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Impact of Different Ovarian Stimulation Protocols on Thyroid Hormone Levels: A Prospective Cohort Study

Buthainah Al-Azzawi[1*]
[1]Department of Biochemistry, College of Medicine, University of Al-Qadisiyah, Iraq

Email: buthainah.al-azzawi@qu.edu.iq

Abstract. Background: Ovarian stimulation is pivotal in assisted reproductive technologies, yet its systemic hormonal effects, particularly on thyroid function, remain underexplored. Specific Background: Estrogen-induced increases in thyroxine-binding globulin and the structural mimicry between hCG and TSH suggest a complex thyroid-ovarian interaction. Knowledge Gap: Prior studies yield conflicting evidence on thyroid hormone alterations during stimulation, with limited attention to regimen-specific effects and longitudinal dynamics in thyroid-naïve women. Aim: This study investigates the temporal impact of distinct ovarian stimulation protocols, Clomid, Pergonal, and their combination, on thyroid hormone levels in euthyroid infertile women. Results: A significant elevation in TSH and reduction in T3/T4 was observed as early as month one in the combination group, month two in the Pergonal group, and month three in the Clomid group ($P<0.05$). Novelty: This study delineates protocol- and time-dependent thyroid disturbances, offering mechanistic clarity on drug-specific endocrine crosstalk. Implications: Findings support tailored thyroid monitoring during ART and propose a stratified approach based on stimulation regimen and exposure duration to prevent potential subclinical hypothyroidism and optimize fertility outcomes.

Highlights:

1. Combination therapy (Clomid + Pergonal) caused the earliest and most significant thyroid disruption-elevated TSH and decreased T3/T4 from Month 1.
2. Thyroid dysfunction varied by stimulation protocol: Clomid-only showed delayed effects (Month 3), while Pergonal-only effects began in Month 2.
3. Clinical recommendation: Thyroid monitoring is crucial during ovarian stimulation, especially with combination regimens.

Keywords: Ovarian Stimulation, Clomiphene Citrate, Pergonal, Thyroid hormones, Infertility

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Introduction

Ovarian stimulation has become essential in assisted reproductive technologies (ART), to facilitate multifollicular growth, which is crucial for good IVF/ICSI result(1). However, there is increasing evidence that these methods cause considerable hormonal swings that affect endocrine systems(2), including thyroid gland function, and may eventually effect reproductive axis. The thyroid-reproductive interface is biologically feasibl because thyroid hormones directly affect ovarian steroidogenesis and endometrial receptivity, and because both systems share complex feedback mechanisms via the hypothalamic-pituitary axis (3).

It has been proposed that there are two primary pathophysiological linkages. The oestrogen surge during stimulation initially boosts hepatic synthesis of thyroxine-binding globulin (TBG), which lowers free thyroxine (fT4) concentrations and causes compensatory TSH elevation via the hypothalamic-pituitary-thyroid axis (4). Between 30 to 40 percent of the amino acid sequences of hCG and TSH are structurally similar, which allows hCG to bind to TSH receptors and generate thyrotropic effects at the pharmaceutical concentrations required to induce ovulation (5). Ironically, despite the possibility of transient hyperthyroidism occurring immediately following hCG administration, the majority of investigations reveal delayed hypothyroid patterns (6).

Clinical evidence is still conflicting in spite of these mechanistic hypotheses. Poppe et al. (2004), showed that gonadotropin stimulation significantly increased TSH (median 44%), especially in women who tested positive for antibodies (3). Müller et al. (2000), also reported 26% decreases in fT4 after COH. On the other hand (2), Reh et al. (2011), discovered that euthyroid women's TSH levels did not significantly alter during IVF cycles (7). This study addresses critical gaps by:

1) Comparing distinct drug regimens (anti-estrogen vs. gonadotropin vs. combination),
2) Evaluating temporal dynamics beyond single-cycle assessments, and
3) Focusing on thyroid-naïve populations without autoimmunity.

