ORIGINAL RESEARCH ARTICLE

A comparative study on the clinical efficacy and pregnancy outcomes of methimazole and propylthiouracil in managing pregnancy complicated with hyperthyroidism

DOI: 10.29063/ajrh2024/v28i10.14

*Wanjing Hu, Liangjiang Wang, Julian Jiang, Jingwei Li and Lihong Jiang**

Gynecology and obstetrics, Taizhou Women and Children's Hospital of Wenzhou Medical University, TaiZhou, 318000, China

***For Correspondence:** Email: *pvxqzh75123dhclc@163*; Phone: 13736686286

Abstract

The objective of the study was to compare the clinical efficacy and pregnancy outcomes of methimazole and propylthiouracil in managing hyperthyroidism during pregnancy. This retrospective analysis included 100 pregnant women with hyperthyroidism, who were divided into two groups: the methimazole group (Group A) and the propylthiouracil group (Group B). Indicators such as thyroid function, liver function, pregnancy outcomes, and newborn health were closely monitored. The results revealed that both groups experienced a reduction in thyroid function indicators, with Group B showing a more modest decrease. Group B exhibited a higher incidence of liver injury but also achieved more full-term pregnancies. There were no significant differences in adverse reactions, miscarriage rates, or cesarean rates between the two groups. Apgar scores were higher in Group B, while neonatal weights were comparable. We conclude that propylthiouracil improved thyroid function more substantially than methimazole although it was associated with a higher risk of liver injury. *(Afr J Reprod Health 2024; 28 [10]: 141-147).*

Keywords: Methimazole, Propylthiouracil, Pregnancy, Hyperthyroidism

Résumé

L'objectif de l'étude était de comparer l'efficacité clinique et les issues de grossesse du méthimazole et du propylthiouracile dans la gestion de l'hyperthyroïdie pendant la grossesse. Cette analyse rétrospective a inclus 100 femmes enceintes atteintes d'hyperthyroïdie, réparties en deux groupes : le groupe méthimazole (groupe A) et le groupe propylthiouracile (groupe B). Des indicateurs tels que la fonction thyroïdienne, la fonction hépatique, l'issue de la grossesse et la santé des nouveau-nés ont été étroitement surveillés. Les résultats ont révélé que les deux groupes ont connu une réduction des indicateurs de la fonction thyroïdienne, le groupe B présentant une diminution plus modeste. Le groupe B présentait une incidence plus élevée de lésions hépatiques, mais réalisait également davantage de grossesses à terme. Il n'y avait aucune différence significative en termes d'effets indésirables, de taux de fausses couches ou de césariennes entre les deux groupes. Les scores d'Apgar étaient plus élevés dans le groupe B, tandis que les poids néonatals étaient comparables. Nous concluons que le propylthiouracile améliore la fonction thyroïdienne de manière plus substantielle que le méthimazole, bien qu'il soit associé à un risque plus élevé de lésions hépatiques. *(Afr J Reprod Health 2024; 28 [10]: 141-147).*

Mots-clés: méthimazole, propylthiouracile, grossesse, hyperthyroïdie

Introduction

Hyperthyroidism is a frequently encountered endocrine disorder, particularly prevalent during pregnancy[1]. When pregnancy is complicated by hyperthyroidism, it can adversely affect the health of both the mother and the baby, leading to complications such as gestational hypertension, preterm birth, and intrauterine growth restriction[2-3]. Thus, administering effective treatment for pregnancy-related hyperthyroidism is essential. Currently, propylthiouracil and methimazole are the primary medications used to treat hyperthyroidism[4]. Both drugs have proven effective in improving thyroid function and reducing adverse reactions[5]. They function by inhibiting thyroid peroxidase, which suppresses the coupling of tyrosine and iodination, ultimately decreasing thyroid hormone synthesis[6]. Importantly, these medications do not affect iodine absorption or the release of pre-synthesized hormones. Nevertheless, there is a relative lack of comparative studies examining the

use of propylthiouracil and methimazole for managing hyperthyroidism during pregnancy[7-8]. Therefore, this study aims to compare the clinical efficacy and pregnancy outcomes of these two medications in pregnant patients with hyperthyroidism, providing clinicians with improved treatment options and guidance.

