Research Advances in Gestational Isolated Hypothyroxinemia (Postprint)

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Abstract

Isolated hypothyroxinemia in pregnancy is a manifestation of thyroid hormone deficiency during gestation, which may affect fetal neurological development and increase the risks of miscarriage, preterm birth, and gestational diabetes; however, its specific mechanisms, optimal treatment protocols, and long-term effects remain somewhat uncertain. This article summarizes the differences in thyroid hormone levels between pregnancy and non-pregnancy states, and comprehensively analyzes the etiology of this disease, its effects on mother and infant, and treatment protocols by reviewing relevant literature. This article posits that iodine deficiency and iron deficiency are the primary causes of isolated hypothyroxinemia in pregnancy, though conclusive evidence regarding the association between factors such as placental growth factor and this disease remains lacking. At present, only its negative effects on motor and neurological development in perinates are relatively well-established, while adverse pregnancy events caused by the condition have not been definitively confirmed, and the related pathological mechanisms remain incompletely elucidated. Regarding treatment, both the efficacy of thyroid hormone replacement therapy and the optimal timing of intervention remain controversial and urgently require further investigation. This article presents a review of the current research status of this disease, aiming to draw heightened attention from clinicians, promote early identification and intervention, and reduce the occurrence of related adverse pregnancy outcomes.

Full Text

Review and Monograph: Research Progress on Isolated Maternal Hypothyroxinemia during Pregnancy

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Abstract

Isolated maternal hypothyroxinemia (IMH) is a manifestation of thyroid hormone deficiency during pregnancy that may affect fetal neurodevelopment and increase the risk of miscarriage, preterm birth, and gestational diabetes. However, uncertainties remain regarding its specific mechanisms, optimal treatment protocols, and long-term effects. This paper summarizes the differences in thyroid hormone levels between pregnant and non-pregnant states and provides a comprehensive analysis of the disease' s etiology, its impact on both mother and infant, and treatment strategies through a review of relevant literature.

We propose that iodine deficiency and iron deficiency are the primary causes of isolated hypothyroxinemia during pregnancy, though conclusive evidence linking factors such as placental growth factor to the disease remains lacking. Currently, only the negative impact on perinatal motor and neurodevelopment is relatively well-established, while adverse pregnancy outcomes have not been definitively confirmed, and the underlying pathological mechanisms remain incompletely understood. Regarding treatment, the efficacy and timing of thyroid hormone replacement therapy remain controversial and require further investigation. This review aims to raise clinical awareness, promote early identification and intervention, and reduce the incidence of related adverse maternal and neonatal outcomes.

Keywords: Isolated maternal hypothyroxinemia; Pregnancy complications; Iodine deficiency; Fetal neurodevelopment; Thyroxine

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Introduction

Thyroid hormone deficiency during pregnancy primarily leads to several conditions, including gestational hypothyroidism, subclinical hypothyroidism, and isolated maternal hypothyroxinemia (IMH). IMH is defined as pregnant

women who are negative for thyroid autoantibodies, have normal serum thyroid-stimulating hormone (TSH) levels, but exhibit free thyroxine (FT4) levels below the lower limit of the pregnancy-specific reference range. The prevalence of IMH is 1-2% in iodine-sufficient populations. Research indicates that IMH may contribute to adverse pregnancy events such as gestational diabetes, gestational hypertension, preterm birth, and placental abruption. Particularly during early pregnancy, fetal brain development is highly dependent on thyroid hormones, making IMH a potential risk factor for fetal neurodevelopmental disorders. Despite these potential adverse outcomes, treatment strategies for IMH remain controversial. Some studies advocate for thyroid hormone replacement therapy, suggesting it effectively improves pregnancy outcomes, while others argue that evidence is insufficient for improving adverse pregnancy outcomes or offspring intellectual development, and that overtreatment risks make such intervention unnecessary. This controversy presents challenges for clinical management.

