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INFLUENCE OF MATERNAL THYROID DYSFUNCTION ON PRETERM BIRTH.

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Abstract

A frequent endocrine condition during pregnancy, thyroid dysfunction is becoming more well acknowledged as a risk factor for preterm delivery and poor neonatal outcomes. The physiological and pathological functions of thyroid hormones during pregnancy are examined in this review of the literature, with an emphasis on how they affect placentation, systemic inflammation, and uteroplacental hemodynamics. A higher risk of preterm labor, intrauterine growth restriction, and preeclampsia is linked to both overt and subclinical types of hypothyroidism and hyperthyroidism. Additionally, even in euthyroid women, thyroid autoantibodies and autoimmune thyroid disorders might make pregnancy health more difficult. This review emphasizes the significance of early diagnosis and tailored treatment by combining data from current research to clarify the pathways connecting thyroid dysfunction to unfavorable pregnancy outcomes.

Keywords: pregnancy, preterm birth, placentation, hypothyroidism, hyperthyroidism, autoimmune thyroiditis, inflammation, fetal development, neonatal outcomes.

ВЛИЯНИЕ МАТЕРИНСКОЙ ДИСФУНКЦИИ ЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ПРЕЖДЕВРЕМЕННЫЕ РОДЫ

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Аннотация

Функциональные нарушения щитовидной железы являются частой эндокринной патологией, встречающейся у беременных женщин. Всё больше данных указывает на их роль в развитии преждевременных родов и неблагоприятных перинатальных исходов. В данном обзоре анализируются как физиологические, так и патологические эффекты гормонов щитовидной железы в период беременности. Особое внимание уделяется их влиянию на процессы формирования плаценты, регуляцию воспалительных реакций и кровоснабжение матки и плаценты. Оба клинически выраженные и субклинические варианты гипотиреоза и гипертиреоза ассоциированы с повышенным риском таких осложнений, как преэклампсия, задержка внутриутробного роста плода и преждевременные роды.

Дополнительно рассматривается влияние аутоиммунных заболеваний щитовидной железы и наличие антител к тиреоидным антигенам, которые могут оказывать негативное воздействие на течение беременности даже при нормальной функции железы. Обзор объединяет данные современных исследований, направленных на понимание механизмов связи между нарушением функции щитовидной железы и акушерскими осложнениями, и подчеркивает важность своевременного выявления и индивидуализированного подхода к лечению.

Ключевые слова: беременность, преждевременные роды, плацентация, гипотиреоз, гипертиреоз, аутоиммунный тиреоидит, воспаление, развитие плода, неонатальные исходы.

ҚАЛҚОНСИМОН БЕЗ ДИСФУНКЦИЯСИНИНГ МУДДАТДАН ОЛДИНГИ ТУҒРУҚҚА ТАЪСИРИ

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Аннотация

Ҳомиладорлик даврида қалқонсимон без фаолиятининг бузилиши кенг тарқалган эндокрин муаммолардан бири ҳисобланади. Сўнгги йилларда бундай ҳолатлар муддатидан олдинги туғруқ ва янги туғилган чақалоқда

кузатиладиган неонатал ҳолатлар билан боғлиқ муаммолар долзарб бўлиб қолмокда.Ушбу адабиётлар таҳлилида қалқонсимон без гормонларининг ҳомиладорликдаги физиологик ва патофизиологик роли ўрганилади. Асосий эътибор гормонларнинг плацента шаклланишига, яллиғланиш жараёнларига ва бачадон-плацента қон айланишига таъсирига қаратилган. Гипотиреоз ва гипертиреознинг яширин (субклиник) шакллари преэклампсия, эрта туғруқ хавфини ошириши мумкин.

Бундан ташқари, қалқонсимон без автоиммун касалликлари ва тиреоид автоантителарнинг мавжудлиги ҳатто гормон даражалари нормал бўлган аёлларда ҳам ҳомиладорликни мураккаблаштириши мумкин. Мавжуд илмий тадқиқотлар натижалари таҳлил қилиниб, қалқонсимон без фаолиятининг бузилиши билан боғлиқ ҳомиладорлик асоратлари механизмини яхшироқ тушуниш имкони яратилади ва бундай ҳолатларни эрта ташхислаш ҳамда шахсий ёндашувнинг аҳамияти таъкидланади.

Калит сўзлар: ҳомиладорлик, муддатидан олдинги туғруқ, плацента, гипотироидизм, гипертироидизм, аутоиммун тироидит, яллиғланиш, ҳомила ривожланиши, неонатал натижалар.

