperemesis gravidarum (HG) commonly occurs during pregnancy, and it can mimic various other conditions during pregnancy, especially endocrinology-related disorders. It may be related to increased production of the human chorionic gonadotropin (hCG), since the severity of hyperemesis depends on the level of hCG, and it is usually manifested by vomiting, nausea, irritability, weakness, drowsiness or even depression (8).

In this comprehensive review, some of the most common endocrinological diseases that can complicate pregnancy will be included. Each endocrinological disorder brings its own set of considerations and potential consequences for pregnant women. Their effects on maternal health and fetal development will be explored, together with the intersection with the pregnant state.

Table 1. Effects of normal pregnancy on specific hormones

Hormone(s)	Pregnancy levels	Etiology of pregnancy-related levels
LH and FSH	Undetectable during pregnancy	Suppressed by a high level of estrogen and progesterone
GH	Total GH increased	Placental production
Prolactin	Progressive increase	Oestrogen stimulates pituitary prolactin realise
Insulin	Gradually increased during pregnancy (up to 3 times), reached maximum values during the last trimester	Insulin sensitivity decreases by 50% – 60% (estrogen, cortisol, and human placental lactogen can block insulin)
Glucagon	Increased between the 16th and the 28th week of gestation	Due to insulin resistance
TSH	Suppressed particularly in the first trimester	Structural similarity of TSH and HCG causes HCG-mediated TSH receptor stimulation
T4	Increased production	HCG-mediated stimulation
f-T4 f-T3	Upper end of the normal range, reduced later in the pregnancy	Hemodilution
Total T4 and T3	Higher levels	Increase in thyroid binding globulinw
PTH	Upper end of the normal range, reduced later in the pregnancy	
CRH	Increases up to 1000 times compared to pre-pregnancy values	Placental production
ACTH	Levels increase progressively throughout pregnancy	Placental production
Cortisol	Elevated total plasma cortisol, nearly threefold normal levels	Increased binding globulins
free Cortisol	Doubles from the first to the third trimester of pregnancy	Increase in CRH secretion, which in turn stimulates the production of ACTH in the placenta and the pituitary

LH - luteinizing hormone, FSH - follicle-stimulating hormone, GH - growth hormone, TSH - thyroid stimulating hormone, T4 - thyroxin, T3 - triiodothyronine, fT4 - free thyroxin, fT3 - free triiodothyronine, PTH - parathyroid hormone, CRH - corticotropin-releasing hormone, ACTH - adrenocorticotrophic hormone. Modified table of Frise CJ, et al (1)

Diabetes mellitus and pregnancy

Pregnant women are affected by two main types of diabetes: pre-existing diabetes (type 1 and type 2) and gestational diabetes mellitus (GDM) (9). In type 1 diabetes, pancreatic β-cells involved in insulin production are destroyed by immune system cells, and patients with this type of diabetes require permanent insulin substitution. Type 2 diabetes is a metabolic condition characterized by insulin resistance, and most commonly it can be managed through lifestyle interventions or oral antidiabetic drug use (10). Women with pre-existing diabetes planning for pregnancy should be closely monitored, and their blood glucose levels should be carefully controlled in order to avoid, or at least reduce, potential complications associated with poorly controlled diabetes (11). Even though significant efforts and improvements in surveillance and control of maternal hyperglycemia have been made in the last few decades, diabetes remains the leading cause of maternal, fetal, and neonatal morbidity. Pregnancies carrying the burden of diabetes still have several-fold higher incidence rates of congenital malformations, and poorly controlled diabetes carries an increased risk for fetal macrosomia, stillbirth, miscarriage, preeclampsia, and cesarean delivery (12).

Gestational diabetes mellitus typically occurs in the second and third trimesters of the pregnancy. It refers to impaired glucose tolerance at the onset or first recognition during pregnancy, which usually disappears after delivery. Gestational diabetes occurs when the maternal body cannot produce adequate levels of insulin intended to meet increasing metabolic needs during pregnancy. Furthermore, it carries a risk of future cardiometabolic disorders for both the mother and the offspring (13, 14).

