

The effect of PTU on Adiponectin levels in hyperthyroid women during early pregnancy

Hussain Sabah Hussain¹,
Ali Abdelhussain Ghazzay²

¹Department of biology, collage of science, Alqadisyia University, Aldiwanya\Iraq

²Department of biology, collage of science, Alqadisyia University, Aldiwanya\Iraq

Abstract: This study aims to find out the effects associated with the use of propylthiouracil for pregnant women with hyperthyroidism on Adiponectin.

The current study was conducted on 60 women with hyperthyroidism and 60 women with normal thyroid glands who attended Al-Diwaniyah Teaching Hospital during the period from February 2022 to May 2023, where they were divided into groups according to the time periods of pregnancy. Adipokine were then measured using the enzyme-linked immunosorbent assay (ELISA) which included Adiponectin

Results: shows that there was significant increase in Adiponectin levels during the treatment with PTU in comparison with control groups starts from the first month of pregnancy and elevating through the third month until the fifth month were it was the higher concentration of Adiponectin

Conclusion: PTU has a positive effect on Adiponectin levels in hyperthyroid pregnant.

Key words: hyperthyroidism, pregnant, PTU, Adiponectin

تأثير عقار بروبييل ثيوراسيل على مستويات الأديبونكتين في النساء المصابات بفرط نشاط الغدة الدرقية أثناء الحمل المبكر

حسين صباح حسين¹ ، علي عبد الحسين غزاي²

¹ قسم علوم الحياة ، كلية العلوم ، جامعة القادسية ، الديوانية / العراق *

² قسم علوم الحياة ، كلية العلوم ، جامعة القادسية ، الديوانية / العراق *

خلاصة

تهدف هذه الدراسة إلى معرفة الآثار المرتبطة باستخدام عقار بروبييل ثيوراسيل للحوامل المصابات بفرط نشاط الغدة الدرقية على الأديبونكتين. أجريت الدراسة الحالية على 60 امرأة مصابة بفرط نشاط الغدة الدرقية و 60 امرأة ذوات عدد درقية طبيعية حضرن مستشفى الديوانية التعليمي خلال الفترة من فبراير 2022 إلى مايو 2023 حيث تم تقسيمهن إلى مجموعتين حسب فترات الحمل. تم بعد ذلك قياس الأديبونكتين باستخدام مقاييس الممتز المناعي المرتبط بالإنزيم (ELISA) والذي تضمن الأديبونكتين النتائج: أظهرت وجود زيادة معنوية في مستويات الأديبونكتين أثناء العلاج ب بروبييل ثيوراسيل مقارنة بمجموعات الضبط التي تبدأ من الشهر الأول من الحمل وترتفع حتى الشهر الثالث حتى الشهر الخامس حيث كان تركيز أعلى. الاستنتاج: بروبييل ثيوراسيل له تأثير إيجابي على مستويات الأديبونكتين في حالة فرط نشاط الغدة الدرقية الحامل.

Introduction

Hyperthyroidism occurs due to an increase in the production and secretion of thyroid hormones, and is represented by a decrease or inhibition of the level of thyroid-stimulating hormone (TSHR), accompanied by an increase in the level of T3 and T4 hormones in the blood and peripheral tissues. (1) In women, hyperthyroidism is associated with menstrual disorders (increased or absent periods) and infertility. (2) As a result, the diagnosis of hyperthyroidism during pregnancy is somewhat difficult. The probability of hyperthyroidism occurring in pregnant women ranges between 0.9% - 0.1, while the probability of occurrence of the disease the clinical and subclinical is about 2%. (3,4) The majority of cases are due to GD graves' disease (90-95%).