Introduction

Every year, over 14 million babies are born before their due dates, with incidence rates varying by area from 5% to 17%. The prevalence is significantly lower in Europe (5–9%) and greater in the United States (12–13%), but several Asian nations report quite high percentages. Numerous non-genetic risk factors for preterm delivery have been the subject of extensive research from systematic reviews and meta-analyses. These include factors associated with illnesses, exposures to the environment, medications, and past and present pregnancies. Finding modifiable risk factors, like thyroid dysfunction, is essential for identifying high-risk groups early, allocating healthcare resources as efficiently as possible, and improving our knowledge of the molecular mechanisms that lead to premature labor [1]. Worldwide, preterm birth—defined as delivery before 37 full weeks of gestation—continues to be a leading cause of infant morbidity and death. After diabetes, thyroid dysfunction is one of the most common endocrine conditions during pregnancy. Triiodothyronine (T3) and thyroxine (T4) are thyroid hormones that are essential for embryonic growth, neurodevelopment, and metabolic homeostasis. Because the preservation of a precisely controlled hormonal balance is essential to the health of both the mother and the fetus, their synthesis and regulation are especially important during pregnancy. There is growing evidence that thyroid malfunction, including hypothyroidism and hyperthyroidism, is significantly linked to an increased risk of premature delivery. This review integrates the current body of knowledge regarding the ways in which thyroid disorders affect placental development, inflammatory processes, and fetal outcomes, ultimately contributing to an increased risk of preterm delivery.

Physiological Changes of the Thyroid During Pregnancy. Pregnancy induces significant anatomical and physiological changes in thyroid function. The thyroid gland enlarges, and the levels of total T4 and T3 increase, while thyroid -stimulating hormone (TSH) decreases, particularly during the first trimester, due to the thyrotropic effect of human chorionic gonadotropin (hCG) [2]. These changes necessitate trimester-specific reference ranges for the accurate diagnosis of thyroid disorders. Increased estrogen levels result in elevated thyroxine-binding globulin (TBG), which, in turn, affects the concentrations of free thyroid hormones [3]. Understanding these alterations is crucial for distinguishing between genuine pathological states and normal physiological adaptations.

The maternal thyroid gland undergoes various adaptations to meet the heightened metabolic demands of pregnancy and to support fetal development. These adaptations include increased iodine requirements, alterations in thyroid hormone synthesis, and enhanced renal clearance. In regions with iodine deficiency, these physiological changes may contribute to the development of goiter and hypothyroidism. Additionally, the placenta produces type 3 deiodinase enzymes, which degrade T4 and T3, underscoring the necessity for increased thyroid hormone production in the mother.

Pathophysiological Role of Thyroid Hormones in Placentation. Thyroid hormones play a crucial role in orchestrating early placental development. They regulate essential processes such as trophoblast proliferation, migration, differentiation, and invasion—key functions for successful implantation and the remodeling of uterine spiral arteries [4]. The placental expression of thyroid hormone receptors, transporters, and deiodinases reflects the local regulation of thyroid hormone activity throughout pregnancy. Deficiencies in maternal thyroid hormones, particularly free T4, impair cytotrophoblast invasion and reduce placental vascularization. This results in defective spiral artery remodeling, increased vascular resistance, and potential placental hypoperfusion. Research has shown that inadequate placentation linked to thyroid dysfunction is associated with an elevated risk of preeclampsia, intrauterine growth restriction (IUGR), and preterm delivery [5].

In vitro studies have shown that T3 regulates vascular endothelial growth factor (VEGF) and other angiogenic factors, thereby influencing placental vasculature. Additionally, thyroid hormones modulate integrins and matrix metalloproteinases, which play a crucial role in extracellular matrix remodeling—an essential process for successful placental anchoring and nutrient exchange.

Thyroid Hormones and Placental Function. The placenta expresses thyroid hormone receptors and transporters, which facilitate the transfer of hormones from mother to fetus. Thyroid hormones regulate trophoblast proliferation, invasion, and angiogenesis—critical processes for successful placentation [6]. Abnormal maternal levels of TSH and FT4 have been associated with altered placental hemodynamics, including increased resistance indices in the uterine and umbilical arteries, which are indicators of poor placental perfusion [7]. These placental dysfunctions may, in part, contribute to the increased risk of preeclampsia, fetal growth restriction, and preterm birth. Thyroid hormones regulate a wide range of placental functions, including syncytia trophoblast differentiation and endocrine activity. Research has shown that abnormal maternal thyroid levels, particularly low free T4, are linked to impaired cytotrophoblast invasion and defective spiral artery remodeling, which contribute to placental ischemia. These alterations may induce oxidative stress, upregulate antiangiogenic factors, and lead to poor placental perfusion—key features of disorders such as preeclampsia and preterm labor.