It affects approximately 15% of pregnancies worldwide, accounting for approximately 18 million births annually (15). It is expected that the prevalence of diabetes will continue to rise in the foreseeable future, mainly due to the widespread adoption of high-carbohydrate diets and the global epidemic of obesity (16). Obesity prevalence has become a rising concern worldwide. Concomitant increases in obesity and diabetes prevalence undoubtedly link significant interferences shared between the accumulation of excessive body fat and impaired glucose tolerance (17). Preconceptional obesity, as well as excessive gestational weight gain, are recognized as risk factors for gestational diabetes, along with advanced maternal age, family history of diabetes, certain ethnic and racial backgrounds, previous history of gestational diabetes, or giving birth to a macrosomic fetus (18). Diagnosis is usually made between the 24th and 28th gestational week, up to the 32nd gestational week due to increasing levels of the placental hormones which play an important role in increased insulin resistance. If diabetes is diagnosed before the 20th week of pregnancy, it is considered pregestational diabetes first diagnosed during pregnancy. Gestational diabetes mellitus

(GDM) can be diagnosed through an oral glucose tolerance test (oGTT) with 75 g of glucose between 24 and 28 weeks of gestation. Alternatively, GDM can also be diagnosed by a random venous blood sample with high plasma glucose values (between 8.5 and 11.0 mmol/l) or fasting plasma glucose (FPG) values (between 5.1 and 6.9 mmol/l). The threshold values for oral glucose load test with 75 g for the diagnosis of GDM are fasting plasma glucose 5.1 mmo/l, 1h plasma glucose (after load) 10.0 mmo/l, and 2h plasma glucose 8.5 mmol/l. If the fasting plasma glucose level is 7.0 mmol/L or higher, or if the random plasma glucose level is 11.0 mmol/L or higher, the diagnosis of overt diabetes is made (**table 2**) (19).

Table 2. Threshold Values for the Diagnosis of Diabetes Mellitus in Pregnancy

Glucose Measure	Glucose Concentration Threshold
GDM	OGTT - 75 g
FPG	5.1 - 6.9 mmol/L (92 - 125 mg/dL)
1-h plasma glucose	10.0 mmol/L (180 mg/dL)
2-h plasma glucose	8.5 - 11.0 mmol/L (153 - 199 mg/dL)
OVERT DIABETES	
FPG	7.0 mmol/L (126 mg/dL)
2-h plasma glucose following 75 g OGTT	≥ 11.1 mmol/l (200 mg/dl)
Random plasma glucose	≥ 11.1 mmol/L (200 mg/dL)

FPG - fasting plasma glucose; GDM - gestational diabetes mellitus; OGTT - oral glucose tolerance test.
From: Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy, 2013 (19)

Prenatal care and preconceptional counseling are crucial for women with glycemic control deterioration. Effective management is the key link in the control chain leading to the health of both the mother and the newborn. Therefore, close monitoring of glucose blood levels, maintaining a healthy diet, engaging in physical activities when it is not contraindicated, or applying pharmacological treatment when it is indicated, leads future mothers and their offspring to healthy and carefree perspectives (20). The treatment of pregnant women with pre-gestational and gestational diabetes mellitus is essential for maintaining metabolic control, which means keeping the glycemic values within the range of reference values. This helps to prevent diabetes-related complications such as fetal macrosomia, injury to the birth canal of the mother, fetal birth injuries, shoulder dystocia, and metabolic instability of the newborn. Additionally, the treatment aims to decrease the risk of metabolic syndrome in the mother after childbirth, as well as in the child at an early age.

Monitoring glycemic levels through repeated blood glucose measurements after meals is essential to determine the effectiveness of therapy and the need for oral medications or insulin. The recommended glycemic values with therapy are fasting glycemia of 5.3 mmol/l (3.3 - 5.9 mmol/l), 1-hour postprandial 7.8 mmol/l, and 2-hour postprandial 6.7 mmol/l (21). In patients with well-managed blood glucose levels on a diabetic diet, it is recommended to monitor pregnancy every 2 to 4 weeks and conduct regular glucose self-testing.

If blood glucose levels are not within the target range despite following the diet, pharmacological treatments are introduced. Biguanide preparations, such as metformin, according to recent studies, are highly effective in good glycemic control, have a lower percentage of neonatal hypoglycemia compared to the group of patients on insulin therapy, and with no difference in the occurrence of congenital fetal anomalies. The administration of metformin during pregnancy may confer several advantages, including a reduction in maternal weight gain and insulin requirements, a lower incidence of operative delivery, and a potential reduction in hypertensive disorders. Furthermore, neonates born to mothers who received metformin therapy may experience a decrease in the incidence of extreme weight gain, macrosomia, severe hypoglycemia, and the need for neonatal unit care (22). This must be balanced against the potential risk of SGA, its impact on long-term health, infant obesity, and cardiometabolic consequences (23). If blood glucose levels are very high, or remain high despite metformin, insulin therapy is required. In collaboration with the endocrinologist, the type and dosage of insulin are determined until satisfactory glucose regulation is achieved. Close pregnancy monitoring and strict blood glucose control on insulin therapy patients are necessary due to the risk of fetal hypoglycemia and a large risk for gestational age fetus.

