Thyroid Screening During Pregnancy and Fetal Outcome

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Abstract

Background: Physiological changes associated with pregnancy require an increased availability of thyroid hormones to meet the needs of both the mother and the fetus during pregnancy. This review will focus on the transient impairment of thyroid function during early pregnancy resulting in recurrent miscarriages and other adverse fetal outcomes.
Objective: Our goal is to evaluate the relationship between subclinical hypothyroidism (SCH) and the risk of miscarriage before 20 weeks of pregnancy, and evaluate whether screening should be implemented in pregnant women at risk of SCH.
Methods: Through the process of a structured literature review, PubMed, Scopus and Medline was searched from 2003 to 2017. The following search terms were used: subclinical, hypothyroidism, thyroid, and miscarriage. The following search terms were filtered out of our search: postpartum, autoimmunity, autoimmune, in vitro, and menstrual irregularity. Studies comparing the prevalence of miscarriage before 20 weeks of pregnancy and subclinical hypothyroidism were selected.
Results: Six articles satisfying the inclusion criteria were analyzed. Pregnant women with untreated SCH had a higher prevalence of miscarriage in the first 20 weeks of pregnancy when compared to pregnant women who had received medical intervention. Higher maternal Thyroid-stimulating Hormone (TSH) levels even within the normal reference range are associated with an increased risk of recurrent miscarriage. Evidence suggests that treating SCH in pregnant women in their first trimester can prevent recurrent miscarriage as well as other adverse obstetric outcomes associated with SCH.
Conclusions: Screening for Thyroid-stimulating hormone (TSH) and Thyroxine (T4) levels in pregnant women with a higher risk of SCH can prevent multiple obstetric complications. However, further research is needed to determine the hormone levels required during specific stages of gestation. This would have a positive impact on diagnosis and future medical interventions for maternal and fetal health.

Research Question

In the first trimester of pregnancy, will thyroid screening for subclinical hypothyroidism along with treatment, reduce the risk of miscarriage and other adverse fetal outcomes compared to euthyroid women?

Background

The thyroid is commonly characterized by its metabolic association in regards to hormone production and plays an essential role in growth, body maturation and pregnancy (Khatawkar & Awati, 2015). Thyroid disease is the second most common endocrine disorder that affects women of reproductive age (Reid, Middleton, Cossich, Crowther, & Bain, 2013). Subclinical hypothyroidism (SCH) is asymptomatic and can only be recognized through biochemical testing (Reid, Middleton, Cossich, Crowther, & Bain, 2013). The prevalence of this disease accounts for 4-15% globally (Unnikrishnan et al., 2013). SCH is classified as having a normal reference range of T4 hormone (0.9-1.95 ng/ml), while its thyroid stimulating hormone (TSH) levels are slightly elevated (4.5 - 10.0 mIU/L) (Fartourechi, 2009). For the fetus, maternal thyroid levels are critical to its neuronal brain development and maturation. Abnormal thyroid levels may lead to various obstetric outcomes such as, premature birth, low birth weight (LBW), and neonatal respiratory distress (Lazarus, 2011). For the mother, some adverse health effects include miscarriage, pre-eclampsia, placental abruption, anemia (Reid, Middleton, Cossich, Crowther, & Bain, 2013).