Method

Eighty women participate in this study they were divided as following

1) Control group (n=20): Thyroid and infertility-free healthy volunteers.
2) Patients group (n=60): Infertile women with normal baseline thyroid function were

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divided into the following stimulation groups:

Group A (n=20): 100 mg/day of clomiphene citrate, days 2–6 of the cycle.

Group B (n=20): Human menopausal gonadotropin (Pergonal®, 75 IU FSH/LH daily, days 2–8) of the cycle.

Group C (n=20): Clomid (days 2–6) followed Pergonal (days 7–12).

Exclusion criteria include autoimmune disorders, abnormal baseline thyroid levels, and a history of thyroid illness.

Assays for Hormones

ELISA (Abbexa, UK) was used to quantify serum TSH, T3, and T4 at baseline (pre-treatment) and on day 12 of each menstrual cycle for three months in a row.

Mean ± SD is used to express the data. One-way ANOVA and unpaired *t*-tests were employed for comparisons (GraphPad Prism 8.0). Relevance: $P<0.05$.

Results and Discussion

A. Results

Baseline Hormones: No intergroup differences in TSH, T3, or T4 at baseline ($P>0.05$; Figure 1).

Monthly Thyroid Hormone Dynamics: -

Month 1: Group C: Significant increase in TSH ($P<0.05$) and decrease in T4 ($P<0.05$) as compared to control as shown in (Figure 2)

Groups A & B: No significant changes (Figure 2).

Month 2: Groups B & C: significant increase in TSH and decrease in T3and T4 ($P<0.05$) as shown in (Figure 3).

Group A: No significant changes (Figure 3).

Month 3: All groups: Marked increase in TSH while decrease in T3and T4 ($P<0.05$) as compared to control (Figure 4).

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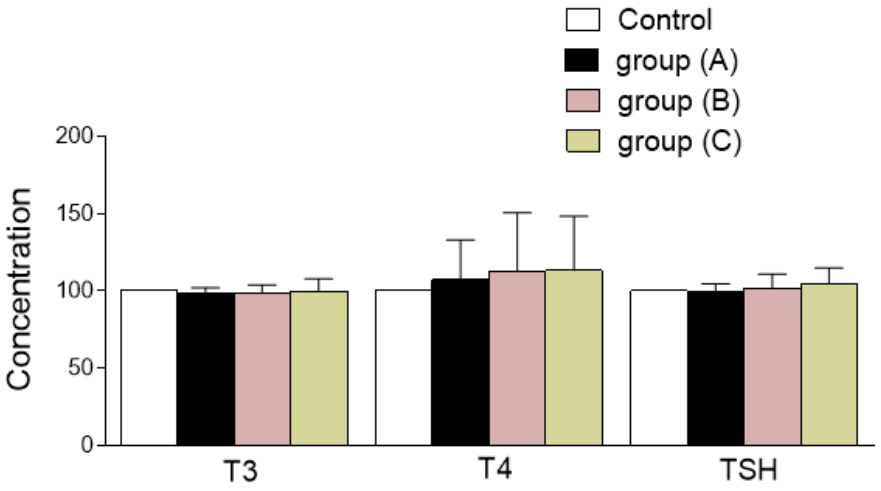

Figure 1. The levels of T3, T4, and TSH hormones were measured (in ng/dL) for the three different ovarian stimulation program groups (A, B, and C). No significant difference was found in measuring the baseline hormone among the different groups as compared to the control group. A refers to (Clomid group), B refers to (Pergonal group), and (C) refers to (Mix group).

