

Levothyroxine in Women with Clinical Hypothyroidism Undergoing *In-Vitro* Fertilization: A Case Report

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ABSTRACT

Hypothyroidism is characterized by a high thyroid stimulating hormone (TSH) level and low thyroid hormones (T3 and/or T4). Abnormalities in ovulation, infertility, and recurrent pregnancy losses can arise due to hypothyroidism. Pregnancy is a physiological status that mandates an increase in levothyroxine doses for euthyroid women with primary hypothyroidism. Serum levels of thyroid stimulating hormone can increase significantly during *In-Vitro* fertilization among women treated for hypothyroidism, and hypothyroidism that is either undiagnosed or under-treated can contribute to infertility and result in miscarriages. Throughout the literature, artificial pregnancies, *In-Vitro* fertilization (IVF) mainly, have required a more aggressive increase in the levothyroxine dose. Here, we report the case of a 40-year old hypothyroid woman with a history of nine abortions after IVF procedures who presented for treatment of her hypothyroidism. We present in details the modification process of her levothyroxine dose according to monthly TSH levels starting from her ninth miscarriage through her tenth IVF procedure and all throughout the pregnancy, until the successful delivery of a healthy baby.

Keywords: Pregnancy, Hypothyroidism, Levothyroxine, *In-Vitro* Fertilization, Abortion

Introduction

Pregnancy is a physiological condition that alters most of the female hormonal economy. The thyroid gland and thyroidal function are majorly altered during pregnancy. During the first trimester of pregnancy, high levels of β HCG promote, through its weak intrinsic thyroid-stimulating role, higher levels of serum thyroid hormones, and lowered TSH (Alexander *et al.*, 2004). The fact that a woman with normal thyroid function pre-conception remains euthyroid during her pregnancy draws the attention to the antagonist role driven by estrogen during pregnancy. Estrogen-promoted serum thyroid hormone-binding globulin (TBG) lower serum levels of thyroid hormones, namely T4 (Alexander *et al.*, 2004; Hallengren *et al.*, 2009). Hence, the opposing role of β HCG and estrogen maintain the euthyroid status throughout pregnancy (Hallengren *et al.*, 2009). Consideration of pregnancy for a hypothyroid woman

sheds light on the inability of the thyroid gland to secrete thyroid hormones despite the stimulating effect of β HCG (Alexander *et al.*, 2004; Hallengren *et al.*, 2009; Kaplan, 1996; Mandel, 2004). Given the estrogen-driven low serum levels of T4, a hypothyroid female mandates an increase in her levothyroxine dose to compensate for the discrepancy caused by pregnancy (Mandel *et al.*, 1990; Pekonen *et al.*, 1984). Growing evidence suggests females with artificial conception methods i.e. *In Vitro* fertilization (IVF) are at a higher risk for the decompensated thyroid function and serum thyroid hormones levels compared to females with natural conception (Kaplan, 1996; Busnelli *et al.*, 2015). No schemes exist to illustrate the mode of levothyroxine dose modification (Busnelli *et al.*, 2015). This justifies the need to report cases of levothyroxine dose modification for hypothyroid females with artificial conception and hence we report the following case.

Case Presentation

We present the case of a 40-year old woman who presented to the clinic for follow up during pregnancy. The patient reported failure to conceive using *In Vitro* fertilization (IVF) for nine consecutive times. The patient has had hypothyroidism for 11 years after a total thyroidectomy procedure had been done. The patient was on a sole medication: levothyroxine. The dose of her medication has been modified throughout her follow up and IVF trials. The modification is depicted in the [Table 1](#).

Until September 16, 2020, the patient was kept on levothyroxine 125 mcg per os as a daily dose through Monday until Friday and on 100 mcg per dose as a daily dose on Saturday and Sunday. On November 24, 2020, symptoms of tachycardia and tremors and a low TSH level of 0.085 mandated lowering the daily dose of levothyroxine through Monday to Friday to 100 mcg. After the ninth miscarriage on December 25, 2020, the levothyroxine daily dose on Saturday and Sunday was lowered to 100 mcg while TSH level was 0.109. Loss of the potential pregnancy mandated lowering levothyroxine dose.

On April 15, 2021, after the 10th IVF procedure, the levothyroxine daily dose was increased to 200 mcg on Friday, Saturday and Sunday. A TSH level of 27 and the potential for pregnancy required an increase in levothyroxine daily dose to match the deficit caused by pregnancy. On May 10, 2021, a further increase in the daily dose of levothyroxine to 200 mcg on Monday through Friday and 100 mcg on Saturday and Sunday was implemented. This increase is due to an elevated TSH of 7.5.

As the pregnancy continued and due to a TSH of 0.045, the daily levothyroxine dose was changed to 100 mcg on Monday through Saturday and 200 mcg on Sunday. This regimen was changed on September 25, 2021 because TSH was elevated to 3.5. The most stringent criteria used for levothyroxine

adjustment mandates a TSH level equal or below 2.5 mIU/l during pregnancy in the first trimester, and equal or below 3 mIU/l in the second and third trimester. The modification comprised an increase in the dose given on Friday to 200 mcg instead of 100 mcg. The change was reverted to the previous regimen on January 14, 2022, 2 months after delivery.