Methods

General information

A total of 116 pregnant women with hyperthyroidism were collected from the electronic medical system of the hospital from August 2020 to August 2022. Then, according to the inclusion and exclusion criteria, 100 patients meeting the requirements were finally screened. Subsequently, our hospital's obstetrics department (Taizhou Women and Children's Hospital of Wenzhou Medical University, TaiZhou, China) (Our hospital has extensive experience in managing thyroid disorders, with a dedicated endocrinology department specializing in the treatment of hyperthyroidism, particularly during pregnancy. The team employs a multidisciplinary approach, integrating endocrinologists, obstetricians, and pediatricians to ensure optimal maternal and fetal outcomes) conducted a retrospective analysis of 100 pregnant women with hyperthyroidism. Inclusion criteria: Clinically diagnosed cases of pregnancy-related hyperthyroidism that match relevant diagnostic criteria[9]; singleton pregnancy in the cephalic presentation confirmed by ultrasound; first-time use of the treatment regimen; normal liver function; high compliance and good adherence; complete clinical data is available for the patients.

Exclusion criteria: Patients with known allergy or contraindications to the study drugs; patients with a history of recurrent miscarriage; comorbid with other endocrine diseases; patients with heart, liver, or kidney dysfunction; patients with psychiatric disorders; comorbid infectious or immune disorders. These women were categorized into two groups based on their treatment. The group receiving methimazole was designated as Group A (50 cases), while the group receiving propylthiouracil was designated as Group B (50 cases). The average age of patients in group A was 28.45±0.81 (21 to 38) years, and the average gestational age was 36.53±0.52 (35 to 42) weeks. The duration of hyperthyroidism was 5 months to 12 years, with an average of 2.32±0.43 years. There were 32 primiparous and 18 multiparous women in this group. The average age of patients in group B was 28.20±1.13 (22 to 38) years, and their average gestational age was 38.34±1.35 (35 to 42) weeks. The duration of hyperthyroidism in this group was 6 months to 13 years, with an average of 2.55±0.72 years, and there were 34 primiparous and 16 multiparous women. Patient age, duration of hyperthyroidism, gestational age, and parity did not exhibit statistically remarkable differences between groups (P>0.05), illustrating their comparability (Table 1). Approval for this study was granted by the hospital's ethics committee. Table 1

Treatment methods

For the first 4 weeks of treatment, both groups were instructed to avoid iodine-containing medications and foods. Throughout the treatment period, complete blood counts, liver and kidney functions, thyroid function, electrocardiograms, and other systemic indicators were closely monitored. In case of any discomfort during treatment, the medications were immediately discontinued the patients were advised to notify the attending physician for appropriate management.

Group A received oral methimazole (Merck Pharmaceuticals (Jiangsu) Co., Ltd., National Medicine Permit J20171078, specifications: 10mg×20 tablets) at a starting dose of 30 mg/day at around the 14th week of pregnancy. The medication was packaged in blister packs, each containing 20 tablets. After improvement of the condition, the dosage was gradually adjusted to 5-10 mg/day, for a continuous treatment period of 8 weeks.

Group B received oral propylthiouracil (Lomapharm Rudolf Lohmann GmbH KG, Registration No. H20150035, specifications: 50mg×100 tablets) at a starting dose of 300 mg/day at around the 10th week of pregnancy. The medication was packaged in bottles containing 100 tablets each. After 3 days of treatment, the patient's thyroid function was checked and, if the hormone levels were stable and the condition improved, the dosage was gradually adjusted to 50-100 mg/day, for a continuous treatment period of 8 weeks.

