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Immune-endocrine and Oxidative Stress Alterations Associated with Urinary Iodine Status in Hypertensive Disorders of Pregnancy

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ABSTRACT

Hypertensive disorders of pregnancy (HDP), particularly preeclampsia, involve immune-endocrine dysregulation, oxidative stress, and endothelial dysfunction. This systematic review and meta-analysis evaluated associations between urinary iodine concentration (UIC), HDP, and related biomarkers. PubMed was searched from inception to February 2026, with additional manual screening.

Thirteen studies were included, and six underwent meta-analysis. Women with HDP/preeclampsia had lower UIC than controls (MD −143.647 μg/L; 95% CI −256.362 to −30.933; I^2 =97.8%). TSH and FT3 did not differ significantly, whereas FT4 was reduced in HDP (MD −1.007 pmol/L; 95% CI −1.660 to −0.354; I^2 =0%).

Qualitative evidence indicated alterations in TPOAb, TgAb, CRP, nitric oxide, TBARS, SOD, CAT, OxLDL/Alb, GGT, and lymphocyte percentage. Abnormal iodine status may contribute to HDP through thyroid dysfunction, immune imbalance, oxidative stress, and endothelial inflammation.

Reduced FT4 was the most consistent biochemical abnormality. Further standardized, large-scale studies are needed.

Keywords: Hypertensive disorders of pregnancy; Immune-endocrine dysregulation; Oxidative stress; Preeclampsia; Pregnancy immunology; Thyroid dysfunction; Urinary iodine

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are among the most common and clinically serious complications of pregnancy. Their clinical spectrum includes gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia. These disorders are major contributors to maternal morbidity and mortality and are closely associated with placental hypoperfusion, fetal growth restriction, preterm birth, and other adverse perinatal outcomes.[1–3] In recent years, the understanding of HDP, particularly preeclampsia, has shifted from a condition defined primarily by elevated blood pressure to a systemic disorder involving impaired placentation, vascular endothelial dysfunction, oxidative stress, immune maladaptation, and inflammatory activation. Abnormal immune regulation at the maternal–fetal interface, insufficient trophoblast invasion, and secondary endothelial injury are now considered central

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biological features of disease development. Therefore, examining HDP from the perspective of immune-endocrine imbalance and related biochemical abnormalities may help clarify its pathogenesis and identify earlier, measurable risk signals.[1–3]

Normal pregnancy relies on stable maternal–fetal immune tolerance: regulatory T cells (Tregs) maintain immune suppression at the maternal–fetal interface, natural killer (NK) cells participate in trophoblast invasion and vascular remodeling, and polarized macrophages and balanced cytokines jointly avoid excessive inflammatory activation. When immune tolerance is broken, excessive inflammation, impaired trophoblast infiltration, and endothelial injury will occur, which is the core pathological basis of preeclampsia and other HDP. Iodine deficiency and subsequent thyroid dysfunction can interfere with the differentiation and function of Tregs, NK cells, and macrophages, break the maternal immune homeostasis, and further aggravate the occurrence and development of HDP.

It is necessary to clarify the definition of markers in this study: Classic immune biomarkers mainly refer to inflammatory cytokines and immune cell subsets, while thyroid function indicators (TSH, FT3, FT4) are core components of the maternal immune-endocrine regulatory axis during pregnancy. Thyroid hormones can regulate immune cell activity, immune tolerance, and inflammatory response, and thyroid dysfunction is often accompanied by changes in autoimmune and immune homeostasis. Therefore, this study collectively defines thyroid function indicators, thyroid autoantibodies, inflammatory factors, and oxidative stress markers as immune-endocrine related biochemical markers, focusing on the overall disorder of immune-endocrine network in HDP, rather than limited to classical immune molecules.

Iodine is an essential trace element required for thyroid hormone synthesis. During pregnancy, iodine requirements increase substantially because of enhanced maternal thyroid hormone production, increased renal iodine clearance, and rising fetal demand. The World Health Organization recommends that a median urinary iodine concentration of 150–249 μg/L in pregnant women indicates adequate iodine nutrition, whereas lower concentrations suggest iodine deficiency and higher concentrations may indicate excessive intake.[4] Pregnancy is therefore a period of heightened sensitivity to iodine supply rather than a physiologic state of stable iodine balance. Both insufficient and excessive iodine intake may disturb maternal thyroid regulation and, in turn, affect placental development, vascular homeostasis, endothelial stability, oxidative balance, and pregnancy outcomes.[1,4,5]

Severe iodine deficiency is well established as harmful to both pregnant women and fetuses, contributing to maternal thyroid dysfunction, miscarriage, stillbirth, preterm birth, and impaired fetal neurodevelopment. However, the relationships between mild-to-moderate iodine deficiency, iodine excess, and adverse pregnancy outcomes are less consistent. Recent research has increasingly moved beyond the simple question of whether iodine deficiency is present and has instead focused on how different degrees of iodine exposure may be associated with pregnancy-related risks. Existing evidence suggests that the association between maternal iodine status and outcomes such as fetal growth, birth outcomes, and pregnancy complications may not be strictly linear and may involve threshold effects or bidirectional risks.[1,5] Thus, a simple classification of iodine nutrition as “deficient” or “sufficient” may be inadequate for explaining its relationship with HDP.

A potential biological link between iodine status and HDP lies in the interaction between iodine nutrition, thyroid function, and the immune-endocrine network. Thyroid hormones are involved not only in metabolic regulation but also in placental development, immune tolerance, vascular reactivity, oxidative stress, and endothelial function. Thyroid dysfunction during pregnancy, particularly subclinical hypothyroidism, has been associated with increased risks of gestational hypertension and preeclampsia.[3] Because iodine intake directly influences thyroid hormone synthesis, abnormal urinary iodine status may reflect a broader disturbance in maternal endocrine and immune regulation. This suggests that iodine imbalance may contribute to the development or progression of HDP through altered thyroid function, impaired immune tolerance, increased oxidative stress, and endothelial dysfunction.

A growing number of original studies have examined the relationship between urinary iodine status and HDP across different populations, but the findings remain inconsistent. Some studies have reported lower urinary iodine levels among women with preeclampsia or severe preeclampsia compared with healthy pregnant controls, suggesting that iodine deficiency may be associated with increased HDP risk.[6,9,10] Other studies have suggested that high urinary iodine status may also be linked to HDP

or other adverse pregnancy outcomes, indicating a possible non-linear association.[8] In contrast, some investigations have found no significant differences in iodine-related or thyroid-related markers between women with preeclampsia and normotensive controls.[11] These discrepancies may be attributable to differences in study design, population iodine sufficiency, timing of sample collection, definitions of iodine exposure, HDP subtypes, and adjustment for confounding factors.

In addition to urinary iodine itself, several biochemical markers may help explain the potential pathways connecting iodine imbalance with HDP. In this context, immune-related biochemical markers are not limited to classical inflammatory cytokines. Thyroid autoantibodies such as thyroid peroxidase antibody, anti-thyroid peroxidase antibody, and thyroglobulin antibody may reflect autoimmune susceptibility, whereas thyroid function indicators including thyroid-stimulating hormone, free thyroxine, and free triiodothyronine represent changes in the immune-endocrine regulatory axis. Moreover, oxidative stress, antioxidant defense, inflammatory, and endothelial injury markers—including nitric oxide, thiobarbituric acid-reactive substances, superoxide dismutase, catalase, ferric reducing power, C-reactive protein, and oxidized low-density lipoprotein/albumin ratio—may provide measurable evidence of redox imbalance and vascular dysfunction in HDP.[7,10] Integrating these markers may therefore provide a more comprehensive understanding of how abnormal iodine status could be linked to immune dysregulation and hypertensive complications during pregnancy.

Despite growing interest in this field, important gaps remain. First, existing studies have often focused on either urinary iodine status, thyroid dysfunction, or selected biochemical markers in isolation, resulting in fragmented and sometimes conflicting evidence. Second, although previous reviews have examined iodine nutrition and preeclampsia or thyroid dysfunction and HDP separately, few meta-analyses have evaluated urinary iodine levels, HDP risk, and immune-related biochemical or thyroid function markers within a unified analytical framework.[3,5] As a result, the broader relationship among iodine status, immune-endocrine imbalance, oxidative stress, and endothelial dysfunction in HDP remains insufficiently synthesized.