IMH' s adverse effects on maternal and neonatal outcomes and the selection of treatment protocols remain focal points in clinical practice and academic research. However, existing studies often rely on small-scale data with significant regional and racial differences, lacking large-scale prospective studies. Therefore, this review aims to summarize current research findings, explore the disease' s etiology, treatment strategies, and health impacts, and propose future research directions, particularly focusing on early screening, optimal treatment timing, and long-term effects of thyroid hormone replacement therapy.

Literature Search Strategy

We conducted computerized searches of PubMed, the Chinese Medical Journal Network, and CNKI (China National Knowledge Infrastructure) databases from inception to November 2024. Search terms included "isolated maternal hypothyroxinemia during pregnancy," "gestational low T4 syndrome," "etiology," "adverse pregnancy outcomes," "treatment," "Isolated maternal hypothyroxinemia," "Hypothyroxinemia," "etiology," "adverse pregnancy outcomes," and "treatment." Inclusion criteria comprised literature addressing research progress on IMH during pregnancy, including etiology, effects on other diseases, and treatment. Exclusion criteria included irrelevant content, poor-quality studies, unavailable full text, and unpublished literature. A total of 48 articles were ultimately included.

Physiological Changes in Thyroid Function During Pregnancy

Increased Production and Decreased Clearance of Thyroid-Binding Globulin (TBG)

Under the influence of estrogen, TBG production begins to increase and its clearance decreases at 6-8 weeks of gestation, reaching a plateau in the second trimester at levels 1.5-2.5 times higher than in non-pregnant states, where it remains relatively stable until term. As the primary thyroid hormone transport

protein during pregnancy, increased TBG binds more free thyroid hormone. Additionally, during early pregnancy, the affinity of thyroxine (T4) and triiodothyronine (T3) for TBG increases by 50%, reducing levels of the biologically active components free thyroxine (FT4) and free triiodothyronine (FT3). This reduction in FT4 and FT3 subsequently triggers increased TSH through negative feedback regulation.

Elevated Human Chorionic Gonadotropin (hCG) Levels and Thyroid Hormone Secretion

Earlier beliefs held that the placenta produced large amounts of chorionic products with thyroid-stimulating activity that promoted thyroid hormone secretion. Recent research indicates that hCG is the most likely thyroid stimulant. hCG shares structural similarity with the α-subunit of TSH and can bind to TSH receptors on thyroid follicular cells, exerting its stimulatory effect by activating intracellular messengers such as cAMP. Increased hCG during pregnancy stimulates the thyroid to secrete more thyroid hormones, leading to elevated FT3 and FT4 levels, which in turn reduce TSH secretion. Studies have demonstrated a significant correlation between decreased TSH and increased hCG.

Fetal Dependence on Maternal Thyroid Hormones

The fetal thyroid originates from the endoderm, formed by fusion of the median primordium at the base of the pharynx and paired lateral primordia from the fourth pharyngeal pouch. These structures begin migrating around gestational days 20-22 via the thyroglossal duct, reaching the anterior neck by approximately day 50. Before 16 weeks of gestation, the fetal thyroid is not fully developed and cannot produce thyroid hormones independently. The fetus relies entirely on maternal thyroid hormones, which are transferred across the placenta as T4 and small amounts of T3 to support fetal growth and brain development. Thyroid hormones during early pregnancy are crucial not only for fetal growth and nervous system development but also for embryo implantation and placental development. Therefore, thyroid hormone deficiency in early pregnancy may adversely affect both fetal development and maternal health. After 16 weeks, the fetal thyroid begins functioning and producing hormones, though still insufficient to meet all requirements, necessitating continued placental transfer of maternal thyroid hormones to promote fetal development. After 20 weeks, fetal dependence on maternal thyroid hormones gradually decreases, though studies indicate that term infants still derive approximately 30% of their thyroid hormones from the mother.