Hypothyroidism and Preterm Birth. Hypothyroidism, both overt and subclinical, is more prevalent during pregnancy than hyperthyroidism. Subclinical hypothyroidism is characterized by elevated TSH levels with normal FT4 and is often asymptomatic. Studies have shown that subclinical hypothyroidism is associated with a 1.5- to 2-fold increased risk of preterm delivery [8]. Overt hypothyroidism, defined by elevated TSH and decreased FT4, is even more strongly linked to adverse outcomes, including spontaneous abortion, placental abruption, and preterm birth [8]. The underlying pathophysiological mechanisms include impaired placental development, heightened systemic inflammation, and reduced oxygen and nutrient supply to the fetus. In addition to preterm birth, maternal hypothyroidism has been associated with an increased risk of miscarriage, gestational hypertension, intrauterine growth restriction (IUGR), and neurocognitive delays in offspring. Some studies suggest that even isolated hypothyroxinemia, in which FT4 is low but TSH remains normal, may negatively affect pregnancy outcomes. Levothyroxine therapy is often recommended, particularly when thyroid peroxidase (TPO) antibodies are present, although further research is needed to refine treatment thresholds.

Hyperthyroidism and Preterm Birth. Although less prevalent, hyperthyroidism also contributes significantly to adverse pregnancy outcomes. The most common causes include Graves' disease and gestational transient thyrotoxicosis [9]. Hyperthyroidism increases the risk of preeclampsia, low birth weight, and preterm labor. One study demonstrated a 1.7-fold increased risk of preterm birth among hyperthyroid women [10]. The underlying mechanisms may involve heightened sympathetic activity, increased metabolic demands, and altered vascular function in the placenta. Additionally, fetal hyperthyroidism resulting from maternal antibodies can independently elevate the risk of preterm delivery.

Hyperthyroidism during pregnancy also increases the risk of complications such as thyroid storm, congestive heart failure, and placental abruption. In cases of untreated or poorly controlled Graves' disease, the transplacental passage of thyroid -stimulating immunoglobulins can lead to fetal and neonatal thyrotoxicosis, resulting in tachycardia, fetal goiter, and preterm labor. While beta-blockers may be effective in managing symptoms, their use requires caution due to potential fetal side effects.

Autoimmune Thyroid Disease. Autoimmune thyroiditis, including Hashimoto’s and Graves’ disease, is a common cause of thyroid dysfunction during pregnancy. The presence of thyroid peroxidase antibodies (TPO-Ab) has been linked to an increased risk of miscarriage, preterm birth, and preeclampsia, even in euthyroid women [11]. It is hypothesized that these antibodies may directly impact placental tissues or indicate a systemic immune imbalance that disrupts pregnancy maintenance.

Recent meta-analyses suggest that TPO-Ab positivity doubles the risk of preterm birth, even in the absence of abnormal thyroid hormone levels. This may reflect the broader immunological dysregulation associated with autoimmunity. Elevated levels of interleukin-6, TNF-α, and C-reactive protein in TPO-Ab-positive women further support the notion that chronic inflammation plays a role in adverse pregnancy outcomes.

Inflammation and the Thyroid–Placenta Axis. Thyroid dysfunction is closely associated with systemic inflammation, which plays a crucial role in the initiation of preterm labor. The placenta, functioning both as an endocrine and immune organ, responds to thyroid hormone levels. Dysregulation of thyroid hormone signaling impacts the expression of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, which are known to stimulate uterine contractions and cervical ripening [12]. Furthermore, the activation of inflammasomes in the placenta, particularly in cases of hypothyroidism, has been observed, further implicating inflammatory pathways in the relationship between thyroid dysfunction and preterm birth [13].

Inflammasome activation is especially relevant in preeclampsia and placental insufficiency, both of which are major contributors to preterm birth. Activation of the NLRP3 inflammasome has been linked to increased secretion of IL-1β in trophoblasts under stress conditions. Chronic low-grade inflammation, commonly seen in autoimmune thyroiditis, may sensitize the uterus to contractile stimuli or lower the threshold for the initiation of inflammatory labor.

Placental Hemodynamics and Mediation Effects. A large population-based study showed that maternal FT4 levels in early pregnancy were positively associated with increased resistance in uterine and umbilical arteries—markers of impaired placental perfusion. Mediation analysis suggested that this hemodynamic alteration partially explains the link between thyroid dysfunction and preeclampsia or preterm birth [6]. These findings highlight the importance of early thyroid screening and monitoring of placental function.

Advanced Doppler ultrasound techniques have enabled researchers to correlate maternal thyroid levels with placental blood flow indices. High resistance flow patterns in the uterine arteries suggest impaired trophoblast invasion. These vascular changes are often seen in association with elevated FT4 levels, which may promote antiangiogenic signaling or endothelial dysfunction. Thus, subtle abnormalities in maternal thyroid function may have measurable effects on placental development and function.