Therefore, this systematic review and meta-analysis aimed to investigate the association between urinary iodine levels and HDP and to evaluate immune-related biochemical and thyroid function markers associated with abnormal iodine status in affected pregnancies. Specifically, we sought to determine whether urinary iodine levels differ between women with HDP and normotensive pregnant controls, assess the relationship between different urinary iodine categories and HDP risk, and synthesize evidence on thyroid function, thyroid autoimmunity, oxidative stress, inflammatory, and endothelial-related markers. By integrating these dimensions, this study aims to provide a more comprehensive assessment of whether abnormal iodine status may contribute to HDP through immune-endocrine imbalance, oxidative stress, and vascular dysfunction.

MATERIALS AND METHODS

Study Design

This study was a systematic review and meta-analysis. It was structured around the central line of "urinary iodine levels–hypertensive disorders of pregnancy–immune-related biochemical markers." The basic framework of PRISMA 2020 was followed in literature screening, data extraction, synthesis, and reporting.[13] Because the available literature consisted mainly of observational studies, including case-control, nested case-control, cohort, and cross-sectional studies, the present review should be interpreted as an evidence synthesis of heterogeneous observational data.

In this study, the term "immune-endocrine related biochemical markers" was defined relatively broadly. It included not only thyroid autoimmunity-related indicators such as TPOAb/anti-TPO, TgAb, and Tg, but also biochemical markers related to immune tolerance during pregnancy, the thyroid immune-endocrine axis, oxidative stress, and vascular endothelial injury, such as TSH, FT4, FT3, CRP, NO, TBARS, SOD, CAT, FRP, and OxLDL/Alb. This broad definition was adopted because evidence on immune dysregulation in HDP is not confined to classical inflammatory factors; rather, it more often manifests as an intertwined state involving immune, endocrine, oxidative stress, and endothelial dysfunction.

We strictly distinguish 2 categories of indicators herein: classical immune biomarkers include TPOAb, TgAb, CRP, NO, and lymphocyte percentage; endocrine biomarkers mainly refer to thyroid function indicators (TSH, FT3, FT4). All the above indicators are collectively named immune-endocrine related biochemical markers in this research.

Literature Search Strategy

PubMed was searched as the primary database, and the reference lists of eligible articles were manually reviewed to identify additional relevant studies. The search period covered database inception to February 2026. To improve both coverage and specificity, a combination of subject terms and free-text terms was used. The search strategy comprised 3 groups of keywords. The first group concerned iodine nutrition, including "iodine," "urinary iodine," "urinary iodine concentration," "UIC," and "iodine status." The second group concerned hypertensive disorders of pregnancy, including "hypertensive disorders of pregnancy," "gestational hypertension," "preeclampsia," "pre-eclampsia," and "eclampsia." The third group concerned immune-related biochemical indicators, including "TSH," "FT4," "FT3," "thyroglobulin," "Tg," "thyroid peroxidase antibody," "TPOAb," "anti-TPO," "TgAb," "CRP," "nitric oxide," and "oxidative stress."

The search formula was adjusted as appropriate according to database characteristics. In PubMed, the basic logic was as follows: (iodine OR urinary iodine OR urinary iodine concentration OR UIC OR iodine status) AND (hypertensive disorders of pregnancy OR gestational hypertension OR preeclampsia OR pre-eclampsia OR eclampsia) AND (TSH OR FT4 OR FT3 OR thyroglobulin OR Tg OR TPOAb OR anti-TPO OR TgAb OR CRP OR nitric oxide OR oxidative stress).

Given the internationally used standard for judging urinary iodine status in pregnant women, the WHO-recommended median urinary iodine range of 150–249 μg/L in pregnant women was used as a reference framework for interpreting iodine nutritional status, rather than as a strict eligibility threshold for study selection.[4]

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) the study population consisted of pregnant women; (2) outcomes involved HDP, gestational hypertension, preeclampsia, or highly related adverse pregnancy outcomes; (3) the study reported iodine nutrition-related indicators, mainly urinary iodine concentration, urinary iodine-to-creatinine ratio, or other measures reflecting iodine status; (4) the study reported at least 1 immune or biochemical indicator relevant to the present topic, or provided an effect estimate that could be extracted for the association between urinary iodine and HDP; (5) the publication was an original study, including case-control studies, nested case-control studies, prospective cohort studies, or cross-sectional studies; and (6) the article provided at least 1 type of analyzable data, such as mean and standard deviation, median and quartiles, event counts, ORs, RRs, or corresponding 95% CIs.

The exclusion criteria were as follows: (1) reviews, commentaries, case reports, conference abstracts, animal experiments, or mechanistic basic studies; (2) failure to report iodine nutrition-related indicators, or mention of iodine without an analyzable exposure variable; (3) outcomes unrelated to HDP or its clinical spectrum, with no results directly extractable for the present study; (4) incomplete data that precluded retrieval of original grouped data or conversion to comparable effect estimates; and (5) duplicate publications or obviously overlapping samples, in which case only the study with more complete information, richer indicators, or a stronger design was retained.

Each study adopted different urinary iodine stratification thresholds: some used 150 μg/L as the cut-off value for adequate iodine, some set multiple gradient groups (<50, 50–99, 100–149, 150–249, ≥250 μg/L), and a few set high-iodine group as ≥500 μg/L. The inconsistent division of exposure groups is an important confounding factor for outcome analysis.

Literature Screening and Data Extraction

After retrieval, titles and abstracts were first screened to remove clearly irrelevant records, after which full texts were reviewed to determine eligibility. Studies whose titles or abstracts provided insufficient information but were close to the target topic were also taken into the full-text review stage so as to reduce the risk of omission. When discrepancies existed between different sources of the same study, the full-text article was treated as authoritative, with supplementary materials or appendices consulted when necessary.

Data were extracted using a predesigned standardized form. Extracted items included author, year of publication, country, study design, sample size, case and control grouping, iodine nutrition indicators, immune/biochemical markers, primary outcomes, statistical form, and data available for meta-analysis. For continuous outcomes, sample size, mean, and standard deviation were primarily extracted; if the original article reported median and quartiles, approximate conversion was performed. For ratio outcomes, event counts or adjusted ORs/RRs with 95% CIs were extracted. Indicators closely related to the study question but not eligible for quantitative pooling, such as TPOAb, anti-

TPO, TgAb, CRP, NO, TBARS, SOD, CAT, FRP, and OxLDL/Alb, were included in the qualitative synthesis to preserve the completeness of the topic element "immune-related biochemical markers."

Quality Assessment

Because the included studies were observational in design, quality assessment was performed according to study type. Case-control and cohort studies were assessed using the Newcastle–Ottawa Scale (NOS).[14] Cross-sectional studies were appraised using an appropriate checklist-based approach. Particular attention was paid to the clarity of case definition, the selection of controls or comparison groups, the comparability between groups, the ascertainment of exposure or outcomes, and the completeness of reported data. Given the heterogeneity in study design, exposure categorization, and outcome reporting across the included studies, quality assessment was used primarily to support cautious interpretation of the evidence rather than to exclude studies solely on the basis of summary scores.

All included observational studies were assessed by Newcastle–Ottawa Scale (NOS) for case-control and cohort studies, and unified checklist for cross-sectional studies. The evaluation dimensions mainly included 4 parts: study subject selection, comparability between groups, exposure/outcome ascertainment, and data integrity. Overall, most case-control studies had high scores in case definition and control selection, but a few studies lacked effective confounding factor adjustment; prospective cohort studies performed well in outcome follow-up; cross-sectional studies had limitations in temporal sequence judgment. No studies with extremely low quality were excluded in this review, and all potential bias factors have been fully considered in the result interpretation.

Outcome Definitions

In light of the study topic and the existing literature, 1 primary outcome and 2 categories of secondary outcomes were defined. The primary outcome was the difference in urinary iodine levels between women with HDP/preeclampsia and normal pregnant controls. The first category of secondary outcomes was the association between different levels of urinary iodine exposure and the risk of HDP or preeclampsia, that is, pooled analyses of adjusted ORs or RRs. The second category of secondary outcomes comprised immune-related biochemical markers. These were further divided into 2 parts: markers amenable to quantitative meta-analysis, mainly thyroid-related indices including TSH, FT4, and FT3; and markers included only in qualitative synthesis, such as TPOAb/anti-TPO, TgAb, Tg, CRP, NO, TBARS, SOD, CAT, FRP, OxLDL/Alb, GGT, and lymphocyte proportion.

