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Effects of Subclinical Hypothyroidism on Reproduction: Screening and Treatment

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Abstract

Subclinical hypothyroidism (SCH) has been studied since 2011 in regard to its effect on infertility. It is recommended that those who have been diagnosed with SCH before and during pregnancy have a TSH level <2.5 mIU/L. This achievement is best reached by using the supplementation of levothyroxine (LT4, T4). It is known that thyroid dysfunction in infertility exists. Abnormal thyroid levels have been hypothesized to have a pathophysiologic effect on oocytes and other reproductive cycles, which can correlate to infertility. Thyroid autoimmunity plays a role in the development of SCH. Thyroid autoimmunity in pregnancy can trigger SCH which would lead to adverse obstetrical outcomes. This review was based on a case study of a 32-year-old female, in the postpartum period, with newly diagnosed hypothyroidism. In addition to this case study, phis particular literature search will discuss SCH and infertility with screening and treatment recommendations. Clinical relevance to this issue will reveal evidenced-based information on how to best screen and treat individuals with SCH and possible infertility and obstetrical outcomes.

Keywords: Subclinical hypothyroidism, infertility, hypothyroidism

Background

Thyroid dysfunction is a common finding in women of reproductive age. The burden of thyroid disease affecting women before, during, or after pregnancy is substantial. Hypothyroidism is a clinical and metabolic state resulting in decreasing levels of free thyroid or resistance to hormone action. Hypothyroidism left untreated can lead to reproductive health problems which include infertility, miscarriage, and adverse obstetric and fetal outcomes (American Society for Reproductive Medicine, 2015). Thyroid Autoimmunity (TAI), which is the presence of autoantibodies, is the most common cause of hypothyroidism in women of the reproductive age (Rao, Zeng, Zhao, & Tang, 2018). Subclinical Hypothyroidism (SCH) is represented by an elevated TSH but a normal free T4 (Rao et al., 2018). There is now evidence that inadequate treatment of SCH can also lead to infertility, miscarriage, and other adverse obstetrical and neonatal neurodevelopment outcomes (American Society for Reproductive Medicine, 2015). Guidelines for management of these disorders during pregnancy were published in 2011 by the American Thyroid Association (ATA) with significant clinical and scientific advances established and updated as of 2017 (Alexander, Pearce, Brent, Brown et al., 2017).

Patients who are clinically hypothyroid warrant thyroid hormone replacement. Administration of synthetic thyroid hormones, levothyroxine (T4, LT4), liothyronine (T3), and liotrix (T4/T3) produce the same effects on the body's tissues as one's own thyroid hormones (Woo & Robinson, 2016). Woo and Robinson (2016) identify these medications are all pregnancy category A, which indicates they are safe for use in pregnancy. Levothyroxine is used most frequently to prevent over treating the patient and the overarching goals of treatment are to normalize thyroid levels with minimal adverse effects (Woo & Robinson, 2016). Untreated SCH during pregnancy increases risk and incidence of maternal hypertension, pre-eclampsia,

postpartum hemorrhage, ventricular dysfunction, spontaneous abortion, fetal death, or still born (Woo & Robinson, 2016). Rao et al., (2018) suggest even mild asymptomatic SCH may have adverse effects on cognitive function of offspring.

After a thorough review, there is not enough evidence to recommend for or against screening for thyroid dysfunction in preconception or early pregnancy in patients with no known history of thyroid disease and asymptomatic (Maraka, Singh Ospina, Mastorakos, & O'Keeffe, 2018). However, when indicated upon clinical signs and symptoms and possible infertility issues a screening may be necessary. The purpose of this report is to address thyroid dysfunction, explicitly addressing SCH, effects on infertility and obstetric outcomes, and recommendations on screening and treatment.

Case report

This case is on a 32-year-old female, LJ, who presents to primary care with concerns of increasing fatigue, feeling cool, abnormally dry skin, recent weight gain, irregular periods with heavy menstruation, and constipation. These symptoms were first noticed in October just after her last child was born. She shares, “The only thing that makes her feel warm is going to the club to sit in the hot tub.” LJ has been applying Jergens lotion twice daily and after showers to help with the dry skin. She reports 6-7 hours of sleep per night and has increased her caffeinated coffee intake to more than a pot of coffee a day. She is no longer breast feeding as her job is too time consuming. LJ has not noticed a change in her appetite and reports being too busy to exercise. She denies alcohol, tobacco, and illicit drug use. LJ reports no known allergies to medications and takes one pre-natal vitamin daily and a probiotic. A history of hypertension, which she is no longer being treated for, is shared but she is otherwise healthy. She has had three

successful and uncomplicated cesarean sections, the most recent being 11 months ago. LJ has a known family history of thyroid problems, diabetes mellitus, cancer, and heart disease. She is happily married to a husband who is supportive and together they have three children. She works full-time as a security secretary, Monday-Friday, 8:00am-5:00pm.

