Subclinical Hypothyroidism: significance in conception and pregnancy – a narrative review

Syed Shahinul Haque [1], Syed Mohsin Raza [2]

(1) Dr Syed Shahinul Haque, MBBS, MRCGP UK, Consultant Family Medicine PHCC, Qatar
(2) Dr Syed Mohsin Raza, MBBS, MRCGP UK, Consultant Family Medicine PHCC, Qatar

Corresponding Author:
Dr Syed Shahinul Haque, MBBS, MRCGP UK,
Consultant Family Medicine PHCC,
Qatar
Email: sshaque@doctors.org.uk

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Abstract

Subclinical Hypothyroidism in pregnancy and during conception has long been an area of controversy with little consensus on whether or not it should be treated. It is also an area in which the evidence base is gradually developing. This narrative review aims to summarise the research to date in this field and provide pragmatic recommendations for the Primary Care Physician when confronted with this scenario.

Key words: Subclinical Hypothyroidism, Conception, Pregnancy, Levothyroxine, Hypothyroidism.

Introduction

It is a not an uncommon scenario in Primary Care for a patient to attend their family practitioner after having tried and failed to conceive. Initial investigations may reveal a picture consistent with Subclinical Hypothyroidism (SCH); the patient may request thyroxine – should we treat? Furthermore, a pregnant patient may have first trimester blood results which show SCH – should this be treated? What is the evidence of benefit, if any? What are the risks associated with treatment? Increasingly moreso, clinicians are opting to treat empirically (1). Anecdotally, multiple colleagues have noted successful conception shortly after starting treatment with low dose Levothyroxine (LT4). This narrative review will focus on the issue of SCH, its significance for females trying to conceive, its effects on pregnancy, and consider the question of whether or not it should be treated with LT4 in both of these scenarios.

Physiology

There are significant changes in thyroid physiology during pregnancy (2). In general, it is accepted that there is a transient rise in free Thyroxine (FT4), stimulated by high circulating human chorionic gonadotrophin (hCG) concentration during the first trimester, followed by a decrease in the second and third trimesters, albeit within the normal range. Likewise, free triiodothyronine (T3) levels also undergo subtle and similar changes mimicking T4. Furthermore, significant modifications in the peripheral metabolism of maternal thyroid hormones occur. Therefore, both TSH and free thyroid hormone reference intervals change throughout pregnancy. Consequently, it is important to follow pregnancy trimester-specific reference ranges where available when evaluating the thyroid status of a patient.
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Hypothyroidism

It is well established that untreated hypothyroidism in pregnancy can result in multiple adverse outcomes (3,4). Several studies have shown associations between overt thyroid dysfunction and infertility (5,6,7). Therefore it is well accepted that overt hypothyroidism, as a form of thyroid dysfunction, should be treated in women trying to conceive. In fact, the UK NICE guidelines recommend optimising thyroid function in those women in whom a deficiency has been identified, prior to any attempts at conception (8). Likewise, the negative repercussions of overt hypothyroidism on pregnancy outcomes means the recommendation to treat overt hypothyroidism in pregnancy is well established.

Subclinical Hypothyroidism – definitions
Numerous studies have attempted to establish normal TSH pregnancy ranges, however, owing to the variation in geography and ethnicity, such normal reference ranges are probably not valid (9,10,11). The American Thyroid Association recommends using pregnancy trimester-specific reference ranges for TSH to establish maternal thyroid status. These should be based on data from a healthy, Thyroid Peroxidase Antibody (TPO-Ab) negative, iodine-sufficient female population of local origin (12). In practice, they recognise that this may not be possible and thus, where unavailable, they recommend using an upper limit of ~ 4.0 mU/L

Adverse outcomes of SCH on pregnancy

Most studies in this area have shown an increased risk of adverse pregnancy outcomes. These studies can be grouped into the following broad categories based upon adverse outcomes. Studies looking at:

1. Pregnancy loss
2. Adverse perinatal outcomes (i.e. premature delivery, hypertensive disorders)
3. Adverse neurocognitive outcomes in offspring

Pregnancy loss
This is a difficult endpoint to study since most pregnancy losses occur early in pregnancy with the patient unaware of their pregnancy status. However various studies have shown an increase in pregnancy loss with higher levels of maternal TSH. Negro et al reported a significant increase in pregnancy loss in TPOAb negative women with TSH ranges between 2.5 and 5.0mU/L compared with those with TSH less than 2.5 mU/L (13). In a Dutch prospective cohort study with 2,497 pregnant women without overt hypothyroidism, higher levels of maternal TSH increased the risk of pregnancy loss (14). Another prospective cohort study by Liu et al reported a graded increase in the risk of miscarriage as concentrations of maternal TSH increased (15). A retrospective study that tested thyroid function in samples taken at between 11 and 13 weeks of pregnancy from 202 cases that subsequently miscarried, showed higher mean TSH and lower mean T4 concentrations, compared to 3,592 normal pregnancies (16).

Adverse perinatal outcomes
Casey et al conducted a prospective study of more than 17,000 pregnant patients and demonstrated a higher risk of placental abruption and preterm delivery for women with SCH compared to euthyroid women. Their babies were also more likely to have respiratory distress syndrome and be admitted to the neonatal intensive care unit (17). Wilson et al, in 2012, showed an increased incidence of gestational hypertension and eclampsia (18). Several other studies comparing pregnant women with SCH and those that are euthyroid have demonstrated various adverse outcomes in the former group including gestational diabetes (19), preterm rupture of membranes (20), preterm delivery (21), intrauterine growth restriction and low birth weight (22). Although these studies are quite varied in terms of TSH cut off points, different end points used, as well as study design, overall they do show an increase in pregnancy complications with higher maternal TSH concentrations. Furthermore, these risks seem to increase in TPOAb positive women.