Data Standardization and Conversion

Because the included studies differed in indicator units and reporting formats, data standardization was performed before formal pooling. Urinary iodine concentration was uniformly converted to μg/L; if reported in μg/dL, values were multiplied by 10 to obtain μg/L. FT4 values reported in ng/dL were converted to pmol/L using 1 ng/dL = 12.87 pmol/L, and FT3 values reported in pg/mL were converted to pmol/L using 1 pg/mL = 1.536 pmol/L. All continuous variables entered the quantitative synthesis only after unit harmonization so as to ensure comparability of effect estimates.

For studies reporting only medians and quartiles, approximate estimation methods proposed by Wan et al and Luo et al were used to convert medians and quartiles into means and standard deviations before inclusion in the meta-analysis.[15,16] It should be noted that such conversions introduce a degree of approximation error, and results derived from converted data were therefore interpreted cautiously. When a study contained multiple case subgroups sharing the same control group, case subgroups were combined while ensuring that the control group was not counted repeatedly, thereby avoiding weight distortion caused by duplicate inclusion of controls.

Statistical Analysis

All statistical analyses were performed in Stata 19.5. Mean difference (MD) was used as the effect measure for continuous outcomes. For ratio outcomes, adjusted ORs or RRs were extracted and, when necessary, natural logarithms were taken and pooled using the generic inverse-variance method. Because the included studies differed objectively in regional populations, disease severity, sampling time points, statistical forms, and background iodine nutrition status, random-effects models were used as the primary pooling strategy to better accommodate genuine between-study differences.

Heterogeneity was assessed using Cochran's Q test and the I^2 statistic. When heterogeneity was high, it was not simply bypassed; instead, it was interpreted in the text in light of study design, case definitions, exposure

stratification, and data-conversion procedures. Given that the number of studies included in each quantitative outcome was small, and that most primary and secondary meta-analyses involved fewer than 10 studies, publication-bias analyses such as funnel plots and Egger's test were not further performed. Instead, caution in result interpretation was used as a compensatory measure. All statistical tests were two-sided, and $p<.05$ was considered statistically significant.[13]

For ratio outcomes, this study combined adjusted ORs and RRs for pooled analysis. The basis for combination was that both indicators reflected the association strength between exposure and outcome after confounding adjustment. It should be noted that OR and RR have different statistical implications: RR is more suitable for cohort studies, while OR is commonly used in case-control studies. The differences in study design, confounding factor types, and adjustment methods among included studies will inevitably bring bias to the pooled results.

RESULTS

Literature Screening and Overview of Included Studies

A total of 13 original studies were included in the systematic review. Study designs included case-control studies, nested case-control studies, and prospective cohort studies, and study settings covered China, Brazil, Turkey, Mexico, South Africa, the Democratic Republic of the Congo, and Finland. According to study design, outcome type, and data extractability, 6 studies were ultimately included in the formal quantitative synthesis. Of these, 4 studies were used in the primary meta-analysis of urinary iodine level differences between cases and controls, and 2 studies were used in the effect analysis of urinary iodine exposure levels and the risk of HDP/preeclampsia. The remaining studies were included in sensitivity analysis or qualitative synthesis because their exposure indicators were not fully consistent with the main analysis, they lacked normal control groups, or, although they involved immune-related biochemical markers, they did not provide directly poolable dispersion data. Overall, the current evidence shows a relatively concentrated quantitative base for urinary iodine differences, whereas evidence on immune-related biochemical markers is more scattered. The literature screening flow is shown in Figure 1, and the basic characteristics of the included studies are presented in Table 1.

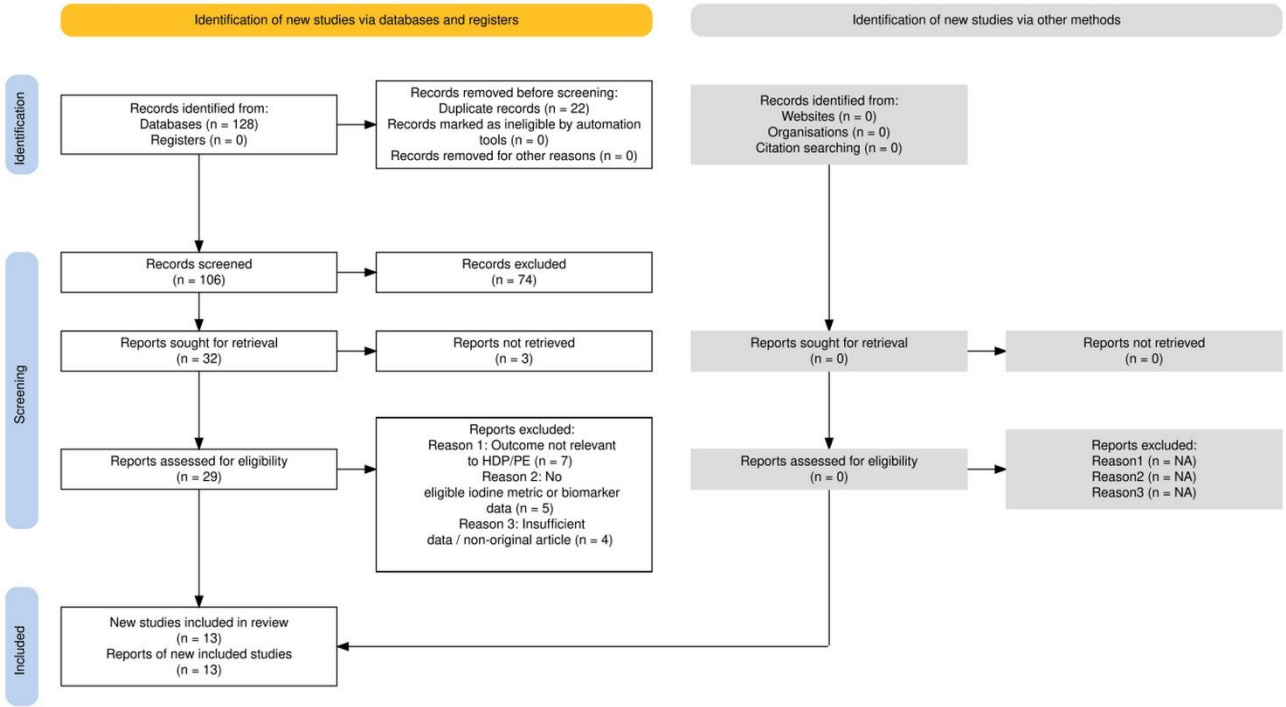

Figure 1. PRISMA Flow Diagram of Literature Screening

Table 1. Basic Characteristics of the Included Studies

Author (Year)	Country	Study Design	Sample Size	Study Population/ Grouping	Iodine Nutrition Indicator	Immune-related Biochemical Markers	Main Outcome
Gulaboglu (2010)[9]	Turkey	Case-control study	58	40 pregnant women with severe preeclampsia vs 18 healthy pregnant women	Spot urinary iodine concentration	Mg, T3, T4, TSH, FT3, FT4	Biochemical differences between the preeclampsia group and controls
Cuellar-Rufino (2017)[10]	Mexico	Case-control study	57	20 pregnant women with HDP vs 37 normal pregnant women	Spot urinary iodine concentration	TSH, FT4, FRP, SOD, CAT, TBARS	Differences in oxidative stress/antioxidant status between HDP and normal pregnancy
Torlinska (2018)[17]	United Kingdom	Prospective cohort study	3140	Singleton pregnancies; iodine status assessed by urinary iodine and urinary iodine-to-creatinine ratio	Urinary iodine concentration and urinary iodine-to-creatinine ratio	No core immune markers	Adverse obstetric outcomes in the context of mild-to-moderate iodine deficiency
de Morais (2020)[8]	Brazil	Prospective cohort study	214	Grouped by urinary iodine as <150, 150–249, 250–499, and ≥500 µg/L	Repeated measures of urinary iodine concentration	TSH, FT4, TPOAb, TgAb, Tg	HDP, gestational diabetes, and neonatal outcomes under different iodine statuses
Businge (2021)[18]	South Africa	Cross-sectional/case-control study	195	95 normal pregnant women, 50 with preeclampsia, and 50 with severe preeclampsia	Urinary iodine concentration	TSH, OxLDL, aortic augmentation index, pulse wave velocity, Tg	Changes in endothelial dysfunction and thyroid-related indicators across disease severity

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Table 1. Continued...