Failure to treat hyperthyroidism during pregnancy leads to an increased risk of fetal loss, premature delivery and fetal deformities, in addition to complications in the deterioration of the health of the pregnant woman herself, such as high blood pressure during pregnancy and congestive heart failure (CHF) (5,6) The molecular biology evaluation procedure for the status of the thyroid gland was adopted in great depth, the

receptor stimulating thyroid hormone and the sodium gate, iodine, are among the significant molecules that have been approved and classified in abundance. And a treatment for thyroid diseases and another section under development. (7) Lipid cytokines play an essential role in metabolic control, a lot of recent research has indicated a link between lipid cytokines and thyroid function (8) Medical treatment for hyperthyroidism is represented by anti-thyroid drugs (ATDS) in midterm pregnancy (MMZ), propylthiouracil (PTU) is usually used, and carbimazole is also used because it undergoes metabolic processes that convert to methimazole (9) The thing that causes concern is that the antithyroid drug has a property of penetrating the placenta (10). Even in the case of the presence or absence of a significant difference in the possibility of penetrating the placenta between the two treatments, methimazole and propylthiouracil, there are great recommendations to use the lowest possible therapeutic dose. It is recommended to use propylthiouracil in the first trimester of pregnancy when methimazole is most effective in penetrating the placenta. (11) In addition, PTU is associated with a high affinity for serum albumin, although evidence indicates that the drug crosses the placenta not entirely dependent on protein transit. (12)

Adiponectin:

Adiponectin is an adipokines produced by AT adipose tissue and secreted abundantly into blood serum (range 5-30 ug/ml) representing 0.01% of total serum proteins. (13)

Adiponectin stimulates glucose consumption, inhibits lipolysis and reduces glucose production by the liver, with an important role in the function of insulin sensitivity. (14) All these functions together give an anti-diabetic, anti-inflammatory and anti-atherosclerotic effect. (15) Levels of Adiponectin in the bloodstream are inversely correlated with blood glucose, insulin sensitivity and inflammatory response and are observed to be an indicator of obesity and metabolism related diseases (16)

Adiponectin carries out the biosynthetic function through two transmembrane-coupled protein-coupled receptors, Adipo R1 and Adipo R2, which are widely present in many tissues. (17) The receptors Adipo R1 and Adipo R2 are also present in the cells of the placenta in humans. During pregnancy, Adiponectin plays an essential role in regulating metabolism in both the mother, the fetus, and the placenta as well (18) generally before the second trimester of pregnancy. There is an increase in the structure of adiponectin in the bloodstream, which then decreases as pregnancy progresses. (19) Functionally, adiponectin stimulates the differentiation of trophoblast cells, although this adiponectin may play an essential role in the formation of syncytiotrophoblast (20)

It is secreted in large quantities as an opposite action to increase the sensitivity to insulin, adiponectin secreted by the mother, as it reduces the effect of insulin in the placenta, and thus the transfer of amino acids from the mother to the fetus decreases, which leads to a decrease in fetal growth. (21)

Methodology

Timing and study design

This research was conducted during the period from January 2022 to February 2023. A total of 120 participant in the study (60 patients and 60 control) who attend the center of diabetes in al diwanya hospital and the hospital of gynecology and obstetrics in al diwanya and its districts.

The patients were diagnosed with hyperthyroidism according to the symptoms and hyperthyroidism control test score.

Information were taken about the patients under the supervision of consultant doctor and after getting the approval from the patient himself, information were listed in info-panel.

The groups in this study are as follows:

Control groups

Composed of 60 young healthy euthyroid pregnant, divided into 3 control groups based on the duration of the pregnancy and as following:

Group 1 contains 20 euthyroid pregnant in the first month of pregnancy

Group 2 containing 20 euthyroid pregnant in the third month of pregnancy

Group 3 containing 20 euthyroid pregnant in the fifth month of pregnancy.

Treatment groups are as follows:

Group 4 containing 20 pregnant with hyperthyroidism in the first month of pregnancy

Group 5 containing 20 pregnant with hyperthyroidism in the third month of pregnancy
 Group 6 containing 20 pregnant with hyperthyroidism in the fifth month of pregnancy
 Each of the treatment groups were compared with the same duration of pregnancy of control groups .

Blood samples collection

Peripheral whole blood (5 ml) of was aspirated from each controls and patient groups using plastic disposable syringe. This blood was immediately dispensed into gel tube, and in water bath, allowed to clot for ten minutes at 37C , at that moment were centrifuged at (3000 rpm) for 10 minutes. Then clear serum was obtained and stored frozen at -18 C until being used for hormonal and immunological parameters assay. The hemolysed samples were discarded

Human Adiponectin

Assay Principle

This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). absorbance is measured at 450 nm.