Observational indicators

Thyroid function indicators (Thyroid-stimulating hormone (TSH), Free thyroxine (FT4), Free

triiodothyronine (FT3), and thyroid antibody indicators (thyroid peroxidase antibodies (TPOAb), anti-thyroglobulin antibodies (TGAb)): All research subjects had fasting venous blood samples collected before treatment and prior to childbirth. Serum was separated by centrifugation (10 minutes at 3000r) for testing using the Architect i2000 automated electrochemiluminescence immunoassay analyzer and radioimmunoassay methods.
Liver function: A comparison of the incidence and timing of liver function damage between the two groups.
Pregnancy outcomes: A comparison of premature birth rates, miscarriage rates, and cesarean section rates between the two groups.
Patient complications: A comparison of the incidence of pregnancy-induced hypertension, gestational diabetes, and heart failure among patients in the two groups.
Apgar score and body weight of newborns: Apgar scores were obtained 5 minutes after birth for the newborns[10].

Statistical analysis

Data were analyzed using SPSS 25.0. Intergroup comparison of measurement data were conducted using independent sample t-tests, while count data were analyzed with the chi-square test. A significance level of $P<0.05$ was set for all tests.

Ethical considerations

This retrospective study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the ethics committee of the Taizhou Women and Children's Hospital of Wenzhou Medical University. Due to the nature of the study, informed consent from individual patients was waived as the data was derived from anonymized medical records. All data handling followed strict confidentiality guidelines to protect patient privacy.

Results

Thyroid function indicators

Initial levels of TSH, FT4, and FT3 did not differ significantly between the groups prior to treatment. However, after the intervention, both groups showed a decline in TSH, FT4, and FT3 levels. Notably, Group B exhibited a smaller reduction in these thyroid hormones compared to Group A, and this difference was statistically significant ($P<0.05$) (Table 1).

Liver function

Group B exhibited a delayed onset of liver function impairment as opposed to Group A ($P<0.05$). Nonetheless, the frequency of liver function damage was notably greater in Group B than in Group A ($P<0.05$) (Table 2).

Pregnancy Outcome

Group B exhibited a substantially greater rate of full-term deliveries than Group A ($P<0.05$). No noteworthy differences were identified in the percentage of preterm births, miscarriages, and cesarean sections between the groups ($P>0.05$) (Table 3).

Patient complications

The overall frequency of adverse reactions in Group A and Group B was 12.00% and 4.00% correspondingly, with no remarkable variation between the two groups ($P>0.05$) (Table 4).

Apgar score and neonatal body weight

At 5 minutes after birth, the Apgar scores for newborns in Group B were higher than those in Group A, with a statistically significant difference ($P<0.05$). Meanwhile, there were no notable differences in neonatal body weight between the groups ($P>0.05$) (Figure 1).

Discussion

Hypermetabolism, heightened appetite, weight loss, palpitations, and profuse sweating are the primary indicators in individuals with hyperthyroidism. If left untreated, it can result in thyrotoxic heart disease, potentially endangering the patient's life[11]. The increased release of endogenous hormones during pregnancy can affect the synthesis and metabolism of thyroid hormones, exacerbating hyperthyroidism and jeopardizing the health of both the mother and the baby[12-13].

Table 1: General information

	Group A (50 cases)	Group B (50 cases)	P
average age	28.45±0.81 (21 to 38) years	28.20±1.13 (22 to 38) years	P>0.05
average gestational age	36.53±0.52 (35 to 42) weeks	38.34±1.35 (35 to 42) weeks	P>0.05
Average duration of hyperthyroidism	2.32±0.43 years (5 months to 12 years)	2.55±0.72 years (6 months to 13 years)	P>0.05
Primipara/Multipara	32/18	34/16	P>0.05

Table 2: Liver function

Group (n)	**Liver function injury (%)**	**Time of occurrence of liver function injury（d）**
A (50)	3 (6.00)	18.94±1.46
B (50)	11 (22.00)	37.60±3.53
χ2/t	5.316	
P	0.021	

Thus, timely regulation of thyroid function is essential for improving the clinical outcomes in pregnant women with hyperthyroidism. At present, methimazole and propylthiouracil are widely acknowledged as the primary treatment choices for addressing hyperthyroidism during pregnancy in clinical practice[14]. Methimazole, in particular, is extensively utilized as a method of controlling hyperthyroidism, credited to its extensive clinical utility, low relapse rate, excellent efficacy, and notable safety profile[15]. Using propylthiouracil offers specific benefits, notably its capacity to minimize effects on fetal thyroid function and decrease the risk of neonatal hypothyroidism, all while maintaining a generally favorable safety profile[16-17]. Nevertheless, individual variations in dosing and other factors can lead to side effects for both medications, highlighting the importance for continued dialogue about the most effective treatment strategies for hyperthyroidism during pregnancy.