Methods

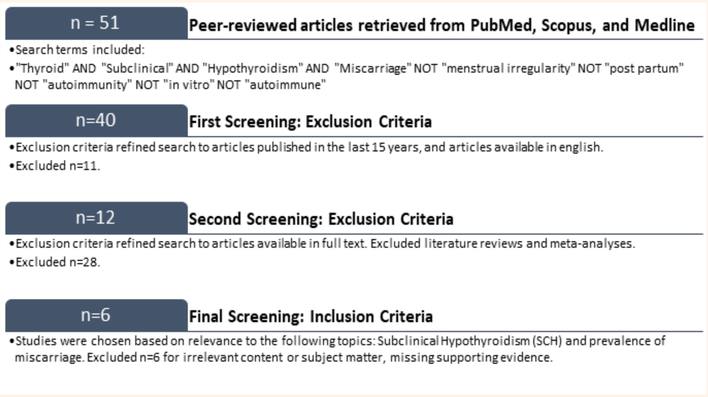

Figure 1. Methodology Flowchart Illustrating Literature Selection Process

Results

Author(s)	Sample Population	Study Design	Results	Conclusions
De Vivo et al. (2010)	N=208 women that had early miscarriages •N=176 euthyroid •N=24 positive thyroid antibodies •N=8 SCH	Retrospective Cohort study: Miscarriages classified by •Very early pregnancy loss (VEPL) •Early pregnancy loss (EPL) occurrences Analysis made between type of miscarriage and levels of thyroid hormone during their pregnancy	• VEPL & SCH were associated with higher levels of TSH (p=0.04) • SCH had a lower gestational age of miscarriage than women with thyroid antibodies	Women suffering from SCH have a lower gestational age at abortion than those affected by autoimmune disease. Very early screening for thyroid disorders is useful to evaluate the need for hormonal supplementation during pregnancy.
Dal Lago et al. (2011)	N=463 (patient group) Euthyroid women that had two or more miscarriages within the first 10 weeks of pregnancy N= 101 (control group) women with history of normal pregnancies	Retrospective Cohort study: •Test for TSH levels, T3 and T4 after injecting TRH into the body •Compared those levels to the iTSH index (testing TRH reactivity)	Basal TSH serum levels are higher in patients 2.1 µUI/ml (95% CI: 2.0–2.2 µUI/ml) than in control – 1.3 µUI/ml (95% CI 1.2–1.4 µUI/ml) p<0.001 Not clinically relevant due to inability to find cut off value Serum Tests after TRH testing – Probability of RM based on TRH reactivity Mostly found in women with low baseline TSH (<1.5)	iTHS is a good comparison for thyroid levels , to determine or characterize euthyroid women that may have a miscarriage as a result of thyroid dysfunction or impairment. The evaluation of serum TSH and TRH reactivity (iTSH) in these selected women may help to identify those at risk of RM TSH levels during basal and after TRH were significantly higher than controls
Raber, Nowotny, Vytiska-Binstorfer & Vierhapper. (2003)	N=283 women with primary and secondary infertility 4 groups based on thyroid function •N=76 SCH •N=155 Mild hypothyroidism •N=17 Euthyroidism •N=35 no TRH testing at first visit	Cohort study: •223 followed for 5 years (60 lost to follow-up) •More miscarriages in groups 1 and 2 hypothyroidisms) •All women with TRH-stimulated TSH response to (>15 mIU/L) were treated with T4 therapy •Routinely visit to adjust T4 therapy until gestation.	No correlation between abortion and the presence of autoimmune thyroiditis No significant difference found in abortion rates between groups 1 and 2 (18% and 29% respectively for 95% CI) Pregnancy rates were similar amongst the 4 groups, had 37% higher rate than expected. [group 1: 31% (95% CI: 20±40%), group 2: 46% (95% CI: 31±52%), group 3: 31% (95% CI: 15±47%), group 4: 30%(16±44%)].	TRH testing for monitoring thyroid function is beneficial due to the high fecundity rate. Those who refused TRH testing (group 4) had similar rates of pregnancy and abortion, however conception took longer (18 months vs 6-9 months).
Abalovich et al. (2013)	N=77 pregnant women newly diagnosed with hypothyroidism N= 64 with SCH •1a – serum TSH>2.5 mIU/L during 1st Trimester OR >3-4.2 mIU/L during 2nd and 3rd trimester •1b serum TSH >4.21-10 mIU/L N=13 with overt hypothyroidism	Retrospective Cohort study: •All patients were treated with LT4 immediately until serum TSH was ≤2.5 mIU/L in 1st trimester •Patients received the appropriate dose of LT4 to achieve a euthyroid state during pregnancy	a significant difference (p<0.0001) in the appropriate LT4 dose was observed between group 1 and group 2. 1.31 (±0.36) vs 2.33 (±0.59). No miscarriages or premature deliveries Did not affect congenital malformations	When hypothyroidism is newly discovered during pregnancy, initiation of treatment with the following LT4 doses: 1.20 lg/kg/day for SCH with TSH £ 4.2 mIU/L, 1.42 lg/kg/day with TSH > 4.2–10, and 2.33 lg/kg/day for OH. This approach ensures patients will attain the euthyroid state thus preventing obstetric complications Taking LT4 as early as possible will prevent miscarriages, and this is done by promptly achieving a euthyroid states
Ma et al. (2015)	N= 1671 pregnant women •N= 675 (Group 1) screened for SCH •N= 996 (Group 2 - control) no screening or treatment	Single Blind, Randomized Control Study : •Group 1 screened for thyroid function and antibodies during early pregnancy. If diagnosed with SCH, was treated with LT4 •Group 2 – blood serum stored after delivery – levels of thyroid indicators (T4, TPOab, TSH) measured •Pregnancy outcomes and relative thyroid function compared between groups	Miscarriage risk was lower in Group 1 3.1 % vs 8.5% p <0.001 Fetal macrosomia was more prevalent in control group (7.1 %) vs those that were screened (3.4%) p=0.001	Screening and intervention of SCH can significantly reduce the incidence rate of miscarriage.
Liu et al. (2014)	N= 3147 women at low risk for thyroid dysfunction, 4 to 8 weeks gestation Total 6 Groups •N=1961 Euthyroid •N= 755 SCH (split into SCH1 & SCH2 based on limit cut off TSH) •N= 227 Isolated TAI •N= 204 SCH + TAI (split into 1 and 2 based on TSH cut off) *TAI = antibody positive	Prospective cohort study: •Screened for TSH, FT4, TPOAb and TgAb → divided into groups based on classification •Followed through with pregnancy with focus on miscarriage - before 20 weeks gestation	Gestational age of SCH patients were lower than euthyroid 11.13 weeks v. 9.33 weeks p=0.024 Only 3.5% (110 women) had miscarriages Miscarriage rates were highest among SCH patients with the presence of TAI (7.1% vs. 2.2%, aOR 3.40[CI 1.62–7.15]; p=0.002)	Euthyroid women that are TAI positive have a higher risk of developing SCH during the first trimester Women with SCH and TAI are at an increased risk of miscarriage between four and eight gestational weeks. Women with a combination of SCH and TAI were found to have the highest risk and earlier gestational ages of miscarriage.