Delivery planning is an integral part of optimal care for pregnant women dealing with diabetes. Considering the type of diabetes and overall health, women dealing with diabetes, especially those with pre-existing diabetes, have a higher probability of labor induction or cesarean delivery. Timing and delivery mode should be carefully made, especially since diabetic mothers face a higher risk of fetal macrosomia and shoulder dystocia (24, 25). Gestational diabetes can complicate pregnancies and delay the production of alveolar surfactant, resulting in a higher risk of respiratory distress syndrome in infants born before 39 weeks of gestation. Therefore, if glycemic control is adequate, and with no other perinatal complications, delivery should be planned after 39+0 weeks of gestation. The mode of delivery depends on obstetric indications.

Diabetes management continues after childbirth. Blood sugar levels should be closely monitored, especially if insulin is used during pregnancy. Breastfeeding can also impact blood sugar levels and might require adjustments to diabetes management (26). Finally, managing diabetes during pregnancy can be emotionally challenging. Patients need to seek support from healthcare providers, family, and friends. Connecting with support groups can provide a sense of understanding and shared experiences. Every high-risk pregnancy is a unique challenge, and it is crucial for high-risk patients to work closely with healthcare providers to develop a personalized plan that ensures the well-being of both the mother and the baby (27).

Diabetes is a lifelong metabolic condition associated with hyperglycemia, leading to complications affecting various organs and systems, often associated with other endocrine dysfunctions (28).

Thyroid gland disorders and pregnancy

Thyroid gland disorders can greatly impact pregnancy and potentially affect both the mother and the developing fetus. Thyroid dysfunction affects about 4% of pregnant women and is the second most common endocrine disorder in females (29). Two common thyroid disorders that can affect pregnancy are hypothyroidism and hyperthyroidism, with hypothyroidism being significantly more prevalent. Adequate thyroid function and balance are essential for fetal development. Maternal thyroid dysfunction is associated with an increased risk of various adverse maternal and child outcomes. Physiological changes in thyroid function during pregnancy provide sufficient thyroid hormone to both the mother and fetus. This is particularly important during the first trimester because the fetal thyroid starts to produce considerable amounts of hormones after the 20th week of gestation, until the fetus heavily depends on the maternal supply (30). Pregnant women with pre-existing thyroid disorders should work closely with their healthcare provider to manage their condition throughout pregnancy. This usually involves regular monitoring of thyroid hormone levels and adjusting medication doses, if necessary. Additionally, some women may develop thyroid issues for the first time during pregnancy, which is known as gestational thyroid dysfunction. This condition typically involves mild thyroid hormone imbalances and can resolve after pregnancy (31).

At the beginning of the pregnancy, total thyroxine levels reach the upper reference range limit for non-pregnant women. Human chorionic gonadotropin (hCG) acts as a potent stimulator of thyroid-stimulating hormone (TSH) receptors and interferes with thyroid function and regulation. During the first trimester, hCG stimulates TSH receptors, which increases the function of the thyroid gland while decreasing TSH levels. At the end of the first trimester of pregnancy, after the 12th week of pregnancy, the level of hCG decreases and TSH increases again (32, 33). The value of thyroid hormone during pregnancy is dependent on the week of gestation. To effectively detect and manage thyroid dysfunctions during pregnancy, a trimester-specific thyroid reference range is necessary across different regions and laboratories (34).

Hypothyroidism is a condition where the thyroid gland fails to produce adequate amounts of hormones, regardless of the presence of antibodies, as in the case of Hashimoto's thyroiditis. In patients with adequate iodine consumption, the most frequent cause of hypothyroidism is autoimmune thyroiditis (35). According to the American Thyroid Association (ATA), hypothyroidism is defined as elevated levels of TSH of more than 10 mU/L regardless of serum free-T4 levels (36). Subclinical hypothyroidism is an increased TSH level, above 4 mU/L, with a normal thyroxine level (36). It is essential to maintain adequate levels of thyroid hormones during pregnancy, especially during the first trimester when the fetal central nervous system is developing. Subclinical hypothyroidism should be treated if TSH levels are above 4 mU/L, and if TSH is above 2.5 mU/L with the presence of thyroid antibodies. However, the effects of thyroid autoimmunity and subclinical hypothyroidism in pregnancy are still controversial. Untreated hypothyroidism during pregnancy can lead to severe complications, including intellectual and developmental issues in the child, preeclampsia, anemia, miscarriage, or preterm birth (37, 38).

In most cases, levothyroxine is the medication of choice, and its use is safe and effective during pregnancy. The dosage of levothyroxine is individual and depends on gestational age and whether a pregnant woman has preexisting hypothyroidism and thyroid antibodies (39). During the prenatal period, iodine supplementation is recommended to optimize normal thyroid function. The recommended daily iodine intake is 150 micrograms during preconception, pregnancy, and lactation. However, excessive iodine intake, over 1100 micrograms daily, could lead to thyroid dysfunction (40).