A 10-point review of systems is completed, and the physical exam reveals the following pertinent positives: Vital signs are reviewed, the reported blood pressure is 130/80, which is increased by 14 mmHg systolic and 10 mmHg diastolic. Movement is rather slow with dull facies and fatigued appearance. Thickened tongue is evidenced by teeth indentations on the lateral edges. Excessively dry cool skin is noted on bilateral upper extremities. Thyroid is palpable. Bowel sounds are hypoactive. Deep tendon reflexes on patellar and biceps appear hyporeflexic. Diagnostics include the following non-fasting labs: CBC (within normal limits), BMP (within normal limits), serum betaHCG (negative), and TSH (elevated 6.160 mIU/L). Previous lab results prior to pregnancy were all within normal limits, including a TSH.

LJ's presentation, clinical manifestations, and diagnostics are pertinent for postpartum thyroiditis, indicating hypothyroidism. Discussion was held regarding cause of hypothyroidism. Counselling was completed on Levothyroxine use and importance of taking it on an empty stomach and without other medications. LJ will proceed by taking 25 mcg of levothyroxine daily and recheck a TSH in 4-6 weeks. Constipation is discussed with the patient that this is most likely due to her hypothyroidism. However, I did encourage exercise, increase water intake, and the use of MiraLAX once a day until her stools are of normal consistency. Education was completed on dry skin being consistent with hypothyroidism. I encouraged the use of Vanicream BID and after showers. In addition, 1,000 mg of Fish Oil PO daily. LJ was appreciative of the homeopathic suggestions.

Literature review

Methods

A systematic literature search was performed using a combination of the following key words: Subclinical hypothyroidism, infertility, hypothyroidism, miscarriage, pregnancy, complication, elevated TSH, birth defect, and thyroid dysfunction. The search was restricted to CINAHL and PubMED through the University of North Dakota Harley French Library. Practical screening was completed, and inclusion criteria included the following: publication dates from 2011 through 2018, controlled vocabulary terms as above, and full text articles from educational journals. Content included any SCH, TAI, and some hypothyroidism and effects on reproduction. This search yielded 382 studies, with 12 full text articles were screened. 2 studies were excluded due to being out of date rage, resulting in 10 eligible studies were included in this synthesis. One animal study was included because of the yield that could be true in future human studies. The quality of evidence is high including systematic reviews and randomized control studies (RCT). The following literature review will deviate mildly from the case study presented to focus on SCH and reproductive problems.

Concept 1: Screening

Screening is defined as a systematic search for a health condition testing otherwise healthy people (Alexander et al., 2017). Screening for thyroid dysfunction is a controversial topic. Routine screening women at risk of conception along with optimization of their thyroid status could result, as many studies like Alexander et al., (2017) has shown, in significant health benefits for their offspring and their obstetrical progress. Alexander et al., (2017), also suggests, that regardless if it is before conception or during pregnancy, due to the potential dangers of the

SCH on the fetus, universal screening to evaluate thyroid function should be done in all women. ATA argues that this is an inexpensive way to attempt control of SCH risks pre-conception because levothyroxine is an inexpensive drug. According to the American Endocrine Society (AES), based on the potential benefits of early detection and treatment of SCH, routine screening is recommended for SCH in adults including pregnant women and those who want to become pregnant, as it significantly outweighs the risks (Maheshwari, Bhide, Pundir, & Bhattacharya, 2017).

In opposition, this could also be an expensive route, cause increased anxiety, frequent monitoring for euthyroid, unneeded drug use, and potential harm. In a systematic review, by Maheshwari et al., (2017), administration of thyroxine during pregnancy has failed to demonstrate appreciable health benefits in those with a TSH <4 mIU/L. Thyroid function during pregnancy is difficult to manage and interpret compared to nonpregnant patients, because of altering anatomy of the thyroid during pregnancy along with age (Alexander et al., 2017). Therefore, optimization of TSH pre-conception should be practiced. Ideal pre-conception TSH should be <2.5 mIU/L, which will generate an inevitable increase in numbers of pre-conception women who will need treatment and monitoring (Alexander et al., 2017). ATA, American College of Obstetrics and Gynecology (ACOG), and Royal College of Obstetrician and Gynecologists (RCOG) suggest routine pre-conception testing for all is not recommended because of limited data from large scale randomized trials in the general population (Maheshwari et al., 2017). To date, studies evaluating this continue to demonstrate mixed conclusions on screening. The gap in this concept includes the unexpected pregnancies and lifelong follow-up compliance.