Author (Year)	Country	Study Design	Sample Size	Study Population/ Grouping	Iodine Nutrition Indicator	Immune-related Biochemical Markers	Main Outcome
Businge (2022)[19]	South Africa	Case-control/cross-sectional study	153	51 normal pregnant women, 51 with preeclampsia, and 51 with severe preeclampsia/eclampsia	Urinary iodine concentration and urinary iodine-to-creatinine ratio	Tg, TSH, FT3, FT4, NO	Gradient of iodine deficiency and thyroid function changes across disease severity
Businge (2023)[20]	South Africa	Case-control study	180	60 normal pregnant women vs 120 women with preeclampsia	Urinary iodine concentration	TPOAb, TSH, FT3, FT4, Tg	Thyroid autoimmunity and iodine status in preeclampsia
Queiroz (2025)[21]	Brazil	Cross-sectional study (HDP only)	250	Comparison among HDP subtypes	Urinary iodine concentration	TSH, anti-TPO	Differences in urinary iodine and thyroid function in pregnant women with hypertensive disorders
Businge (2025)[22]	Democratic Republic of the Congo	Case-control study	360	240 women with preeclampsia vs 120 non-preeclamptic pregnant women	Urinary iodine concentration	TSH, FPG, OxLDL/Alb, K^{+}/Mg^{2+}, lymphocyte percentage, CRP, GGT, NO, Se	Multi-biomarker screening for preeclampsia
Charoenratana (2016)[12]	Thailand	Cohort study	399	Pregnant women	Urinary iodine	TSH, FT4, CRP	Evaluation of thyroid-immune interaction in pregnancy
Yang (2018)[6]	China	Cohort study	2347	Pregnant women	Urinary iodine	TSH, FT4, CRP	Evaluation of thyroid-immune interaction in pregnancy

Table 1. Continued...

Author (Year)	Country	Study Design	Sample Size	Study Population/ Grouping	Iodine Nutrition Indicator	Immune-related Biochemical Markers	Main Outcome
Xiao (2017)[7]	China	Cohort study	1569	Pregnant women	Urinary iodine	TSH, FT4, CRP	Evaluation of thyroid-immune interaction in pregnancy
Reische (2021)[11]	United States	Cohort study	450	Pregnant women	Urinary iodine	TSH, FT4, CRP	Evaluation of thyroid-immune interaction in pregnancy

CAT: catalase; FPG: fasting plasma glucose; FRP: ferric reducing power; FT3: free triiodothyronine; FT4: free thyroxine; GGT: gamma-glutamyl transferase; HDP: hypertensive disorders of pregnancy; NO: nitric oxide; OxLDL: oxidized low-density lipoprotein; Se: selenium; SOD: superoxide dismutase; T3: triiodothyronine; T4: thyroxine; TBARS: thiobarbituric acid-reactive substances; Tg: thyroglobulin; TgAb: thyroglobulin antibody; TPOAb: thyroid peroxidase antibody; TSH: thyroid-stimulating hormone; UIC: urinary iodine concentration.

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Primary Meta-analysis of Urinary Iodine Levels and Hypertensive Disorders of Pregnancy

Using pregnant women with HDP or preeclampsia as the case group and healthy pregnant women as controls, urinary iodine levels were pooled under a random-effects model. The results showed that urinary iodine levels were overall lower in the case group than in the control group, with a pooled effect of MD = −143.647 μg/L (95% CI: −256.362 to −30.933), and the difference was statistically significant (p=0.0125). Heterogeneity testing indicated substantial between-study variability, with I^2=97.80%. Looking at the individual studies, the effect directions were generally consistent across the 4 included studies, all showing lower urinary iodine levels in cases than in controls: the mean differences were −166.400 μg/L in Gulaboglu 2010, −43.550 μg/L in Cuellar-Rufino 2017, −63.990 μg/L in Businge 2022, and −293.270 μg/L in Businge 2025.

These findings indicate that women with HDP generally exhibit lower urinary iodine levels, suggesting a statistical association between abnormal iodine nutrition and disease occurrence. It should be noted, however, that heterogeneity was high in this part of the analysis, indicating marked differences across studies in population source, case definition, disease severity, timing of measurement, and background regional iodine status. For example, some studies focused on severe preeclampsia, whereas others enrolled the broader spectrum of HDP, and differences across disease spectra may have produced differences in biochemical alterations. In addition, some study data were converted from medians and quartiles, which may also have contributed to result fluctuation. Accordingly, this result is better understood as a clear overall trend in direction, though with variation in magnitude, rather than as an effect size suitable for precise extrapolation. Detailed results are shown in Figure 2.

In addition, the included studies had different inclusion criteria for disease severity: some subjects were limited to severe preeclampsia, while others covered all types of HDP. Existing qualitative data showed that urinary iodine concentration gradually decreased and oxidative stress markers increased with the aggravation of preeclampsia severity, indicating that the degree of iodine abnormality and related metabolic disturbance may be correlated with HDP severity. Due to the inconsistent severity classification standards of each study, quantitative subgroup analysis could not be performed.

The extremely high heterogeneity (I^2=97.80%) of urinary iodine pooled results is derived from multiple aspects: First, the included studies were conducted in different countries and regions, and the baseline iodine nutritional level of local pregnant women was significantly different. Second, the research objects covered severe preeclampsia and mixed HDP populations, with inconsistent disease composition. Third, partial data were converted from median and quartile to mean and standard deviation, which introduced conversion errors. Fourth, the time of urine sample collection and laboratory detection methods varied among studies. All the above factors jointly led to high between-study heterogeneity.

Considering the limited number of included quantitative studies and the existence of data conversion, formal leave-one-out sensitivity analysis was not performed. Qualitative stability evaluation showed that all 4 individual studies had consistent effect directions: urinary iodine level in HDP/preeclampsia group was lower than that in the control group, which indicated that the overall pooled trend was stable and reliable.

Effect Analysis of Urinary Iodine Exposure Levels and the Risk of Hypertensive Disorders of Pregnancy

For the exposure–outcome relationship, this analysis should not be interpreted as providing a stable summary effect. Rather, it suggests that deviation from an appropriate iodine range may be associated with HDP risk, but the available studies remain too heterogeneous to support a unified quantitative conclusion. The random-effects model yielded an overall effect of exp(theta) = 0.830 (95% CI: 0.023 to 29.393), with no statistically significant difference (p=0.9186) and substantial heterogeneity (I^2=86.58%).

Closer inspection of the individual studies showed that the directions of effect were not consistent. In de Morais 2020, compared with the UIC 150–249 μg/L group, pregnant women with UIC ≥ 250 μg/L had a higher adjusted risk of HDP, with RR = 4.60 (95% CI: 1.172–18.062). By contrast, Yang 2018 showed that, using UIC < 50 μg/L as the reference, the adjusted OR for preeclampsia in the UIC 150–249 μg/L group was 0.12 (95% CI: 0.013–1.119), suggesting in direction that an adequate urinary iodine level might be protective. Because the 2 studies differed in reference-group definition, exposure stratification, and outcome definition, the pooled analysis did not yield a stable significant result. This indicates that the current

evidence is more supportive of the general proposition that abnormal urinary iodine exposure may be associated with the risk of HDP, rather than supporting a single-direction, uniform-strength risk conclusion.[6,8] The pooled results are shown in Figure 3.

This pooled analysis combined adjusted OR and RR from 2 studies with different designs, which was an important reason for the non-significant overall result and high heterogeneity. The difference in reference group setting, confounding factor adjustment items, and statistical indicators made the pooled effect unable to reflect a unified risk relationship.

The definition of urinary iodine exposure categories was highly heterogeneous across studies: the cut-off value of iodine deficiency/excess, the setting of reference group, and the number of stratification groups were not unified, which directly affected the comparability of risk effect values and led to the unstable results of combined OR/RR.