Statistical analysis:

Statistical analysis of the present Data was presented as mean \pm SD. Multiple comparisons were performed using Two-way ANOVA followed by least significant difference (LSD) as a post hoc test. The 0.05 level of probability was used as the criterion for significance. All statistical analyses were performed using SPSS software version 32

Results and discussion

The following table shows the changes in the level of adiponectin in the blood of pregnant women, the PTU-treated groups, compared with the control group, and as shown

Table 3-6 means and SD of Adiponectin in all study groups

| Groups | Period | | | Mean \pm SD |
|---------------------------------|-----------------------|-----------------------|-----------------------|-----------------|
| | 1 st month | 3 rd month | 5 th month | |
| Control | 3.24 \pm 0.93 | 3.82 \pm 0.53 | 4.15 \pm 0.83 | 3.74 \pm 0.85 |
| Treatment | 4.39 \pm 0.2 | 5.21 \pm 0.3 | 9.67 \pm 0.43 | 6.42 \pm 2.36 |
| mean \pm SD | 3.82 \pm 0.88 | 4.51 \pm 0.82 | 6.91 \pm 2.87 | 5.08 \pm 2.22 |
| LSD _{0.05} | 0.266 | | | 0.217 |
| LSD _{0.05} interaction | 0.376 | | | |

There was a significant increase at $P < 0.05$ for the level of adiponectin for the treatment group in the first month G3 compared with the control group G1 as well as among the treatment group in the third month G4 compared with the control group G2 and also a significant increase between the treatment group in the fifth month G6 and the group Control G3, with a significant increase among the treatment group as well, where the highest percentage was in the treatment group in the fifth month of pregnancy G6 and the lowest in the treatment group in the third month G5 and the first month group G4, respectively. A significant increase was also observed among the control groups themselves with the progression of pregnancy where it was more in the group of the fifth month G3, than in the two groups of the third month, G2, and the group of the first month, G1, respectively