Concept 2: Treatment

There is controversy regarding treatment of SCH in the infertile female patient because of the risks and benefits (American Society for Reproductive Medicine, 2015). The mechanism for the T4 treatment for fertility has not been clarified in detail. It is suggested it may have an effect on the hypothalamus-pituitary-gonadal axis and menstrual abnormalities, anovulation, and hyperprolactinaemia (Yoshioka, Waka, Amino, Nobuyuki et al., 2015). Levothyroxine is rated category A, safe in pregnancy (Woo & Robinson, 2016). Evidence suggests that a TSH > 4 mIU/L during pregnancy is associated with miscarriage (American Society for Reproductive Medicine, 2015). There is good evidence that levothyroxine treatment in pregnant women with SCH with TSH levels >4 mIU/L had improved pregnancies and miscarriage rates (American Society for Reproductive Medicine, 2015). Infertile women with SCH, per the guidelines of the AES, American Association of Clinical Endocrinologists (AACE), and ATA support use of levothyroxine if offspring are wanted (Yoshioka et al., 2015). Treatment with low dose LT4 should be started if SCH is diagnosed; levels should be <2.5 mUI/L to be therapeutic and low risk during pregnancy (Yoshioka et al., 2015). There is a very high success rate in pregnancies and shorter infertility periods for those patients who had SCH and were treated with levothyroxine, showing that T4 enhanced fertility in those who were infertile (Yoshioka et al., 2015). If SCH is untreated, there is good evidence that SCH diagnosed in pregnancy is associated with adverse neurodevelopmental outcomes (American Society for Reproductive Medicine, 2015).

In SCH female populations undergoing invitro fertilization (IVF), despite T4 treatment, less implantation and less live birth rates occurred than in euthyroid women (Yoshioka et al., 2015). In contrast, Yoshioka et al., (2015) although recognizing that T4 therapy was doubtful in other reports, found that clinical pregnancies were significantly higher in treated infertile patients

with SCH who participate in IVF than those not receiving treatment. Yoshioka et al., (2015) suggests that TSH may predict fertilization in IVF and reflect the importance of thyroid hormones in oocyte physiology. It can stimulate oocytes directly to improve embryo quality in IVF (Yoshioka et al., 2015). Limitations exist in the type of studies performed including the need for more RCT involving infertile patients and effectiveness of T4 treatment.

Concept 3: Infertility

SCH is more prevalent in infertile women and highest among those with ovulatory dysfunction. Thyroid autoimmunity (TAI) is one of the most important issues regarding the care of infertile pregnant women (Oiwa, Minemura, Nishio, Yamazaki, & Komatsu, 2019). Thyroid autoimmunity is defined by Wang, Haining, Gao, Hongwei et al., (2017), as a presence of thyroid autoantibodies, which is the most common cause for miscarriages in infertile women and also associated with pregnancy complications. Women who have normal TSH levels but test positive for thyroid antibodies are at 2-3-fold higher risk for miscarriage than those who are not positive for antibodies (Wang et al., 2017). It is suggested that those with thyroid autoimmunity are predisposed to develop SCH or overt hypothyroidism because pregnancy can trigger this progression (Wang et al., 2017). T4 treatment does have a potential to reduce miscarriage rate, so supplementation is recommended for women who have TAI who are undergoing IVF (Rao et al., 2018). In opposition, ATA and AES declare there is insufficient evidence and lack of RCT to recommend for or against treating women with normal TSH but positive antibodies and recurrent miscarriages (Wang et al., 2017). The small studies described in Rao et al., (2018), observed no difference in miscarriage rates for women who underwent T4 treatment for TAI. LT4 should be reconsidered when making decisions about treatment based on TSH for those who have thyroid autoimmunity based on risks and benefits. Data assessing effect of SCH on fertility is limited due

to the variations of SCH and lack of adequate control groups with TAI (American Society for Reproductive Medicine, 2015)