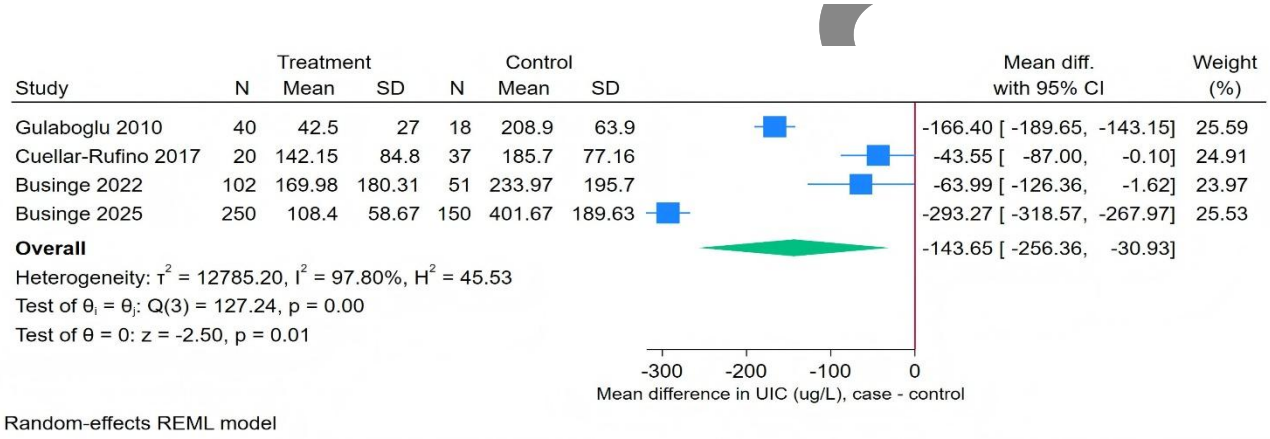

Figure 2. Forest Plot of the Difference in Urinary Iodine Levels Between Women with HDP/Preeclampsia and Controls

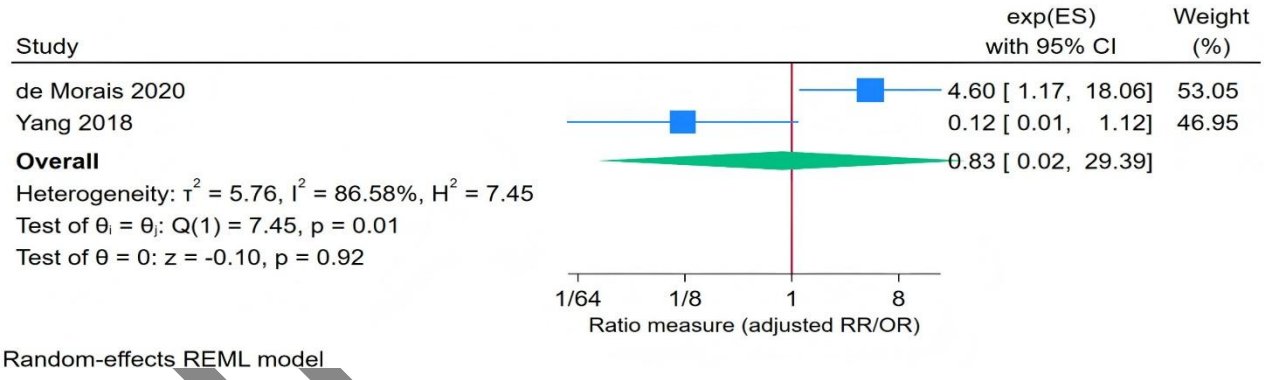

Figure 3. Forest Plot of Different Urinary Iodine Exposure Levels and the Risk of HDP/Preeclampsia

Quantitative Meta-analysis of Immune-Related Biochemical Markers

In line with the study objective concerning "immune-related biochemical markers," thyroid function-related indicators were included in a secondary meta-analysis (Table 2). The markers currently amenable to quantitative pooling were mainly TSH, FT4, and FT3. Strictly speaking, these 3 are not classical inflammatory cytokines, but they are closely related to immune tolerance during pregnancy, iodine nutritional status, the thyroid immune-endocrine axis, and placental dysfunction; for this reason, they can be regarded as the core quantifiable component of "immune-related biochemical markers" within the framework of the present study.

Meta-analysis of TSH

Five studies were included in the pooled analysis of

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TSH. Under the random-effects model, TSH levels in the case group showed an upward trend relative to controls, with a pooled MD of 0.879 mIU/L (95% CI: −0.555 to 2.313), but the difference did not reach statistical significance (p=0.2295), and heterogeneity was high (I^2=98.67%). Among individual studies, Businge 2025 produced the largest effect size, showing a 3.790 mIU/L increase in the case group relative to controls, whereas the remaining studies had relatively smaller effect sizes, most fluctuating around the null.

These results suggest that although TSH showed an upward trend in some studies, it did not yield stable and consistent quantitative evidence overall. The high heterogeneity indicates that TSH does not change uniformly across populations, disease spectra, and thyroid function backgrounds. Accordingly, within the present study, TSH is better treated as an auxiliary indicator that may participate in the immune-endocrine abnormalities of HDP rather than as the most stable quantitative abnormal signal. The pooled effect for TSH is shown in Figure 4.

Meta-analysis of FT4

Three studies were included in the pooled analysis of FT4. The random-effects model showed that FT4 levels were lower in the case group than in controls, with a pooled MD of −1.007 pmol/L (95% CI: −1.660 to −0.354), a statistically significant difference (p=0.0025), and low heterogeneity (I^2=0%). At the individual-study level, both Cuellar-Rufino 2017 and Businge 2022 showed lower FT4 in cases, and the difference in Businge 2022 reached statistical significance.

Among all secondary indicators in this study, FT4 was the most stable. This result suggests a relatively consistent downward trend in FT4 among women with HDP, which may reflect the combined effects of abnormal iodine nutrition, dysregulated thyroid function, and disturbances in the regulatory systems. The forest plot for FT4 is shown in Figure 5.

Meta-analysis of FT3

Two studies were included in the pooled analysis of FT3. The random-effects model showed no statistically significant difference in FT3 between cases and controls, with a pooled MD of 0.066 pmol/L (95% CI: −0.865 to 0.997; p=.8895) and high heterogeneity (I^2=93.90%). The forest plot for FT3 is shown in Figure 6.

Table 2. Summary of quantitative meta-analysis results

Outcome	No. of Studies	Effect Size Type	Pooled Effect (95% CI)	*p*	I^2 (%)	Interpretation
Urinary iodine level (HDP/PE cases vs controls)	4	MD	−143.647 (−256.362 to −30.933)	0.0125	97.80	Urinary iodine levels were significantly lower in cases than in controls
Urinary iodine exposure and risk of HDP/PE	2	Ratio effect[a]	0.830 (0.023 to 29.393)	0.9186	86.58	The pooled result was not significant and heterogeneity was high
TSH	5	MD	0.879 (−0.555 to 2.313)	0.2295	98.67	The case group showed an upward trend, but the difference was not statistically significant
FT4	3	MD	−1.007 (−1.660 to −0.354)	0.0025	0	Cases had significantly lower FT4 with good consistency
FT3	2	MD	0.066 (−0.865 to 0.997)	0.8895	93.90	No statistically significant pooled difference; directions were inconsistent across studies

Ratio effect estimates were pooled from adjusted RRs and adjusted ORs and should therefore be interpreted with caution.

[b]CI: confidence interval; FT3: free triiodothyronine; FT4: free thyroxine; HDP: hypertensive disorders of pregnancy; MD: mean difference; OR: odds ratio; PE: preeclampsia; RR: relative risk; TSH: thyroid-stimulating hormone.