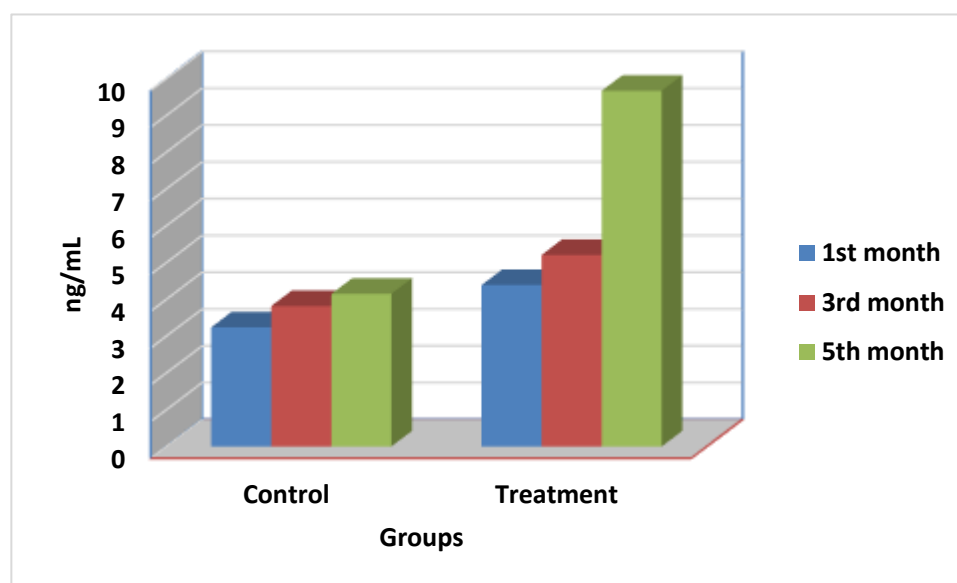


Figure 3-4 means of Adiponectin levels in all study groups

Normal pregnancy has been classified as a diabetogenic state. On the other hand, adipose tissue is currently considered an active organ capable of secreting substances such as adipokines, which play an essential role in the pathogenesis of insulin resistance, in addition to its other functional role. (22). reported that ADP can increase the production of thyroid hormones; particularly FT4(23). Hyperthyroidism is associated with a decrease in fat volume and muscle mass and a decrease in body fat stores, so an increase in the level of ADP may be a compensatory mechanism against insulin resistance in people with hyperthyroidism (24). Pregnancy is a system of endocrine glands and complex metabolic adaptations that aim to provide the appropriate conditions to produce the energy necessary for the growth and development of the fetus (25). Santini et al. indicated that there is no difference in the level of adiponectin in people with hyperthyroidism. (26) Saito et al. state that adiponectin was higher in people with hyperthyroidism compared to healthy people or those with hypothyroidism (27). Aydogan and Sahin, shows that the relationship between the function of thyroid and adipokine is fluctuating, and this is due to several reasons, including Different characteristics of the patient, the presence of autoimmune diseases, and most likely the nutritional states(28) Laboratory study on rats treated with PTU during pregnancy showed that adipokines increased with the progression of pregnancy, (29) While Paredes et al. indicated that overweight pregnant women have lower Adiponectin levels than normal or underweight women (30).

Conclusion:

PTU effect on the levels of Adiponectin that causes to increase its levels during the first and second trimester, that increase could be related to thyroid hormone, a further study should be done.

Recommendation:

We recommend that periodic test should be done to adiponectin for its important in maternal health and fetal development.

References

1. Seo, G.H.; Kim, T.H.; Chung, J.H. Antithyroid Drugs and Congenital Malformations: A Nationwide Korean Cohort Study. *Ann.Intern. Med.* 2018, *168*, 405–413
2. Quintino-Moro, A.; Zantut-Wittmann, D.E.; Tambascia, M.; Machado, H.d.C.; Fernandes, A. High Prevalence of Infertility among Women with Graves' Disease and Hashimoto's Thyroiditis. *Int. J. Endocrinol.* 2014,
3. Cooper, D.S.; Laurberg, P. Hyperthyroidism in Pregnancy. *Lancet Diabetes Endocrinol.* 2013, *1*, 238–249.