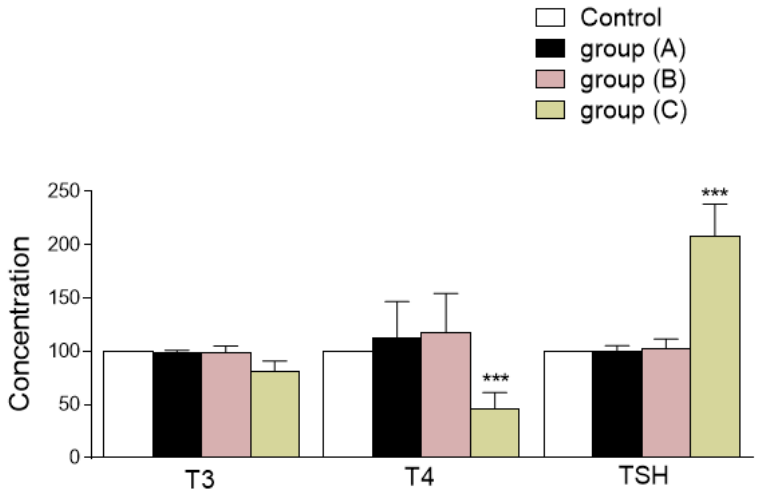

Figure 2. The levels of T3, T4, and TSH hormones were measured for the three different ovarian stimulation program groups (A, B, and C). A significant increase in the level of TSH hormone ($P<0.05$) was noted in the C group from the first month after ovarian stimulation as compared to the control group. This was associated with a significant decrease ($P<0.05$) for the T4 hormone level, while T3 show no significant difference. A (Clomid group), B (Pergonal group), and (C) (Mix group).

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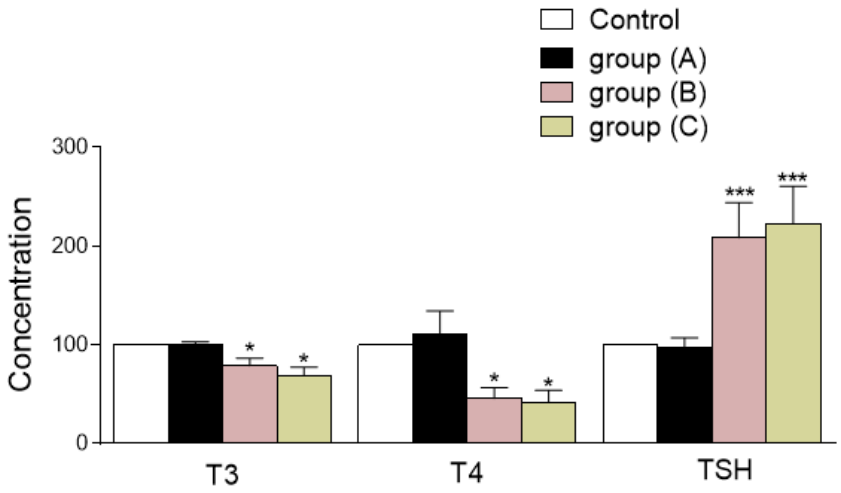

Figure 3. The levels of T3, T4, and TSH hormones were measured for the three different ovarian stimulation program groups (A, B, and C). A significant increase in the level of TSH hormone (P<0.05) was noted in the B and C groups in the second month after ovarian stimulation as compared to the control group. This was associated with a significant decrease (P<0.05) for T4 and T3 hormone levels. A (Clomid group), B (Pergonal group), and (C) (Mix group).