Table 1: Dose modification of levothyroxine dose in microgram according to monthly thyroid stimulating hormone levels in uIU/L.

| Dose modification date | TSH level | New dose of levothyroxine (microgram) | | | | | | | Reason for dose modification |
|--|-----------|---------------------------------------|---------|-----------|----------|--------|----------|--------|--|
| | | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday | Sunday | |
| 16 Sept 2020 9th IVF before miscarriage | 0.14 | 125 | 125 | 125 | 125 | 125 | 100 | 100 | |
| 24 Nov 2020 | 0.085 | 100 | 100 | 100 | 100 | 100 | 125 | 125 | Tachycardia Supra-therapeutic |
| 25 Dec 2020 after 9th miscarriage | 0.109 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | Miscarriage |
| 21 Jan 2021 before 10th IVF | 1.34 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | |
| 15 April 2021 1 month after 10th IVF | 27 | 100 | 100 | 100 | 100 | 200 | 200 | 200 | IVF procedure |
| 10 May 2021 | 7.5 | 200 | 200 | 200 | 200 | 200 | 100 | 100 | High TSH |
| 1 June 2021 | 0.045 | 100 | 100 | 100 | 100 | 100 | 100 | 200 | Low TSH |
| 24 July 2021 | 1.67 | 100 | 100 | 100 | 100 | 100 | 100 | 200 | |
| 18 August 2021 | 1.9 | 100 | 100 | 100 | 100 | 100 | 100 | 200 | |
| 25 September 2021 | 3.5 | 100 | 100 | 100 | 100 | 100 | 200 | 200 | Value above trimester reference range during pregnancy (3rd trimester) |
| 14 January 2022 After 2 months from Delivery date | 2.78 | 100 | 100 | 100 | 100 | 100 | 100 | 200 | Delivery |

TSH, Thyroid Stimulating Hormone; IVF, *In-Vitro* Fertilization

Discussion

Failure to optimize thyroid function is associated with a higher risk of miscarriage, premature birth, gestational hypertension, postpartum hemorrhage and inadequate fetal growth (Leung *et al.*, 2012). Various reports suggest a 30% increase in the pre-pregnancy levothyroxine dose as sufficient for optimization of thyroid function (Kiran *et al.*, 2022). Increases in levothyroxine dosage administered in pregnancy is indispensable in the majority of patients although the patient is euthyroid. This increase is usually advised in the first semester. A study done by Kashi, *et al.* in 2015, 84% of the pregnant hypothyroid women needed an increase in their levothyroxine dose (Kashi *et al.*, 2015). This finding was concordant with a multitude of studies. A similar finding was depicted in hypothyroid women with IVF

pregnancy in a study conducted by Busnelli, *et al.* in 2015, where 84% of women undergoing IVF required an increase in levothyroxine dose, of which 74% needed the increase during the first 5-7 weeks of gestation, versus 56% of women undergoing natural pregnancy (Busnelli *et al.*, 2015). This promotes the idea that the thyroid is further impaired during pregnancy and is insufficient. Patients with anti-thyroid peroxidase (anti-TPO) negative profile showed less need for an increase in levothyroxine dose compared with anti-TPO positive profile. Hence, autoimmunity in hypothyroid pregnant women required higher levothyroxine dosages (Fröhlich and Wahl, 2017). Kashi, *et al.* suggests that the pattern of levothyroxine modification differs in IVF pregnancies compared to natural pregnancies and reports a more gradual increase in levothyroxine in the latter (Kashi *et al.*, 2015). These studies failed to show the pivotal role of estrogen in IVF-related TSH level variation as claimed by many resources. In a study done on 240 women in 2012, Scoccia, *et al.* reported less implantation, clinical pregnancy, and live birth rates in women with treated hypothyroidism compared to euthyroid women. Hence, the former had a significantly lower chance of achieving pregnancy following IVF (Scoccia *et al.*, 2012). Confounding factors including the state of overstimulation to which the ovaries are subject during IVF need further assessment to conclude the role of each in this conclusion (Scoccia *et al.*, 2012).

Conclusion

Along with evidence from the literature, this case report reflects the importance of optimization of levothyroxine dose during pregnancy using artificial means. Higher doses of levothyroxine proved essential for maintenance of the pregnancy and control of TSH level within normal values. Report of similar approaches during pregnancies with other artificial means is encouraged.

Consent: The patient signed consent and approved to share her images, condition, laboratory and imaging results for the purpose of medical publications. She was informed of her right to refuse to participate and share her condition and she was aware of the purpose of this publication.

Conflicts of Interest: None of the authors has any conflict of interest.

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Ethical Clearance: Retrieval, analysis and sharing of the medical file and images associated was done with previous apprehension of the ethical committee. Case reports are not required to have a written ethical committee approval. A consent signed by the patient is mandatory for data retrieval and publication.

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