Neonatal Outcomes and Long-Term Effects. Infants born to mothers with untreated thyroid disorders face an increased risk not only for prematurity but also for developmental delays and metabolic disorders. Intrauterine hypothyroidism has been shown to impair neurocognitive development and elevate the risk of low birth weight [14]. Even transient maternal thyroid abnormalities can lead to suboptimal fetal outcomes, particularly if they occur during the first trimester, when fetal thyroid function is not yet fully established.

Longitudinal studies have demonstrated that children born to mothers with hypothyroidism are more likely to exhibit lower IQ scores, delayed speech, and motor development impairments. Furthermore, early-life exposure to suboptimal thyroid conditions has been linked to altered hypothalamic-pituitary-adrenal (HPA) axis programming, which may predispose individuals to metabolic and cardiovascular diseases later in life.

Management and Guidelines. Early diagnosis and appropriate management of thyroid disorders during pregnancy are crucial. The American Thyroid Association recommends levothyroxine for overt hypothyroidism and, selectively, for subclinical hypothyroidism [15]. For hyperthyroidism, propylthiouracil is preferred during the first trimester, followed by methimazole in the second and third trimesters. Monitoring every 4–6 weeks is recommended to keep TSH and FT4 levels within trimester-specific targets [16].

Preconception screening is advised for women with a history of thyroid disease, infertility, or autoimmune conditions. During pregnancy, thyroid function should be assessed at least once during the first trimester and subsequently as needed. Additionally, iodine sufficiency should be ensured, either through diet or supplementation, as recommended by the World Health Organization.

Discussion. Thyroid disorders: hypothyroidism, hyperthyroidism, and autoimmune thyroiditis are often underdiagnosed, but they can lead to several complications such as preterm birth, preeclampsia and intrauterine growth restriction [IUGR]. Any disruption in thyroid function can impair placental function, disturb fetal development, and increase the risk of adverse pregnancy outcomes [17]. The relationship between thyroid dysfunction and placental health is complex. Studies altered thyroid hormone levels can affect placental blood flow, with high maternal FT4 levels being associated with increased resistance in uterine and umbilical arteries, suggesting impaired placental perfusion. This vascular alteration has been linked to altered trophoblast invasion, which is critical for effective placental function and proper fetal growth. Thyroid dysfunction can lead to endothelial dysfunction and antiangiogenic signaling, further contributing to placental insufficiency, a common precursor to preterm birth [18]. Thyroid dysfunction in pregnancy is associated with increased systemic inflammation, which can trigger uterine contractions and cervical ripening. Both hypo- and hyperthyroid conditions lead to an upregulation of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, all of which play a role in the initiation of labor. The activation of inflammasomes, particularly the NLRP3 inflammasome in the placenta under conditions of hypothyroidism, further supports the inflammatory pathways implicated in the connection between thyroid dysfunction and preterm birth [19]. Subclinical thyroid disorders are often undetected due to their lack of overt symptoms, yet they can still lead to significant complications. Routine screening for thyroid dysfunction, especially in women at high risk such as those with a history of autoimmune thyroid disease or a family history of thyroid disorders, could help identify at-risk pregnancies and allow for timely intervention. [20]. Monitoring thyroid function throughout pregnancy, along with regular assessment of placental health and fetal development, is crucial in preventing complications such as preterm birth, IUGR, and preeclampsia [21]. Research is needed to refine screening protocols and long-term monitoring strategies for thyroid disorders in pregnancy. More studies should focus on understanding the underlying pathophysiological mechanisms through which thyroid dysfunction leads to pregnancy complications [23]. In conclusion, thyroid dysfunction is a significant remarcable risk factor for pregnancy complications, including preterm birth. Early detection, individualized management, and ongoing research into the mechanisms of thyroid-related pregnancy complications are essential for improving maternal and neonatal outcomes [24].

Conclusion. Thyroid dysfunction is a significant and modifiable risk factor for preterm birth. Both overt and subclinical thyroid disorders impair placental function, contribute to systemic inflammation, and disrupt fetal development. These effects range from altered hemodynamics and hormonal signaling to immune activation and potential epigenetic changes. Early screening, personalized management, and a deeper understanding of the underlying mechanisms are essential to reduce the risk of preterm birth associated with thyroid dysfunction.

Given the high prevalence of thyroid disorders during pregnancy, which often go undiagnosed, a collaborative approach involving endocrinologists, obstetricians, and neonatologists is critical. Tailored interventions, based on biomarkers and risk assessments, could help improve maternal and neonatal outcomes. Future research should focus on refining screening protocols, treatment thresholds, and long-term monitoring strategies for both mothers and their children.

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