Etiology of IMH

Iodine Deficiency and Excess

Iodine is essential for thyroid hormone synthesis, and deficiency is considered a significant factor in IMH development. In 2007, WHO recommended an io-

dine intake of 250 g/L for pregnant women, establishing standards for iodine nutrition during pregnancy and lactation: deficiency (urinary iodine concentration [UIC] <150 g/L), sufficiency (UIC 150-249 g/L), more-than-adequate (UIC 250-499 g/L), and excess (UIC $ $500 g/L). During pregnancy, increased glomerular filtration rate enhances renal iodine clearance, while the increased fetal-maternal iodine gradient further elevates maternal iodine requirements. When maternal iodine becomes insufficient due to various factors, the thyroid cannot effectively synthesize adequate hormones, potentially leading to IMH. Researchers in Saudi Arabia and Iran have experimentally confirmed this relationship. Therefore, clinical practice should monitor iodine status and provide timely supplementation to reduce IMH incidence.

While IMH was previously attributed to iodine deficiency, studies show that excess iodine can also cause IMH. SHI et al. conducted a cross-sectional study in an iodine-sufficient region, finding that pregnant women with excessive iodine intake had a 2.85-fold increased prevalence of IMH compared to those with normal intake, suggesting that iodine excess is also closely associated with IMH development. This phenomenon may result from the Wolff-Chaikoff effect, where high iodine states reduce thyroid hormone formation and release, potentially occurring in pregnant women with underlying thyroid disease. Therefore, iodine supplementation during pregnancy should remain within appropriate ranges, as both deficiency and excess may lead to IMH and affect maternal health and fetal development.

Iron Deficiency

In clinical practice, ferritin levels serve as an important indicator of iron status in pregnant women. POP et al. conducted a cross-sectional study of women at 12 weeks gestation, finding significant differences in ferritin levels between IMH and euthyroid groups. The incidence of low ferritin was 12.3% in the IMH group, significantly higher than the 4.8% in the control group, establishing iron deficiency as an independent risk factor for IMH. The most plausible mechanism involves iron' s role in thyroid peroxidase (TPO), a heme-dependent enzyme whose active center contains iron and iodinates tyrosine residues in thyroglobulin to produce thyroid hormones. Iron deficiency reduces TPO activity, ultimately impairing thyroid hormone synthesis. Previous animal studies also demonstrated that iron deficiency interferes with deiodinase activity by reducing T4-to-T3 conversion and disrupts thyroid metabolism regulation at the central level. Due to increased red blood cell mass and fetal-placental growth during pregnancy, iron requirements are substantially elevated, predisposing pregnant women to iron deficiency anemia and consequently IMH.

Abnormal Secretion of Soluble FMS-like Tyrosine Kinase-1 and Placental Growth Factor

During pregnancy, the placenta produces placental growth factor (PIGF) and soluble FMS-like tyrosine kinase 1 (sFlt-1). PIGF is a pro-angiogenic factor shar-

ing 53% molecular homology with vascular endothelial growth factor (VEGF), while sFlt-1 is an anti-angiogenic factor that antagonizes both PIGF and VEGF. Previous animal experiments showed that after three weeks of exposure to exogenous VEGF receptor inhibitors, capillary density in multiple organs of mice decreased to varying degrees, with the most pronounced reduction (68%) observed in thyroid tissue. Normal regeneration of thyroid capillaries occurred two weeks after exposure cessation, demonstrating that thyroid capillary density can be regulated by vascular regulatory factors. Since the thyroid is a highly vascularized organ, these angiogenic factors may also affect thyroid function and contribute to IMH.