Concept 4: Obstetric Outcomes

SCH during pregnancy, with a TSH outside of normal range, is associated with adverse obstetric outcomes. SCH and pregnancy has long been studied. Of all obstetrical problems, miscarriage was the most significant of adverse pregnancy outcomes in those with SCH (Rao et al., 2018). Pre-eclampsia, perinatal mortality, and recurrent miscarriages were also noted (Van Den Boogaard et al., 2011). Van Den Boogaard et al., (2011), did show the relation between SCH and pre-eclampsia. It is also noted the literature found in Van Den Boogaard's et al., (2011) study is outdated, but it is essentially one of the first studies on thyroid and infertility, which is why it is included. It is also interesting to note the hypotheses addressed in the study that have been evidenced-based to be true. Levothyroxine did not have an improvement on developmental outcomes with those diagnosed with SCH in pregnancy but did improve miscarriage rates (American Society for Reproductive Medicine, 2015). The RCT based meta-analysis by Rao et al., (2018), confirms the benefits of T4 supplementation to decrease risk of miscarriage. It was found not to improve live pregnancy rates, preterm birth, or rates of clinical pregnancy (Rao et al., 2018). Thyroid treatment in patients with thyroid disorders can only be justified if there is an association with the thyroid and obstetric outcomes demonstrated (Van Den Boogaard et al., 2011). Limitations include more studies to help determine if LT4 replacement can improve long term complications in women with SCH.

In summary, based on the potential benefits of early detection and treatment of SCH, routine screening is recommended for SCH in adults, including pregnant women and those who

want to become pregnant, as it significantly outweighs the risks (Alexander et al., 2017). SCH is more prevalent in infertile women and highest among those with ovulatory dysfunction (Oiwa et al., 2019). Thyroid autoimmunity is one of the most important issues regarding the care of infertile pregnant women. LT4 should be reconsidered when making decisions about treatment based on TSH for those who have thyroid autoimmunity (wang et al., 2017). There is a very high success rate in pregnancies and shorter infertility periods for those patients who had SCH and were treated with levothyroxine, showing that T4 enhanced fertility in those who were infertile (Yoshioka et al., 2015). TSH may predict fertilization in IVF and reflect the importance of thyroid hormones in oocyte physiology; it can stimulate oocytes directly to improve embryo quality in IVF (Yoshioka et al., 2015). Levothyroxine did not have an improvement on developmental outcomes with those diagnosed with SCH in pregnancy but did improve miscarriage rates when pregnant (American Society for Reproductive Medicine, 2015). Overall, more controlled studies will need to be done on each of the concepts above along with the pathophysiologic studies in regard to what abnormal TSH levels or positive thyroid antibodies have on the women's reproduction with this diagnosis.

Learning Points

- Based on the potential benefits of early detection and treatment of SCH, routine screening is recommended for SCH in adults including pregnant women (Alexander et al., 2017). Mixed conclusions exist because ATA, ACOG, and RCOG suggest routine pre-

conception testing for all is not recommended because of limited data on from large scale randomized trials in the general population.

- There is good evidence that levothyroxine treatment in pregnant women with SCH with TSH levels >4 mIU/L had improved pregnancies and miscarriage rates (Yoshioka et al., 2015). There is a very high success rate in pregnancies and shorter infertility periods for those patients who had SCH and were treated with levothyroxine, showing that T4 enhanced fertility in those who were infertile (Yoshioka et al., 2015).
- TSH may predict fertilization in IVF and reflect the importance of thyroid hormones in oocyte physiology (Yoshioka et al., 2015). Clinical pregnancies were significantly higher in treated infertile patients with SCH who participate in IVF than those not receiving treatment (Rao et al., 2018).
- Thyroid autoimmunity (TAI) is one of the most important issues regarding the care of infertile pregnant women. Women who have normal TSH levels but test positive for thyroid antibodies are at 2-3-fold higher risk for miscarriage and pregnancy can trigger this progression (Wang et al., 2017). T4 treatment does have a potential to reduce miscarriage rate, so supplementation is recommended for women who have TAI (Owia et al., 2019). However, there is insufficient evidence and lack of RCT to recommend for or against treating women with normal TSH but positive antibodies and recurrent miscarriages.
- SCH during pregnancy with a TSH outside of normal range is associated with adverse obstetric outcomes. Levothyroxine did not have an improvement on developmental outcomes with those diagnosed with SCH in pregnancy but did improve miscarriage rates (American Society for Reproductive Medicine, 2015). Thyroid treatment in patients with

thyroid disorders can only be justified if there is an association with the thyroid and obstetric outcomes demonstrated (Van Den Boogaard et al., 2011).

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