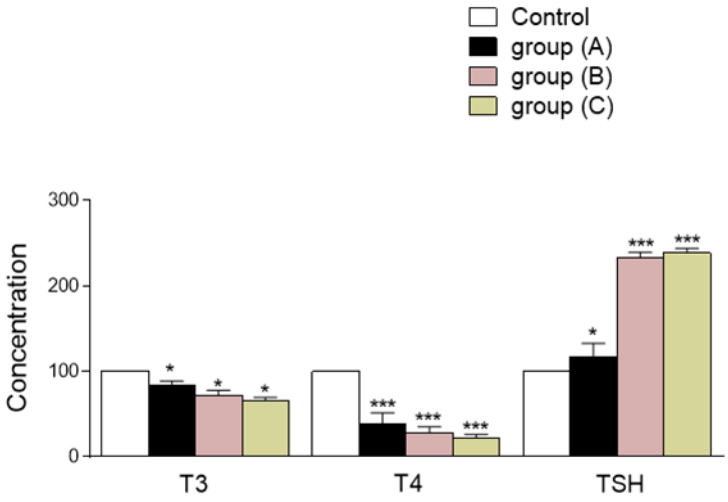

Figure 4. The levels of T3, T4, and TSH hormones were measured for the three different ovarian stimulation program groups (A, B, and C). A significant increase in the level of TSH hormone (P<0.05) was noted in all three groups in the third month after ovarian stimulation as compared to the control group. This was associated with a significant decrease (P<0.05) for T4 and T3 hormone levels. A (Clomid group), B (Pergonal group), and (C) (Mix group).

B. Discussion

Our results provide context for previously contradictory observations by demonstrating protocol-specific and time-dependent thyroid disruption; in the current study, significant increase in TSH (P<0.05) and decrease in T4 within the first month this is in line with Busnelli et al. (2016), who used comparable combination procedures

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to report that 44% of women had TSH >2.5 mIU/L by stimulation day 6 (8).

The mechanism Synergistic effects: hMG-derived hCG directly stimulates TSH receptors, while clomid-induced oestrogen surge raises TBG. This contrasts with Gracia et al. (2012), who reported no discernible early alterations, presumably as a result of differing test timing (post-hCG trigger vs. our day 12 evaluation) (9). In the current study significant TSH elevation was found while T3and T4 reduction emerging in month 2.

Aligns with Poppe et al. (2004) showing progressive TBG increases throughout gonadotropin stimulation, peaking at 2 weeks (3). Explains discrepancies by Reh et al. (2011), who may have missed effects by limiting assessment to 35-day cycles (7). Our findings: No significant changes until month 3 ($P<0.05$ for TSH, T3 and T4). Contrasts with Henawi and Aljahdali (2018), who reported immediate TSH elevation in murine models. This difference could be related to species differences (mice vs. humans) and Clomid's partial estrogen agonist effects may initially buffer thyroid impact (10).

Conclusions

This study establishes that ovarian stimulation invariably affects thyroid function, but the onset, severity, and progression are protocol-dependent. Combination therapy induces the most rapid disruption (within 1 month), while Clomid monotherapy demonstrates surprising latency (3 months). These findings reconcile previous contradictory reports by emphasizing two underappreciated variables, drug-specific mechanisms and cumulative exposure time. We propose a stratified monitoring algorithm based on stimulation regimens. Future research should investigate whether protocol-specific thyroid support can optimize reproductive outcomes, particularly in women undergoing multiple stimulation cycles.

References

[1] A. Pacchiarotti, H. Selman, C. Valeri, S. Napoletano, M. Sbracia, G. Antonini, G. Biagiotti, and A. Pacchiarotti, "Ovarian Stimulation Protocol in IVF: An Up-To-Date Review of the Literature," Current Pharmaceutical Biotechnology, vol. 17, no. 4, pp. 303–315, Mar. 2016.

[2] A. F. Muller, A. Verhoeff, M. J. Mantel, F. H. De Jong, and A. Berghout, "Decrease of Free Thyroxine Levels After Controlled Ovarian Hyperstimulation," The Journal of Clinical Endocrinology & Metabolism, vol. 85, no. 2, pp. 545–548, Feb. 2000.

[3] K. Poppe, D. Glinoer, H. Tournaye, J. Schiettecatte, P. Devroey, A. Van Steirteghem,

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.198

P. Haentjens, and B. Velkeniers, "Impact of Ovarian Hyperstimulation on Thyroid Function in Women With and Without Thyroid Autoimmunity," The Journal of Clinical Endocrinology & Metabolism, vol. 89, no. 8, pp. 3808–3812, Aug. 2004.