Hyperthyroidism refers to an overactive thyroid gland hormone production. It can increase the risk of miscarriage, preterm birth, retroplacental hematoma, and preeclampsia. If hyperthyroidism is severe and not effectively managed, it may cause fetal tachycardia, cardiomyopathy, cardiac insufficiency, and ultimately fetal hydrops and death (41, 42). In severe cases of hyperthyroidism, there's a risk of a thyroid storm, a life-threatening condition that may cause maternal heart failure, and it requires immediate medical attention (43).

The goal of treatment for hyperthyroidism is to normalize thyroid hormone levels with minimal doses of antithyroid drugs. In lesser amounts, all antithyroid medications cross the placenta, but the possibility of fetal thyroid disorder is small. There are two categories of antithyroid drugs, thiourea derivate propylthiouracil (PTU), which inhibits thyroid peroxidase and blocks type I deiodinase enzyme, and imidazole derivates methimazole (MMI) and carbimazole (CBZ) (44), which are widely used, that may be associated with skin aplasia, choanal atresia, esophageal and dysmorphic physiognomy (45). Malformations of the urinary tract, neck, and ace are associated with PTU in the first trimester of pregnancy (46). Even though there is a small risk of congenital anomalies with therapy using CBZ/MMI, it does not appear that this risk is significantly reduced by switching to other medications such as PTU before or at the beginning of pregnancy. However, the potential risks of untreated hyperthyroidism and changing hyperthyroidism therapy during pregnancy remain unclear due to limitations in available data and study variations (47).

Postpartum thyroiditis occurs in the first year following delivery, and it is caused by inflammation associated with thyroid gland destruction. It is an autoimmune disease, a variant of Hashimoto thyroiditis, characterized

by the presence of antithyroid peroxidase (anti-TPO) antibodies. Its evolution is biphasic, starting with hyperthyroidism, and eventually, it leads to hypothyroidism. Main clinical manifestations of this condition are irritability, fatigue, palpitations, and weight loss despite increased appetite (48).

According to recent research, there is a correlation between thyroid disorders and diabetes mellitus. Thyroid hormones have a direct impact on glucose homeostasis, while thyroid dysfunctions are associated with insulin resistance. Autoimmunity is important for understanding the linkage between diabetes mellitus Type 1 and autoimmune thyroid disease, while the relationship between diabetes type 2 and thyroid disorders is more complex (28, 49).

Endocrine disorders that clinicians should not forget about during pregnancy

It is crucial for clinicians to be aware not only of common endocrinological disorders during pregnancy, but also be vigilant about other endocrine diseases that may complicate pregnancy. Collaborating with other specialists for the benefit of patients is of utmost importance. Disorders in calcium metabolism due to parathyroid gland dysfunction can have a severe impact on both the mother and the fetus. Diagnosis of excessive cortisol production in adrenal disorders such as Cushing's syndrome during pregnancy can be challenging, but it is necessary to identify them early to prevent complications. It is essential to recognize the symptoms that may overlap with normal features of pregnancy, such as fatigue, weight gain, hyperglycemia, edema, and emotional stress (50). Pregnant women who have congenital adrenal hyperplasia (CAH) require a careful adjustment of their glucocorticoid treatment plan during pregnancy, delivery, and postpartum. The presence of CAH during pregnancy significantly increases the risks of maternal and fetal complications, such as chorioamnionitis, hypertension, gestational diabetes, cesarean delivery, and infants born small for gestational age (51). If adrenal insufficiency persists throughout pregnancy, it may lead to acute adrenal crises, which can be life-threatening conditions (52). The physiological demands of pregnancy could trigger these crises. Therefore, it is important to monitor the value of serum electrolytes and cortisol in this condition.

A personalized approach towards monitoring pregnant patients can aid in early detection of potential complications and enable the timely provision of appropriate treatment and therapy.

Conclusion

Endocrinological disorders during pregnancy represent a complex and critical area of concern for both maternal health and fetal development. Furthermore, they can have far-reaching implications that extend beyond the duration of pregnancy, having lifelong implications for the future mother and the offspring. Effective management of endocrinological disorders in pregnancy requires a multidisciplinary team approach, involving obstetricians, endocrinologists, nutritionists, and other healthcare professionals. Timely interventions, personalized treatment plans, and close monitoring are at the core of optimal obstetric care for these patients. Given the significance of early detection and timely treatment of such conditions, it would be advisable to incorporate screening for common endocrinological diseases within the first-trimester antenatal examinations. Lifestyle modifications, medication adjustments, and regular prenatal care play crucial roles in optimizing maternal health and birth outcomes.

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