The results of this study indicate that following treatment, both groups of patients exhibited a declining trend in the levels of thyroid function indicators TSH, FT4, and FT3. The decrease in TSH, FT4, and FT3 levels in Group B was notably lower when compared to Group A, with a statistically notable difference. This implies that propylthiouracil could be more successful in mitigating the extent of hyperthyroidism. Yet, more comprehensive studies are warranted to assess the long-term safety and efficacy of both methimazole and propylthiouracil in managing hyperthyroidism in expectant mothers.

Additionally, the study findings reveal that liver function impairment developed later in patients of group B than in those of group A, yet the incidence of liver damage in group B was markedly greater than in group A. This indicates that propylthiouracil treatment may increase the risk of liver function damage. This difference could be linked to how each drug affects the patient's internal organs. Methimazole is mainly excreted through the urinary system, while propylthiouracil is primarily metabolized in the liver, leading to varying degrees of liver damage associated with each medication[18-19]. Additionally, research by Hackmon *et al.* has revealed that propylthiouracil can occasionally cause severe hepatotoxic effects, leading to significant liver impairment[20]. Consequently, rigorous liver function monitoring is essential when employing propylthiouracil in the treatment of hyperthyroidism in pregnant women, and suitable measures should be enacted for prompt intervention and management.

Additionally, this study revealed a significantly higher rate of full-term deliveries among patients in group B compared to group A. However, there were no noteworthy differences in the rates of preterm births, miscarriages, and cesarean sections between the two groups. These findings suggest that propylthiouracil may positively influence the full-term delivery rate, though further research is needed to confirm its effects on other pregnancy outcomes. The study also noted a slightly higher prevalence of adverse reactions, including pregnancy-induced hypertension, gestational diabetes, and heart failure, in group A compared to group B. Nonetheless, the overall incidence of adverse reactions didn't exhibit a substantial contrast between the two groups, indicating a generally sound safety profile for both drugs, albeit warranting additional emphasis on the prevention and management of potential complications.

Table 3: Pregnancy outcome (n, %)

Group (n)	Preterm delivery	Abortion	Cesarean section	Full-term delivery
A (50)	4 (8.00)	3 (6.00)	14 (28.00)	29 (58.00)
B (50)	1 (2.00)	2 (4.00)	8 (16.00)	39 (78.00)
χ^2	1.895	0.211	2.098	4.596
P	0.169	0.646	0.148	0.032

Table 4: Pregnancy outcome (n, %)

Group (n)	Hypertensive disorders in pregnancy	Gestational diabetes mellitus	Heart failure	Overall incidence
A (50)	3 (6.00)	2 (4.00)	1 (2.00)	6 (12.00)
B (50)	1 (2.00)	1 (2.00)	0 (0.00)	2 (4.00)
χ^2				2.174
P				0.140