To further investigate the effects of PIGF and sFlt-1 on maternal thyroid function during pregnancy, KOREVAAR et al. conducted a prospective cohort study of first-trimester pregnant women, measuring sFlt-1, PIGF, TSH, and FT4 levels and analyzing their correlation with IMH. The study found that sFlt-1 levels negatively correlated with FT4 but showed no significant correlation with TSH, while PIGF levels negatively correlated with both TSH and FT4. The researchers concluded that elevated sFlt-1 and PIGF are associated with IMH. Based on animal experiments, sFlt-1 is hypothesized to directly reduce FT4 levels by antagonizing VEGF and inhibiting thyroid angiogenesis, negatively affecting thyroid function without significantly impacting TSH levels except through negative feedback at very high concentrations. Although PIGF is traditionally considered pro-angiogenic, its elevation in this study led to decreased FT4 and TSH levels. This may be related to impaired hCG-mediated thyroid stimulation during pregnancy. Under normal conditions, hCG promotes FT4 synthesis, but PIGF overexpression may affect thyroid vascular perfusion and microenvironmental homeostasis, reducing thyroid sensitivity to hCG and ultimately decreasing FT4 levels. Alternatively, excessive PIGF expression during pregnancy may weaken VEGF signaling, producing anti-angiogenic effects that reduce FT4 levels and negatively affect thyroid function. Since the pituitary is also highly vascularized and susceptible to angiogenic factor changes, TSH levels may also decrease. Animal experiments have supported this hypothesis. However, current research on the effects of sFlt-1 and PIGF on maternal thyroid function is limited, and the specific pathophysiological mechanisms remain unclear, necessitating further investigation.

Other Factors

Beyond the aforementioned factors, other elements may contribute to IMH. Studies suggest IMH is associated with maternal characteristics, including maternal age $ $35 years, non-local residency, multiparity, and pre-pregnancy overweight or obesity. Clinical practice should therefore pay special attention to these maternal factors
increase in NO2 exposure during early pregnancy and PM2.5 exposure during mid-pregnancy is associated with 0.61% and 0.73% decreases in FT4 levels, respectively. Previous animal and human epidemiological studies have linked maternal air pollution exposure during pregnancy to childhood neurodevel-

opmental deficits, possibly through IMH. Additionally, vitamin D deficiency, insulin resistance, and dyslipidemia have been associated with IMH in women of childbearing age. Since treatment measures for IMH remain undefined, clinicians should address these risk factors by supplementing vitamin D, controlling diet, preventing gestational diabetes and dyslipidemia, and managing weight to prevent IMH at its source.

Effects of IMH on Maternal and Infant Outcomes

Impact on Fetal Brain Development and Offspring Cognitive Function

Thyroid hormones play a critical role in fetal brain development. Before the fetal thyroid matures, the fetus depends entirely on maternal thyroid hormones. Inadequate maternal thyroxine levels may suppress fetal brain development, affecting intelligence, motor skills, social abilities, and language development. Studies have linked IMH to offspring neurodevelopmental problems including intellectual disability, delayed speech and language development, and motor coordination disorders, as well as increased risks of autism spectrum disorder and attention deficit hyperactivity disorder. Animal studies have yielded similar findings, with offspring of IMH rats showing significantly increased risks of anxiety, reduced social ability, and repetitive stereotyped behaviors at 40 days after birth. Moreover, the impact of IMH on offspring diminishes with increasing gestational age, with research indicating that the effect on fetal brain development depends on the timing of FT4 deficiency. When IMH occurs in early pregnancy, offspring exhibit problems in visual attention, visual processing, and gross motor skills; when occurring later in pregnancy, offspring may show slowed reaction times and fine motor deficits.

Current understanding of IMH's impact on fetal brain development relies primarily on animal studies, which suggest three potential mechanisms. First, thyroid hormones regulate specific gene expression. Animal experiments have shown that thyroid hormones control expression of key genes in rodent brains, likely through T3 and T4 conversion and action in the brain. After T4 enters the brain via transporters and converts to T3, T3 acts through nuclear receptors to control genes involved in myelination, cell differentiation, and signal transduction. Reduced FT4 may disrupt this gene expression cascade, leading to fetal brain developmental impairment. Second, thyroid hormones regulate embryonic neuronal cell migration, proliferation, and differentiation, which ultimately contribute to cortical formation. Reduced FT4 leads to decreased cortical thickness and impaired cortical maturation. Third, IMH causes delayed neuronal growth by interfering with related protein expression. Animal experiments support epidemiological findings and suggest that the severity of FT4 deficiency determines the type and severity of neurological deficits.