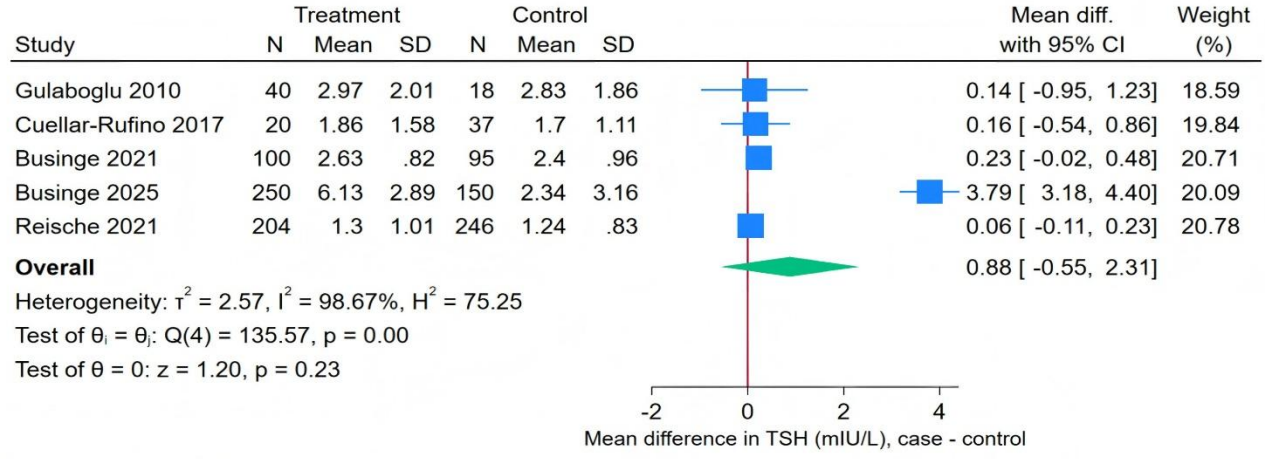

Figure 4. Forest Plot of TSH

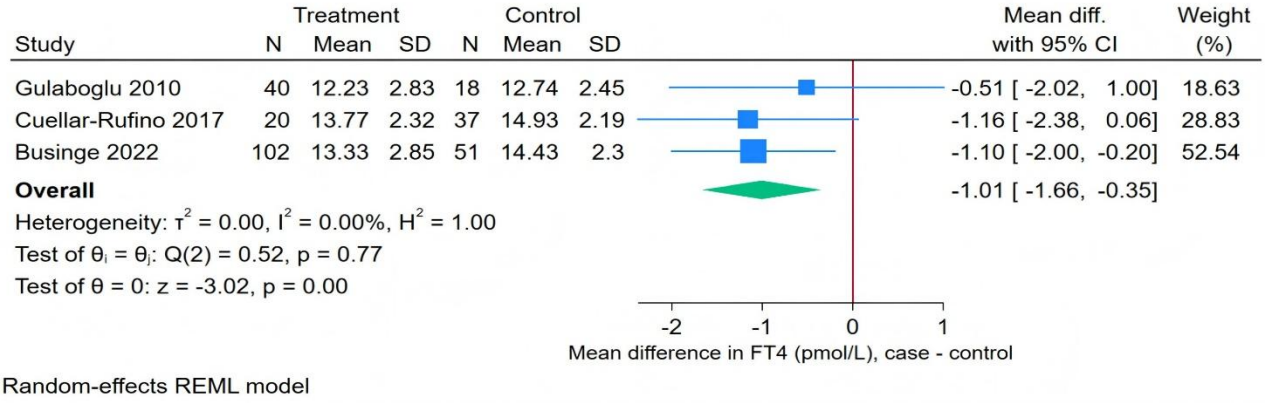

Figure 5. Forest Plot of FT4

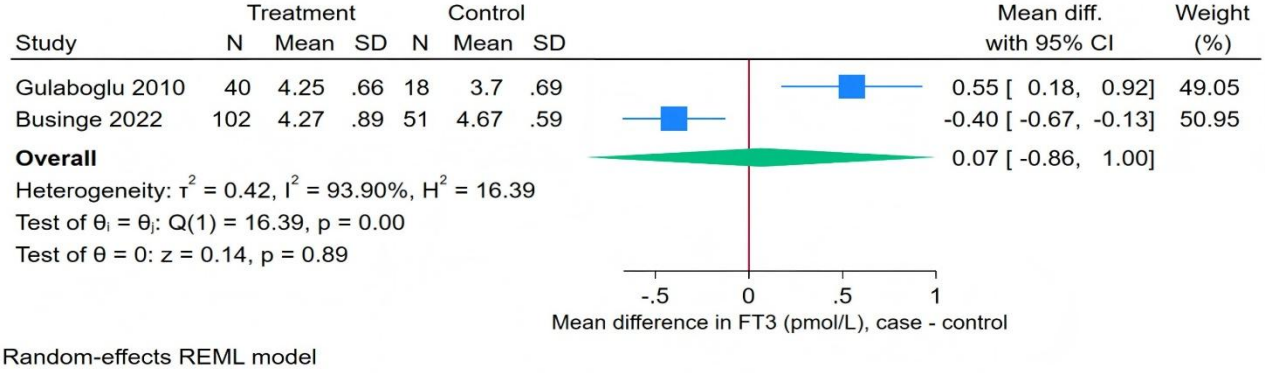

Figure 6. Forest Plot of FT3

Qualitative Synthesis of Immune-related Biochemical Markers

In addition to TSH, FT4, and FT3, the included studies also involved a variety of immune or biochemical indicators relevant to the present topic, including TPOAb/anti-TPO, TgAb, Tg, and several inflammation-, oxidative stress-, and endothelial injury-related markers. Because these indicators were represented by few studies, were reported inconsistently, and in most cases lacked the mean and dispersion data required for quantitative pooling, they were synthesized qualitatively rather than through a unified forest plot.

Thyroid autoimmunity represented by TPOAb and TgAb is an important part of maternal immune homeostasis during pregnancy. Abnormal elevation of these autoantibodies often indicates maternal autoimmune tendency, which can further damage thyroid follicle cells, interfere with thyroid hormone synthesis, and interact with iodine nutritional status. Multiple included studies showed that in iodine-deficient pregnant women, the positive rate and titer of thyroid autoantibodies had an upward trend in preeclampsia patients, but no statistically significant difference was observed in a single study. Different iodine levels also affected the expression of thyroglobulin (Tg): Tg tended to rise in the low-iodine group, which may reflect the compensatory change of thyroid tissue under iodine deficiency. At present, the correlation between thyroid autoimmunity and HDP cannot be confirmed due to limited sample size and inconsistent detection results, but it is speculated that iodine imbalance may aggravate thyroid autoimmune reaction, destroy immune-endocrine balance, and indirectly increase the risk of HDP.

With respect to thyroid autoimmunity-related markers, Xiao et al, in a prospective study conducted in an iodine-sufficient area of China, measured TPOAb, TgAb, and Tg.[7] The results showed no marked differences in TPOAb, TgAb, or TgAb positivity rates across different urinary iodine groups. However, the high urinary iodine group showed higher TSH and lower FT4, whereas the low urinary iodine group showed a tendency toward higher Tg. The main significant outcomes of that study concerned a higher risk of gestational diabetes mellitus with mild iodine deficiency and a higher risk of macrosomia with high urinary iodine, rather than HDP itself.[7]

Regarding the broader relationship among iodine status, thyroid function, and pregnancy outcomes, Yang et al showed that adequate urinary iodine status was associated with a lower incidence of preeclampsia, while clinical hypothyroidism, subclinical hypothyroidism, and some other thyroid abnormalities were related to adverse pregnancy outcomes such as preterm birth, fetal distress, and macrosomia.[6] This study suggests that the interaction between abnormal iodine nutrition and thyroid dysfunction may constitute an important biological basis for adverse pregnancy outcomes.[6]

In the Finnish nested case-control study, Reische et al measured serum iodine, Tg, and TSH and found no significant differences in these indicators between preeclampsia cases and controls, nor were significant associations observed after adjustment.[11] This suggests that not all markers related to iodine nutrition and thyroid function show abnormalities in the same direction across different populations.[11]

Taken together, these studies show that the current evidence for “immune-related biochemical markers” is distinctly unbalanced: thyroid function-related indicators are more repeatedly reported, and FT4 in particular has relatively stable quantitative support; by contrast, thyroid autoantibodies and other immune/inflammatory/oxidative stress markers remain largely limited to single studies or trend-level findings. Therefore, in the present study, the changes of multiple markers suggest possible immune homeostasis disturbance in HDP patients. This state is reflected by the coexistence of thyroid-related biochemical changes and several potential immune-inflammatory signals, although the strength of the evidence is not uniform (Table 3).