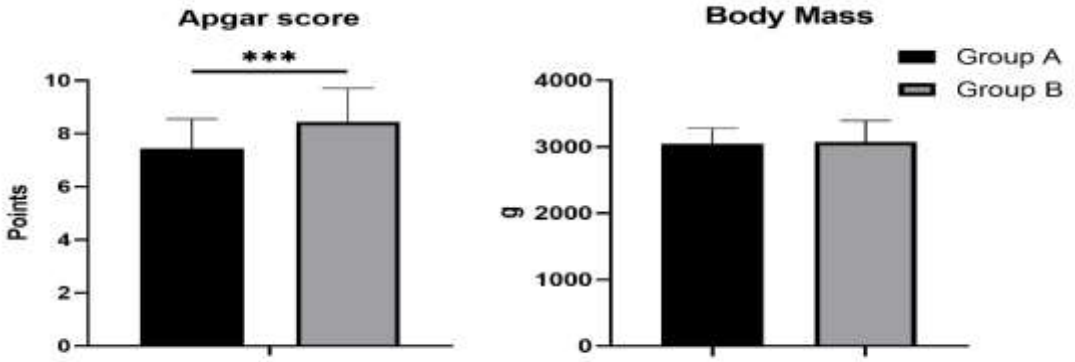

Figure 1: Apgar score and body mass of the infants. ***： $P<0.001$

Lastly, the assessment outcomes of the newborns were juxtaposed. The study revealed a remarkable difference, with the Apgar scores of infants in group B at 5 minutes after birth being higher than those in group A. However, no statistical significance was found in the assessment of birth weight between the two groups of newborns. While this implies a potentially beneficial impact of propylthiouracil treatment on certain newborn indicators, further study is essential to elucidate its effects on other aspects of neonatal outcomes.

Strengths and weaknesses

This study presents several strengths, including its focus on a critical area of maternal health and the comparative analysis of two widely used medications for treating hyperthyroidism during pregnancy. The rigorous design allows for meaningful insights into the efficacy and safety of methimazole and propylthiouracil, providing valuable data for clinicians. However, there are notable weaknesses. The sample size may not adequately represent the broader population, potentially affecting the statistical power of the results. Furthermore, the reliance on existing medical records may lead to inconsistencies in data collection and reporting.

Implications for policy and practice

The findings underscore the importance of careful monitoring and management of hyperthyroidism in pregnant women. Given the differing impacts of methimazole and propylthiouracil on thyroid function and liver health, clinicians should consider these factors when selecting treatment protocols. Policy guidelines may need to be updated to reflect

the nuanced understanding of the safety profiles of these medications, advocating for personalized treatment approaches based on individual patient needs. Moreover, the study highlights the necessity for ongoing research into the long-term effects of these medications on both maternal and neonatal health. Establishing robust monitoring frameworks for liver function and adverse reactions could enhance patient safety and outcomes in clinical practice. Ultimately, these insights may inform clinical guidelines and educational efforts aimed at optimizing care for pregnant women with hyperthyroidism.

In conclusion, this study assessed the clinical effectiveness and pregnancy outcomes of methimazole and propylthiouracil in pregnant women with hyperthyroidism. The findings indicate the potential for propylthiouracil to be more effective in mitigating hyperthyroidism and increasing the rate of full-term deliveries, but its impact on liver function requires monitoring. Furthermore, additional validation and investigation are needed to explore the differences in pregnancy outcomes, complication rates, and newborn indicators between the two patient groups. While these findings provide preliminary guidance for selecting and managing treatment strategies for pregnant women with hyperthyroidism, further research is essential to confirm these results.

Authors' contributions

Wanjing Hu contributed to the conception and design of the study, data collection, and interpretation of the results. Liangjiang Wang played a major role in the data analysis and statistical evaluation. Julian Jiang drafted the manuscript and assisted with literature review. Jingwei Li critically revised the manuscript for important intellectual content. Lihong Jiang provided overall supervision, contributed to the study design, and coordinated the project. All authors reviewed and approved the final manuscript, and agreed to be accountable for all aspects of the work.