Impact on Neonatal Body Weight

The effect of IMH on fetal birth weight remains controversial. WEI Zhanchao et al. conducted a retrospective study of 19,770 pregnant women and found that IMH significantly increased the incidence of macrosomia, particularly in pre-pregnancy obese women, suggesting that early IMH may serve as a warning indicator for macrosomia delivery. DU et al. reached similar conclusions in a prospective study. However, a Japanese study of 4,164 pregnant women found that IMH increased the risk of small-for-gestational-age infants without significant association with large-for-gestational-age or low birth weight infants. Conversely, LI et al.' s study of 7,051 pregnant women in southern China found IMH associated only with increased risk of large-for-gestational-age infants. A meta-analysis showed IMH associated with both macrosomia and small-for-gestational-age infants but not large-for-gestational-age infants. While multiple studies suggest associations between IMH and fetal weight parameters, results remain inconsistent, and no study has definitively established the mechanisms by which IMH affects neonatal weight.

Adverse Pregnancy Outcomes

Preterm Birth YANG et al. investigated the relationship between IMH in early pregnancy and preterm birth and its subtypes in a large prospective study of 41,911 pregnant women. Compared to euthyroid pregnant women, IMH patients had significantly increased preterm birth risk, primarily associated with spontaneous preterm birth with intact membranes rather than preterm premature rupture of membranes or medically indicated preterm birth. The study also found that IMH' s effect on preterm birth risk was related to fetal sex, with more pronounced effects observed in women carrying female fetuses. The increased preterm birth risk in IMH patients may be related to elevated vasopressin levels and increased oxidative stress. The sex-related correlation may result from gender-specific intrauterine metabolic changes in IMH patients, as the intrauterine environment plays a critical role in spontaneous preterm birth. A meta-analysis examining thyroid dysfunction and preterm birth also found IMH significantly associated with increased risks of preterm and very preterm birth. Although many studies support this association, further research is needed to elucidate the underlying pathophysiological mechanisms and optimize clinical strategies to reduce adverse pregnancy events.

Gestational Diabetes Mellitus The relationship between IMH and gestational diabetes remains unclear. XIE Junhao et al. conducted a prospective analysis of 1,903 pregnant women, comparing gestational diabetes incidence, thyroid function, and mid-pregnancy glucose metabolism indicators between IMH and euthyroid groups, concluding that FT4 levels had no significant effect on gestational diabetes incidence but influenced mid-pregnancy glucose metabolism parameters. In contrast, GONG Ajuan identified IMH as a risk factor for gestational diabetes. Due to inconsistent findings, CAROL et al. con-

ducted a comprehensive meta-analysis summarizing heterogeneity in previous studies, ultimately concluding that IMH is significantly associated with gestational diabetes development. However, the study only analyzed the correlation without exploring mechanisms. Some research suggests FT4 levels may affect insulin requirements, but direct evidence for a causal relationship between IMH and gestational diabetes is lacking, necessitating mechanistic studies to clarify the biological connection.

Hypertensive Disorders of Pregnancy WANG et al. examined the relationship between IMH and preeclampsia in 52,027 pregnant women, finding significantly increased preeclampsia risk in IMH patients compared to euthyroid women. Although multiple observational studies have evaluated associations between IMH and gestational hypertension, varying diagnostic methods and IMH definitions have yielded inconsistent results. TOLOZA et al. addressed this through a meta-analysis of 1,530 published studies, ultimately including 19 cohorts comprising 46,528 pregnant women, concluding that only subclinical hypothyroidism was associated with preeclampsia risk, while IMH showed no significant correlation with gestational hypertension or preeclampsia.