[4] S. Mariotti and P. Beck-Peccoz, "Physiology of the Hypothalamic-Pituitary-Thyroid Axis," in Endotext [Online]. South Dartmouth (MA): MDText.com, Inc., Apr. 20, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK285570/

[5] J. Zhang, Y. Wang, X. Mao, Q. Chen, Q. Hong, R. Cai, S. Zhang, and Y. Kuang, "Dual Trigger of Final Oocyte Maturation in Poor Ovarian Responders Undergoing IVF/ICSI Cycles," Reproductive Biomedicine Online, vol. 35, no. 6, pp. 701–707, Dec. 2017.

[6] Y. J. Du, X. Xin, N. Cui, L. Jiang, A. M. Yang, G. M. Hao, and B. L. Gao, "Effects of Controlled Ovarian Stimulation on Thyroid Stimulating Hormone in Infertile Women," European Journal of Obstetrics & Gynecology and Reproductive Biology, vol. 234, pp. 207–212, Mar. 2019.

[7] A. Reh, S. Chaudhry, F. Mendelsohn, S. Im, L. Rolnitzky, A. Amarosa, M. Levitz, S. Srinivasa, L. Krey, A. S. Berkeley, and J. A. Grifo, "Effect of Autoimmune Thyroid Disease in Older Euthyroid Infertile Women During the First 35 Days of an IVF Cycle," Fertility and Sterility, vol. 95, no. 3, pp. 1178–1181, Mar. 2011.

[8] A. Busnelli, E. Somigliana, S. Ferrari, F. Filippi, G. Vannucchi, L. Fugazzola, and L. Fedele, "The Long-Term Impact of Controlled Ovarian Hyperstimulation on Thyroid Function," Endocrine Practice, vol. 22, no. 4, pp. 389–395, Apr. 2016.

[9] C. R. Gracia, C. B. Morse, G. Chan, S. Schilling, M. Prewitt, M. D. Sammel, and S. J. Mandel, "Thyroid Function During Controlled Ovarian Hyperstimulation as Part of In Vitro Fertilization," Fertility and Sterility, vol. 97, no. 3, pp. 585–591, Mar. 2012.

[10] W. M. Henawi and M. O. Aljahdali, "Effect of Clomiphene Citrate on Thyroid Hormones T3, T4 and TSH Levels in Mice Offspring," Endocrinology & Diabetes Research, vol. 4, pp. 1–4, 2018.

[11] M. A. Krassas, G. Poppe, and K. Glinoer, "Thyroid Function and Human Reproductive Health," Endocrine Reviews, vol. 31, no. 5, pp. 702–755, Oct. 2010.

[12] T. A. van den Boogaard, M. E. Vissenberg, E. J. Land, E. van Wely, A. M. van der Post, F. J. Goddijn, and J. B. Bisschop, "Significance of (Sub)clinical Thyroid Dysfunction and Thyroid Autoimmunity Before Conception and in Early Pregnancy: A Systematic Review," Human Reproduction Update, vol. 17, no. 5, pp. 605–619, Sep.–Oct. 2011.

[13] P. Negro, E. Formoso, D. Mangieri, G. Pezzarossa, G. Dazzi, and A. Hassan,

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.198
"Levothyroxine Treatment in Euthyroid Pregnant Women With Autoimmune Thyroid Disease: Effects on Obstetrical Complications," The Journal of Clinical Endocrinology & Metabolism, vol. 91, no. 7, pp. 2587–2591, Jul. 2006.

[14]N. Andersen, M. Laurberg, C. Wu, and J. J. Andersen, "Thyroid Function Changes in Early Pregnancy and Development of Subclinical Hypothyroidism: A Longitudinal Study," The Journal of Clinical Endocrinology & Metabolism, vol. 98, no. 7, pp. 2655–2664, Jul. 2013.

[15]L. E. Alexander, D. Pearce, G. Brent, E. Brown, A. Chen, J. Dosiou, D. Grobman, J. Laurberg, and E. Lazarus, "2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum," Thyroid, vol. 27, no. 3, pp. 315–389, Mar. 2017.