Neurocognitive effect on the offspring

There is a limited evidence base in this area and the results are inconsistent, with some studies showing a negative neurocognitive effect of SCH on offspring and other studies not confirming this. It is an area that requires further study. The inconsistent results may be a reflection of the variation in TSH cut-off points used across the various studies, the time of gestation at which interventions took place, the differing timings of TSH evaluation during pregnancy and so forth.

Effect of SCH on conception

With regards to conception the evidence base is even more sparse. There is some research to suggest that SCH is more prevalent in infertile women: Abalovich et al demonstrated a significantly higher incidence of SCH affecting infertile women compared with controls (13.9% vs 3.9%) (23). A retrospective study by Yoshioka et al found a success rate of conception of 84.1% in infertile women with SCH (TSH >3.0 mU/L) after treatment with LT4 (24) thus suggesting that SCH may have a negative impact on fertility. Similarly, the cross-sectional designed Danish General Suburban Population Survey showed that SCH was associated with impaired fertility (25). On the other hand a cross sectional study of 704 women undergoing fertility treatment found a raised TSH in only 2.3% - this is a similar rate to the general population. Therefore the evidence base in this area is mixed and is currently not considered sufficient to conclude that SCH is associated with infertility.

Treating SCH

This leads onto the issue of treatment of SCH: should it be treated? If so, when?

For conception

Is there mileage in treating SCH to improve conception rates? Although the study by Yoshioka et al, referenced above (24) found an improvement in conception rates with LT4 treatment, a significant percentage (29%) of these pregnancies ended in miscarriage. Most of the research in this area has focused on women undergoing assistive reproductive techniques and to date there have not been any randomised controlled trials examining whether LT4 treatment of SCH in infertile women improves outcomes. As such there is insufficient evidence to recommend treating SCH in women trying to conceive.

During pregnancy

As previously noted, treatment with LT4 is unanimously recommended in cases of overt hypothyroidism, and there are several international guidelines advocating this (10, 26). However, despite emerging evidence of adverse pregnancy and perinatal outcomes associated with SCH, there is little consensus on whether or not to treat it. The American College of Obstetricians and Gynecologists (ACOG) does not recommend treatment (26). The American Thyroid Association (ATA) guidelines (10) recommend testing for TPO Antibodies to establish the presence of Auto-immune Thyroid Disease (AITD) in women with TSH > 2.5IU/L and then treat those who are positive. The European Thyroid Association (ETA) endorses LT4 therapy regardless of TPOAb status (albeit with a weaker recommendation for TPOAb negative patients) (27). Overall it appears from interventional studies using levothyroxine that the combination of raised TSH (SCH) in the presence of AITD (TPOAb positive) is the most responsive cohort to treatment, resulting in the fewest adverse obstetric outcomes (28, 29, 30).

Deciding not to treat SCH

There is established consensus on treating overt hypothyroidism during pregnancy. The recommendation to treat SCH in pregnancy is more nuanced and subject to certain limitations: a reliable diagnosis of SCH, using trimester specific and population based reference ranges, is required; the presence of TPO antibodies to establish the autoimmune status of the patient should be looked for, and, any intervention should be carried out in a timely manner to maximise the positive impact on fetal development, neonatal, and obstetric outcomes. However, treatment with LT4 cannot be considered an entirely benign intervention. Excess thyroid hormones may impair fetal neurodevelopment (31), lower IQ of the offspring and reduce grey matter and cortex volume (32). An association has been shown between high maternal free LT4 levels and low birth weight in offspring (33). Furthermore, whilst LT4 treatment in women with SCH has been found to reduce the risk of pregnancy loss, it can increase the risk of other pregnancy related adverse outcomes; preterm delivery, pre-eclampsia or gestational diabetes (34).

Conclusion

Whilst the treatment of overt hypothyroidism has long been established in pregnant women as well as women trying to conceive, the question of subclinical hypothyroidism remains one in which there is still no consensus. As yet there is insufficient evidence to recommend treating SCH in women trying to conceive. However, the ATA has issued a weak recommendation that LT4 therapy may be considered in women with SCH trying to conceive in order to reduce the risk of progression to overt hypothyroidism once pregnancy is achieved (10). Anecdotally, colleagues have seen successful conception with low dose LT4 treatment in women struggling to conceive. In light of this, in response to the initial question posed, ‘should one treat a patient diagnosed with SCH who is trying to conceive?’, a pragmatic compromise may be to offer low dose LT4 (25-50 mcg) aiming to keep the TSH below 2.5, with regular monitoring throughout pregnancy, explaining to the patient the limitations of this approach, and thus permitting the patient to make an informed choice. The discussion would include an appraisal of the intended benefits as well as the potential pitfalls of LT4 treatment. This approach may be strengthened with a positive finding of TPO antibodies.

With regards to treatment of newly discovered SCH during pregnancy, this remains an area of controversy. Further trials are required to provide a more precise understanding of how to identify women at risk of developing pregnancy complications in order to permit more targeted interventions. In practice, the ATA guideline approach, as outlined above, may be a sensible compromise.

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