Other Adverse Pregnancy Events Comparative studies of pregnancy outcomes between IMH and euthyroid patients suggest IMH may increase the incidence of placenta previa, placental abruption, premature rupture of membranes, fetal distress, and cesarean delivery rates. Questionnaire-based assessments of maternal cognitive function indicate that IMH affects not only fetal neurodevelopment but also maternal cognitive function throughout pregnancy, with IMH patients showing significantly higher cognitive dysfunction scores that increase between 12-24 weeks and decrease by pregnancy' s end. While research on pregnancy outcomes in IMH patients has increased, some studies find no association between IMH and adverse maternal or perinatal outcomes.

Treatment of IMH

Significant progress has been made in understanding IMH' s etiology, effects on mother and child, and treatment options. The associations between iodine deficiency, iron deficiency, and IMH have been validated clinically and supported by pathological mechanisms, though evidence linking placental growth factors and maternal characteristics to IMH remains inconclusive. Future research should focus on how these factors increase IMH risk and explore integrated effects of genetic, immune, and environmental factors to provide new theoretical foundations for early prevention and individualized treatment strategies.

Regarding effects on maternal and infant health, only the negative impact on fetal brain development is relatively well-established, while effects on other pregnancy outcomes require further investigation, and underlying pathological mechanisms remain incompletely understood—representing a major research

challenge. Future large-scale, multicenter prospective cohort studies should evaluate causal relationships between IMH and various maternal-neonatal outcomes and investigate potential biological mechanisms to further explain these associations.

The key unresolved question regarding levothyroxine treatment for IMH is whether correcting IMH with levothyroxine provides substantive benefits for offspring brain development, cognitive function, and adverse pregnancy outcomes. Unfortunately, existing studies yield inconsistent conclusions with insufficient power. Considering suboptimal results may be due to the fact that thyroid hormone receptor genes begin expressing as early as gestational week 8, suggesting thyroid hormones may influence fetal brain development from this point onward, earlier treatment initiation (before week 8) might yield more positive effects on fetal cognitive function. However, treating IMH patients before week 8 places higher demands on diagnostic capabilities. Future research should integrate more sophisticated genomics, metabolomics, and molecular markers to facilitate early IMH diagnosis and promote etiology-based treatment. Furthermore, since IMH involves not only obstetrics and gynecology but also endocrinology, pediatrics, and neurology, enhanced interdisciplinary collaboration and established multidisciplinary cooperative models are needed to advance individualized treatment strategies and provide more precise therapeutic approaches.

Treatment guidelines from different societies and institutions show discrepancies. The 2014 European Thyroid Association guidelines recommend levothyroxine treatment for IMH in early pregnancy but not in mid-to-late pregnancy, while the 2017 American Thyroid Association guidelines do not recommend levothyroxine intervention for IMH patients. In China, research on IMH treatment is limited, and the 2019 Chinese guidelines take an ambiguous stance on levothyroxine treatment, emphasizing instead active identification and treatment of underlying causes. Therefore, clinicians should conduct comprehensive examinations to identify etiologies, minimize IMH incidence, and reduce adverse pregnancy events through regular follow-up and thyroid function monitoring.

Evidence regarding levothyroxine treatment remains limited. CASEY et al. randomized IMH patients at 8-20 weeks gestation to receive either levothyroxine or placebo, adjusting dosage monthly based on thyroid function and assessing offspring neurocognitive function at age 5 years. The study found no significant differences between groups in behavior, attention deficit, hyperactivity, or IQ scores, concluding that levothyroxine treatment does not improve cognitive function in children over 5 years old. However, these negative results may be related to late intervention timing. Another randomized controlled trial by LI et al. included 964 IMH patients and found that levothyroxine treatment in early pregnancy significantly reduced miscarriage rates and neonatal NICU admissions but did not improve other adverse pregnancy outcomes, suggesting potential benefits for select outcomes. While observational studies provide preliminary data, numerous confounding factors prevent definitive conclusions

about whether levothyroxine treatment reduces adverse pregnancy outcomes in IMH patients.

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Note: Figure translations are in progress. See original paper for figures.