4. Dong, A.C.; Stagnaro-Green, A. Differences in Diagnostic Criteria Mask the True Prevalence of Thyroid Disease in Pregnancy: A Systematic Review and Meta-Analysis. *Thyroid Off. J. Am. Thyroid Assoc.* 2019, *29*, 278–289.
5. Andersen, S.L.; Olsen, J.; Wu, C.S.; Laurberg, P. Spontaneous Abortion, Stillbirth and Hyperthyroidism: A Danish PopulationBased Study. *Eur. Thyroid J.* 2014, *3*, 164–172
6. Korevaar, T.I.M.; Muetzel, R.; Medici, M.; Chaker, L.; Jaddoe, V.W.V.; de Rijke, Y.B.; Steegers, E.A.P.; Visser, T.J.; White, T.; Tiemeier, H.; et al. Association of Maternal Thyroid Function during Early Pregnancy with Offspring IQ and Brain Morphology in Childhood: A Population-Based Prospective Cohort Study. *Lancet Diabetes Endocrinol.* 2016, *4*, 35–43.
7. Stathatos, N. Anatomy and physiology of the thyroid gland *The Thyroid and Its Diseases* 2019. (pp. 3-12): Springer.
8. Aydogan Bİ, S. M. Adipocytokines in thyroid dysfunction. *ISRN Inflamm.* (2013). 646271.
9. Moore LE: Thyroid disease in pregnancy: A review of diagnosis, complications and management,2016. *World J Obstet Gynecol* 5: 66-72,.
10. Krassas GE, Poppe K and Glinoeer D: Thyroid function and human reproductive health. 2010,*Endocr Rev* 31: 702-755.
11. Taylor PN and Vaidya B: Side effects of anti-thyroid drugs and their impact on the choice of treatment for thyrotoxicosis in pregnancy,2012. *Eur Thyroid J* 1: 176-185,
12. Momotani N, Noh JY, Ishikawa N and Ito K: Effects of propyl- thiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism,1997. *J Clin Endocrinol Metab* 82: 3633-3636,
13. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int J Mol Sci.* 2017;8:1321.
14. Orrù S, Nigro E, Mandola A, Alfieri A, Buono P, Daniele A, Mancini A, Imperlini E. A functional interplay between IGF-1 and adiponectin. *Int J Mol Sci.* 2017;18:2145.
15. Frankenberg ADV, Reis AF, Gerchman F. Relationship between adiponectin levels, the metabolic syndrome, and type 2 diabetes. *Arch Endocrinol Metab.* 2017;61:614–622.
16. Ruan H, Dong LQ. Adiponectin signaling and function in insulin target tissues. *J Mol Cell Biol.* 2016;8:101–109.
17. Bianco A, Nigro E, Monaco ML, Matera MG, Scudiero O, Mazzarella G, Daniele A. The burden of obesity in asthma and COPD: role of adiponectin. *Pulm Pharmacol Ther.* 2017;43:20–25
18. Castro NP, Euclides VV, Simões FA, Vaz-de-Lima LR, De Brito CA, Luzia LA, Devakumar D, Rondó PH. The relationship between maternal plasma leptin and adiponectin concentrations and newborn adiposity. *Nutrients.* 2017;9:182.
19. Fuglsang J, Skjaerbaek C, Frystyk J, Flyvbjerg A, Ovesen P. A longitudinal study of serum adiponectin during normal pregnancy. *BJOG.* 2006;113:110–113.
20. Benaitreau D, Dos Santos E, Leneveu MC, De Mazancourt P, Pecquery R, Dieudonné MN. Adiponectin promotessyncytialisation of BeWo cell line and primary trophoblast cells. *Reprod Biol Endocrinol.* 2010;8:128.
21. Jones HN, Jansson T, Powell TL. Full-length adiponectin attenuates insulin signaling and inhibits insulin-stimulated amino acid transport in human primary trophoblast cells. *Diabetes.* 2010;59:1161–1170.
22. Ana Bertha Zavalza-Gómez , Roberto Anaya-Prado , Ana Rosa Rincón-Sánchez , José Miguel MoraMartínez Adipokines and insulin resistance during pregnancy. 2008.
23. Fernandez-Real JM, Lopez-Bermejo A, Casamitjana R, Ricart W. Novel interactions of adiponectin with the endocrine system and inflammatory parameters. *Journal of Clinical Endocrinology and Metabolism.* 2003;88:2714–2718.
24. Nese Cinar and Alper Gurlek: Association between novel adipocytokines adiponectin, vaspin, visfatin, and thyroid: An experimental and clinical update,2013.
25. Hauguel de Mouzon S, Lassance L. Endocrine and metabolic adaptations to pregnancy; impact of obesity. *Horm Mol Biol Clin Investig.* 2015;24:65–72.

26. Santini F, Marsilli A, Mammoli C, Valeriano R, Scartabelli G, Pelosini C, *et al.*: Serum concentrations of adiponectin and leptin in patients with thyroid dysfunctions. *J Endocrinol Invest* 2004,
27. T. Saito, T. Kawano, T. Saito et al., “Elevation of serum adiponectin levels in Basedow disease,” *Metabolism*, 2005,vol. 54, no. 11, pp. 1461–1466.
28. Berna Emge Aydogan and Mustafa Sahin : Adipocytokines in Thyroid Dysfunction. 2013
29. Tongjia Xia, Xue Zhang, Datong Deng, Effect of maternal hypothyroidism during pregnancy on insulin resistance, lipid accumulation, and mitochondrial dysfunction in skeletal muscle of fetal rats,2018.
30. Solis Paredes J.M. · Perichart Perera O. · Montoya Estrada A. · Reyes Muñoz E. · Espino y Sosa S. · Ortega Castillo V. · Medina Bastidas D. · Tolentino Dolores M. · Sanchez Martinez M. Nava Salazar S. · Estrada Gutierrez G. Gestational Weight Gain Influences the Adipokine-Oxidative Stress Association during Pregnancy,2021.