Figure 2. Summary of Structured Literature Review

Discussion

Key Findings
- Two of the studies state that SCH is associated with earlier gestational age at miscarriage
- High levels of TSH is indicative of SCH and thus increases the prevalence of miscarriages
- With treatment (levothyroxine/T4 therapy), pregnancy and abortion rates were similar to euthyroid women
- Reduction in screening and treatment can elongate the time for conception, thus SCH can affect fertility as well
- One study suggests congenital malformations are likely not affected by LT4 treatment as a result of SCH
- One study suggests fetal macrosomia is prevalent in those with untreated SCH
- Presence of TPOab and TgAb (thyroid antibodies) in combination of SCH increases the risk of miscarriage during the first trimester

Contextualization of Results
Maternal thyroid hormones are required for the stability of the fetal-placental unit (Raber et al, 2003). Due to the nature of SCH, screening was crucial in diagnosing and treating these women during their pregnancy to prevent miscarriages, or in some cases, to explain why they have RM. As SCH is often asymptomatic, it is not uncommon to be unaware of having SCH. Throughout this research, a large portion of women were discovered to have either SCH or other thyroid dysfunctions. With the treatment of levothyroxine (LT4) as early as possible in the pregnancy (ideally within the first trimester), miscarriage rates reduced dramatically. This treatment also prevented many other obstetric complications that often are associated with SCH. This was expected, as levothyroxine treatment works to increase thyroid hormonal levels. Once these women reach a normalized thyroid levels, obstetric complications that would be associated with SCH or other thyroid dysfunctions should not occur.

Limitations of the Study
- At the time of study, gestational periods varied, which may have been a factor that influenced thyroid hormone levels. Narrowing the mean age down to the first 20 weeks or first trimester, would allow better comparisons
- Language exclusion bias present in choice of research studies. English studies could only be chosen
- Selection bias present in control groups within sample populations. Blind control arms represent the public and will include factors that can influence miscarriages compared to other studies that use known euthyroid women for controls. Results in an exaggerated effectiveness of treatment group.
- Only thyroid disorders were tested for and monitored during these studies, other health conditions were not taken into account, thus there is no way of knowing which patients may have been affected by other pre-existing conditions.