Conflicting interests

The authors declare no competing interests

References

1. Marco Aurélio Knippel Galletta, Mayra de Oliveira Demo, Ana Luiza Tonisi Pinto, Rossana Pulcineli Vieira Francisco and Marcelo Zugaib. Demographic, Clinical, and Obstetrical Characterization of Women with Hyperemesis Gravidarum Using a More Restrictive Diagnosis. Clin. Exp. Obstet. Gynecol. 2022, 49(10), 231. https://doi.org/10.31083/j.ceog4910231.
2. Kobaly K and Mandel S J.Hyperthyroidism and Pregnancy[J].*Endocrinol Metab Clin North Am*,2019, 48 (3): 533-545.
3. Yap Y W, Onyekwelu E and Alam U.Thyroid disease in pregnancy[J].*Clin Med (Lond)*,2023, 23 (2): 125-128.
4. Miao Y, Xu Y, Teng P, Liu F Y, Zang Z Y and Gao Y M.Efficacy of propylthiouracil in the treatment of pregnancy with hyperthyroidism and its effect on pregnancy outcomes: A meta-analysis[J].*PLoS One*,2022, 17 (3): e0265085.
5. Francis T, Francis N, Lazarus J H, Stanford S and Mota D M.Safety of antithyroid drugs in pregnancy: update and therapy implications[J].*Expert Opin Drug Saf*,2020, 19 (5): 565-576.
6. Liu Y, Li Q, Xu Y, Zhang S, Chen J H and Yu T Z.Comparison of the safety between propylthiouracil and methimazole with hyperthyroidism in pregnancy: A systematic review and meta-analysis[J].*PLoS One*,2023, 18 (5): e0286097.
7. Abdi H, Amouzegar A and Azizi F. Antithyroid Drugs[J].*Iran J Pharm Res*,2019, 18 (Suppl1): 1-12.
8. Yoshihara A, Luo Y, Ishido Y, Hirose M, Kawamata T, Yamamoto T, Morita K, Watanabe K and Abe Inhibitory effects of methimazole and propylthiouracil on diiodotyrosine deiodinase 1 in thyrocytes[J].*Endocr J*,2019, 66 (4): 349-357.
9. Alexander E K, Pearce E N, Brent G A, Brown R S, Guber H A, La Franchi S H, Scheller N A, Sosa J A and Sullivan S.2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum[J].*Thyroid*,2017, 27 (3): 315-389.
10. Selvaratnam R J, Wallace E M, Davis P G, Smith S J, Johnson M T and Brown M P.The 5-minute Apgar score and childhood school outcomes[J].*Acta Paediatr*,2022, 111 (10): 1878-1884.
11. Fellbrant K, Shahedi Razavi K, Lindgren O, Sjögren G and Löfgren C S.[Hyperthyroidism - a classic disease][J].*Lakartidningen*,2024, 121.
12. Laurberg P and Andersen S L.ENDOCRINOLOGY IN PREGNANCY: Pregnancy and the incidence, diagnosing and therapy of Graves' disease[J].*Eur J Endocrinol*,2016, 175 (5): R219-30.
13. Andersen S L and Andersen S.Hyperthyroidism in pregnancy: evidence and hypothesis in fetal programming and development[J].*Endocr Connect*,2021, 10 (2): R77-r86.
14. Watkins V Y, Dotters-Katz S K and Kuller J A.Treatment for Hyperthyroidism During Pregnancy[J].*Jama*,2024, 331 (9): 798.

15. Vaidyanathan P.Update on Pediatric Hyperthyroidism[J].*Adv Pediatr*,2022, 69 (1): 219-229.
16. Bhagat M, Singh P, Sunkara S M, Jain R and Kumar A. Effects of Methimazole vs Propylthiouracil in Newborns: A Comparative Review[J].*Cureus*,2023, 15 (7): e41505.
17. Mukul Sharma and Afraim Koty. Determination of Antithyroid Drug Propylthiouracil with Ru (III) in Pharmaceutical Formulations and its Characterization, Current Pharmaceutical Analysis,Volume 19, Issue 5, 2023.
18. Fung S C and Wyssusek K H. Hyperthyroidism and propylthiouracil-induced liver failure in pregnancy[J].*Anaesth Intensive Care*,2015, 43 (6): 793-4.
19. Piantanida E, Ippolito S, Gallo D, Santoro C, Colombo M and Frasoldati A.The interplay between thyroid and liver: implications for clinical practice[J].*J Endocrinol Invest*,2020, 43 (7): 885-899.
20. Hackmon R, Blichowski M and Koren G. The safety of methimazole and propylthiouracil in pregnancy: a systematic review[J].*J Obstet Gynaecol Can*,2012, 34 (11): 1077-1086.