Table 3. Qualitative evidence summary of immune-related biochemical markers not included in the quantitative synthesis

Marker	Study	Comparison	Main Finding	Reason Not Included in Quantitative Synthesis
TPOAb / anti-TPO	Businge (2023)[20]	Preeclampsia vs normal pregnancy	TPOAb tended to be higher in preeclampsia, but the difference was not statistically significant	Lack of stable, extractable dispersion data
TPOAb / anti-TPO	Queiroz (2025)[21]	Comparison among HDP subtypes	No significant association was observed between UIC and anti-TPO	No normal control group; only internal comparison among HDP subtypes
TPOAb	Xiao (2017)[7]	Comparison across urinary iodine groups	No clear difference in TPOAb across urinary iodine groups	Not a disease-versus-control comparison
TgAb	Xiao (2017)[7]	Comparison across urinary iodine groups	No clear differences in TgAb level or TgAb positivity across groups	Not a disease-versus-control comparison
Tg	Reische (2021)[11]	Preeclampsia vs control	No significant difference in Tg between cases and controls	The study used serum iodine and did not follow the urinary iodine main line
Tg	Xiao (2017)[7]	Comparison across urinary iodine groups	Tg showed a U-shaped trend, with a tendency to increase in the low-iodine group	The primary outcome was not HDP/PE
CRP	Businge (2025)[22]	Preeclampsia vs non-preeclampsia	CRP was elevated in preeclampsia	Single-study evidence
NO	Businge (2022)[19]	Normal pregnancy vs preeclampsia vs severe preeclampsia/eclampsia	NO declined with increasing disease severity	Single-study evidence
NO	Businge (2025)[22]	Preeclampsia vs non-preeclampsia	NO was lower in preeclampsia	Single-study evidence
TBARS	Cuellar-Rufino (2017)[10]	HDP vs normal pregnancy	TBARS was elevated in HDP	Single-study evidence
SOD	Cuellar-Rufino (2017)[10]	HDP vs normal pregnancy	SOD was reduced in HDP	Single-study evidence
CAT	Cuellar-Rufino (2017)[10]	HDP vs normal pregnancy	CAT was reduced in HDP	Single-study evidence
FRP	Cuellar-Rufino (2017)[10]	HDP vs normal pregnancy	FRP was reduced in HDP	Single-study evidence

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Table 3. Continued...

Marker	Study	Comparison	Main Finding	Reason Not Included in Quantitative Synthesis
OxLDL / OxLDL-Alb	Businge (2021)[18]; Businge (2025)[22]	Comparison by disease severity / preeclampsia vs non-preeclampsia	Oxidized lipid-related markers were increased in severe disease or in preeclampsia	Indicator definitions and study designs were not fully consistent, precluding direct pooling
GGT	Businge (2025)[22]	Preeclampsia vs non-preeclampsia	GGT was elevated in preeclampsia	Single-study evidence
Lymphocyte percentage	Businge (2025)[22]	Preeclampsia vs non-preeclampsia	Lymphocyte percentage was lower in preeclampsia	Single-study evidence
K^+/Mg^{2+} ratio	Businge (2025)[22]	Preeclampsia vs non-preeclampsia	K^+/Mg^{2+} ratio was markedly increased in preeclampsia	Not a strictly immune marker; more metabolic/electrolyte-related

CAT: catalase; CRP: C-reactive protein; FRP: ferric reducing power; GGT: gamma-glutamyl transferase; HDP: hypertensive disorders of pregnancy; NO: nitric oxide; OxLDL: oxidized low-density lipoprotein; PE: preeclampsia; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; Tg: thyroglobulin; TgAb: thyroglobulin antibody; TPOAb: thyroid peroxidase antibody; UIC: urinary iodine concentration.

Summary of Findings

This chapter systematically analyzed the relationships among urinary iodine levels, HDP, and immune-related biochemical markers. The results showed that urinary iodine levels were overall lower in women with HDP/preeclampsia than in normal pregnant controls, suggesting a statistical association between abnormal iodine nutrition and disease. The risk-effect analysis did not produce a stable significant overall result, but different studies consistently suggested that abnormal urinary iodine exposure may be related to adverse pregnancy outcomes. The secondary meta-analysis showed that FT4 reduction is currently the most stable abnormality among the immune-related biochemical markers that could be quantitatively pooled. Although TSH and FT3 showed certain trends, they have not yet yielded consistent and robust statistical evidence. For TPOAb/anti-TPO, TgAb, Tg, and other inflammation- and oxidative stress-related markers, existing evidence remains mainly qualitative and is still insufficient to support unified quantitative pooling. Overall, the present study supports a link between abnormal urinary iodine status and HDP with its related immune dysregulation, but the abnormal spectrum of immune markers still requires further clarification and deeper discussion in subsequent work.

DISCUSSION

This systematic review and meta-analysis integrated current evidence on the relationship among urinary iodine status, hypertensive disorders of pregnancy, and immune-endocrine biochemical markers. The pooled analysis showed that women with HDP/preeclampsia had significantly lower urinary iodine levels than normotensive pregnant controls. Among the thyroid-related indicators eligible for quantitative synthesis, FT4 was significantly reduced in HDP cases, whereas TSH and FT3 did not differ significantly between groups. Qualitative evidence further suggested that thyroid autoimmunity, inflammatory activation, oxidative stress, antioxidant defense impairment, and endothelial dysfunction may be involved, as reflected by markers such as TPOAb, TgAb, CRP, nitric oxide, TBARS, SOD, CAT, OxLDL/Alb ratio, GGT, and lymphocyte percentage. Overall, the main finding of this study is not that all immune-related biochemical markers are uniformly abnormal, but that altered urinary iodine status and reduced FT4 represent the clearest current signals linking iodine imbalance with HDP, while evidence for other immune-inflammatory and oxidative markers remains limited and heterogeneous.

The finding that urinary iodine levels were significantly lower in women with HDP/preeclampsia has important biological and clinical implications. Pregnancy is accompanied by increased iodine requirements due to enhanced maternal thyroid hormone synthesis, increased renal iodine clearance, and fetal iodine demand. Insufficient iodine supply may therefore impair maternal thyroid hormone production and adaptive endocrine regulation. These disturbances may further affect placental development, vascular reactivity, endothelial stability, oxidative balance, and maternal immune tolerance. Previous studies have reported markedly lower urinary iodine levels in women with severe preeclampsia compared with healthy pregnant controls, suggesting a possible role of iodine deficiency in disease development.[9] Similarly, Cuellar-Rufino et al observed that women with HDP had lower urinary iodine levels together with increased TBARS and reduced SOD, CAT, and FRP, indicating that iodine imbalance may be accompanied by oxidative stress and weakened antioxidant capacity.[10] The present pooled result supports these observations and suggests that lower urinary iodine is not merely an isolated finding in individual studies, but a group-level feature associated with HDP/preeclampsia.

Nevertheless, the substantial heterogeneity observed in the primary analysis must be interpreted carefully. The pooled estimate showed a significant difference in urinary iodine levels between HDP cases and controls, but the heterogeneity was high. This likely reflects real differences across studies rather than simple statistical noise. First, the included populations differed in disease spectrum, with some studies focusing on severe preeclampsia and others including broader categories of HDP. Second, baseline iodine nutrition varied by geographic region, meaning that the same urinary iodine concentration may have different biological implications in iodine-deficient, iodine-sufficient, or iodine-excess populations. Third, sampling time, laboratory methods, and statistical reporting formats differed across studies, and some data required transformation from medians and interquartile ranges to means and standard deviations. Therefore, although the overall direction supports lower urinary iodine levels in

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HDP/preeclampsia, the magnitude of this association should be interpreted cautiously.

The high heterogeneity of the primary outcome was not accidental. Regional iodine status, disease spectrum, data conversion, and experimental methods are the main sources. Therefore, the pooled effect value can only reflect the overall trend, rather than a fixed numerical conclusion.

The risk evidence also suggests that the relationship between iodine status and HDP may not be strictly linear. Some studies have indicated that low urinary iodine is associated with higher risk of preeclampsia, whereas others have suggested that high iodine status may also be linked to HDP.[6,8] These findings are not necessarily contradictory. Rather, they imply that deviation from an optimal iodine range, whether through deficiency or excess, may be unfavorable during pregnancy. This is consistent with the biological role of iodine in thyroid regulation: both inadequate and excessive iodine intake can disturb thyroid hormone synthesis and feedback control. The available studies used different exposure categories, reference groups, outcome definitions, and adjustment strategies, which limits the ability to generate a stable pooled risk estimate. Thus, the current evidence should be interpreted as supporting a possible association between abnormal iodine status and HDP risk, while not yet allowing a definitive conclusion regarding dose-response pattern or threshold effects.