Positive Aspect
Our structured literature review viewed studies across several geographical regions. Demonstrates that SCH and risks of miscarriages can occur globally. Screening can thus be beneficial to every woman as all can be affected similarly.

Implication for Future Research or Policy
- Limit control groups to euthyroid women, as they represent the goal of treatment
- Look at the different cultural or societal factors of various regions to determine if there is an increased risk for SCH and miscarriages based on these
- Acquire better understanding of LT4 dosage levels required during different stages of gestation to reduce the amount of time it takes for patients to reach a euthyroid state.

Conclusion

Thyroid screening during the first trimester of pregnancies is shown to reduce the risk of miscarriage and other obstetric complications through the immediate intervention of levothyroxine (LT4). Thyroid screening should thus be implemented as universal screening during the first trimester of pregnancy. However, further research may be required to implement standard doses of LT4 throughout gestation.

References

Abalovich, M., Vázquez, A., Alcaraz, G., Kitsaigrodsky, A., Szuman, G., Calabrese, C., … Gutiérrez, S. (2013). Adequate Levothyroxine Doses for the Treatment of Hypothyroidism Newly Discovered During Pregnancy. Thyroid, 23(11), 1479–1483. https://doi.org/10.1089/thy.2013.0024

Dal Lago, A., Vaquero, E., Pasqualetti, P., Lazzarin, N., De Carolis, C., Perricone, R., & Moretti, C. (2011). Prediction of early pregnancy maternal thyroid impairment in women affected with unexplained recurrent miscarriage. Human Reproduction (Oxford, England), 26(6), 1324–30. https://doi.org/10.1093/humrep/der069

De Vivo, A., Mancuso, A., Giacobbe, A., Moleti, M., Maggio Savasta, L., De Dominici, R., … Vermiglio, F. (2010). Thyroid function in women found to have early pregnancy loss. Thyroid : Official Journal of the American Thyroid Association, 20(6), 633–637. https://doi.org/10.1089/thy.2009.0323

Fatourechi, V. (2009). Subclinical Hypothyroidism: An Update for Primary Care Physicians. Mayo Clinic Proceedings, 84(1), 65–71. https://doi.org/10.4065/84.1.65

Khatawkar, A. V, & Awati, S. M. (2015). Thyroid gland - Historical aspects , Embryology , Anatomy and Physiology. International Archives of Integrated Medicine, 2(9), 165–171. Retrieved from http://iaimjournal.com/wp-content/uploads/2015/09/iaim_2015_0209_28.pdf

Lazarus, J. H. (2011). Screening for Thyroid Dysfunction in Pregnancy: Is It Worthwhile? Journal of Thyroid Research, 2011, 1–4. https://doi.org/10.4061/2011/397012

Liu, H., Shan, Z., Li, C., Mao, J., Xie, X., Wang, W., … Teng, W. (2014). Maternal Subclinical Hypothyroidism, Thyroid Autoimmunity, and the Risk of Miscarriage: A Prospective Cohort Study. Thyroid, 24(11), 1642–1649. https://doi.org/10.1089/thy.2014.0029

Ma, L., Qi, H., Chai, X., Jiang, F., Mao, S., Liu, J., … Yan, Q. (2015). The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: a prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 7058(June), 1–4. https://doi.org/10.3109/14767058.2015.1049150

Raber, W., Nowotny, P., Vytiska-Binstorfer, E., & Vierhapper, H. (2003). Thyroxine treatment modified in infertile women according to thyroxine-releasing hormone testing: 5 year follow-up of 283 women referred after exclusion of absolute causes of infertility. Human Reproduction, 18(4), 707–714. https://doi.org/10.1093/humrep/deg142

Reid, S. M., Middleton, P., Cossich, M. C., Crowther, C. A., & Bain, E. (2013). Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. The Cochrane Database of Systematic Reviews, 5(5), CD007752. https://doi.org/10.1002/14651858.CD007752.pub3

Bagge, B., Bohlsen, H., Sehgal, R., Relevo, R., Gorman, P., & Helfand, M. (2011). Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism. Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22299183