The current evidence suggests a non-linear (U-shaped) relationship between urinary iodine status and HDP, with higher risk at both insufficient and excessive iodine levels and comparatively lower risk around the WHO-recommended moderate range (150 – 249 μg/L). However, because studies vary in exposure measurement (e.g., timing and assay of urinary iodine), categorization thresholds, and population characteristics, the available stratified findings are not yet sufficient to establish a fully consistent quantitative dose – response curve across studies. Overall, the pattern is plausible and supported qualitatively, but the exact shape and magnitude of risk change across iodine concentrations remain uncertain and warrant further harmonized quantitative verification.

Among the immune-endocrine markers examined, FT4 emerged as the most consistent biochemical abnormality. The quantitative synthesis showed that FT4 levels were significantly lower in women with HDP/preeclampsia than in controls, with low between-study heterogeneity. This finding is particularly important because FT4 provides a mechanistic link between iodine status, thyroid function, and pregnancy vascular pathology. Thyroxine is essential for placental development, trophoblast function, metabolic adaptation, and vascular regulation. Reduced FT4 may reflect impaired thyroid hormone availability in the setting of abnormal iodine nutrition and may contribute to placental dysfunction, endothelial injury, and inflammatory activation. Previous studies have shown that maternal iodine status and thyroid dysfunction are associated with adverse pregnancy outcomes, including preeclampsia, preterm birth, fetal distress, and abnormal fetal growth.[6,7] Therefore, the reduced FT4 observed in this meta-analysis may represent a relatively stable endocrine signal within the broader process of iodine-related immune-endocrine dysregulation in HDP.

FT4 is identified as the most stable and valuable core biomarker for the following biological reasons: First, FT4 is the major circulating prohormone and reflects thyroid hormone synthesis influenced by iodine availability. In peripheral blood it may fluctuate less than TSH in response to short-term physiologic changes, and therefore can serve as a relatively stable indicator of thyroid hormone status. Second, during pregnancy, placental development, trophoblast function, and vascular endothelial stability are highly dependent on FT4, so the change of FT4 is closely linked to the core pathological lesions of HDP. Third, FT3 is mainly transformed from FT4 in peripheral tissues, with a small overall concentration and large fluctuation in disease state; TSH is easily interfered by gestational age, autoimmunity, and regional reference range. Therefore, FT4 has better specificity and stability in reflecting the combined changes of iodine disorder and HDP.

In contrast, TSH and FT3 did not show significant pooled differences between HDP cases and controls. This does not necessarily mean that they are unrelated to HDP. TSH is highly dependent on gestational age, population-specific reference intervals, thyroid reserve, iodine exposure, autoimmunity, and laboratory methodology. FT3 may also vary according to disease stage, compensatory thyroid adaptation, nutritional status, and systemic illness. The absence of significant pooled differences therefore more likely reflects the complexity and variability of thyroid adaptation during pregnancy rather than a complete lack of biological relevance. Under the current evidence base, however, FT4 appears to be a more stable and interpretable marker

than TSH or FT3 in the context of HDP/preeclampsia.

The qualitative findings on immune-related biochemical markers provide further mechanistic clues. Thyroid autoantibodies such as TPOAb, anti-TPO, and TgAb may reflect autoimmune susceptibility and altered maternal immune tolerance. However, available studies have not shown consistent differences in these markers across iodine categories or between HDP and control groups.[7,11] Similarly, inflammatory and oxidative stress markers have been reported inconsistently. Some studies suggest increased oxidative damage and reduced antioxidant defense in HDP, as indicated by higher TBARS and lower SOD, CAT, and FRP.[10] Other markers, including CRP, nitric oxide, OxLDL/Alb ratio, GGT, and lymphocyte percentage, have been evaluated in limited studies and remain insufficient for quantitative synthesis. These findings suggest that immune dysregulation in HDP is unlikely to be captured by a single biomarker. Instead, it may involve interconnected abnormalities in thyroid function, oxidative stress, inflammatory activation, antioxidant capacity, and endothelial injury.

Iodine imbalance can activate oxidative stress pathways and induce endothelial injury: Iodine deficiency combined with thyroid dysfunction will reduce the activity of antioxidant enzymes such as SOD and CAT, weaken the body's antioxidant capacity (decreased FRP); meanwhile, lipid peroxidation products such as TBARS and OxLDL are massively accumulated, causing oxidative damage to vascular endothelial cells. Continuous oxidative stress further reduces the synthesis of nitric oxide (NO), destroys vascular diastolic function, and finally leads to endothelial dysfunction, which is an important intermediate link between iodine disorder and HDP.

The present study therefore helps clarify the current evidence hierarchy. At the strongest level, the meta-analysis supports a significant association between lower urinary iodine levels and HDP/preeclampsia. At the biochemical level, reduced FT4 appears to be the most consistent immune-endocrine abnormality. At the exploratory level, thyroid autoantibodies and oxidative-inflammatory markers provide plausible mechanistic signals but remain insufficiently standardized and too sparsely reported for firm quantitative conclusions. This layered interpretation is important because it avoids overstatement. The evidence does not support a fully unified abnormal immunobiochemical profile in all women with HDP. Instead, it suggests that iodine-related thyroid dysfunction, especially reduced FT4, may represent a central and relatively measurable component of the broader immune-endocrine and oxidative-inflammatory imbalance associated with HDP.

This study has several limitations. First, only 13 studies were included in the systematic review, and 6 contributed to quantitative synthesis, limiting the precision and stability of pooled estimates. Second, heterogeneity was substantial in the urinary iodine analysis, which stemmed from variations in study population, disease definition, iodine status, sampling gestational age, laboratory methods, and data reporting. Third, many immune-related biochemical markers were reported in only 1 or a few studies, preventing robust meta-analysis. Fourth, urinary iodine concentration reflects recent iodine intake and may not fully represent long-term iodine status at the individual level. Finally, adjusted ORs and RRs were not always comparable across studies because of differences in exposure categories, reference groups, and covariate adjustment. Given the limited number of included studies (<10), formal publication bias tests were unavailable, and potential selective publication of positive results may introduce bias. Additionally, 1 study adopted serum iodine instead of urinary iodine; the 2 indicators differ in biological implications and comparability, causing extra analytical bias. These limitations indicate that the findings should be interpreted as an integrated summary of the current evidence landscape rather than definitive proof of causality.

Future studies should use standardized definitions of HDP and preeclampsia, collect urinary iodine and thyroid function data at clearly defined gestational time points, and report iodine categories according to internationally recognized criteria. In addition, future research should incorporate a broader but standardized panel of immune-endocrine, oxidative stress, inflammatory, and endothelial markers, including FT4, TSH, FT3, thyroid autoantibodies, CRP, nitric oxide, antioxidant enzymes, lipid oxidation products, and endothelial injury markers. Large prospective cohort studies are especially needed to clarify whether abnormal iodine status precedes HDP onset and whether reduced FT4 mediates the relationship between iodine imbalance and hypertensive pregnancy complications.

In summary, this study suggests that altered urinary iodine status is associated with HDP/preeclampsia and that reduced FT4 is the most consistent biochemical

abnormality identified. Evidence for TSH, FT3, thyroid autoantibodies, inflammatory markers, oxidative stress indicators, and endothelial dysfunction markers remain less stable, although these markers provide important mechanistic clues. Taken together, the findings support the hypothesis that iodine imbalance may contribute to HDP through thyroid dysfunction, immune-endocrine dysregulation, oxidative stress, and endothelial inflammatory activation.

This systematic review and meta-analysis suggest that altered urinary iodine status is associated with HDP/preeclampsia, with affected women showing significantly lower urinary iodine levels than controls despite substantial heterogeneity. Among thyroid-related markers, reduced FT4 was the most consistent biochemical abnormality, whereas TSH and FT3 showed no stable differences. Evidence for thyroid autoantibodies, inflammatory markers, oxidative stress indicators, and endothelial dysfunction markers remains limited and inconsistent. Overall, abnormal iodine status may contribute to HDP through thyroid dysfunction, immune-endocrine dysregulation, oxidative stress, and endothelial activation, but further large-scale prospective studies using standardized iodine and biomarker assessments are needed.

STATEMENT OF ETHICS

Not applicable. This study is a systematic review and meta-analysis of previously published literature.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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None.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article and its cited reference sources.

AI ASSISTANCE DISCLOSURE

Not applicable.

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