

# Associations Between Subclinical Hypothyroidism and Pregnancy Complications

By Natalie Eidson  
Department of Integrative Physiology, University of Colorado

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Thesis Advisor:

Dr. Teresa Foley, Department of Integrative Physiology

Defense Committee:

Dr. Teresa Foley, Department of Integrative Physiology

Dr. David E. Sherwood, Department of Integrative Physiology

Dr. Matthew McQueen, Department of Integrative Physiology

Dr. Barbara Demmig-Adams, Department of Ecology and Evolutionary Biology

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## **Abstract**

Thyroid disorders are common endocrine disorders in the United States, affecting women more often than men. Due to the higher incidence of thyroid dysfunction in women, recent studies have been conducted to determine whether hypothyroidism could play a role in pregnancy complications. While studies have shown that *clinical* hypothyroidism can pose a threat to both the mother and child, fewer studies have investigated *subclinical* hypothyroidism. Therefore the aim of this systematic review was to determine the associations between subclinical hypothyroidism, in relation to increased thyroid stimulating hormone levels and normal tetraiodothyronine levels in pregnancy complications. The complications that were analyzed included placental abruption, premature delivery, low birth weight, intrauterine growth restriction, fetal and neonatal demise, and fetal distress. Odds ratios and relative risk ratios were collected from 11 independent studies and analyzed using a meta-analysis. A summary estimate was calculated for each complication and the results were plotted on forest plots. Of the six complications measured, intrauterine growth restriction, placental abruption, fetal distress and fetal/neonatal demise were found to be associated with subclinical hypothyroidism. Further research is suggested in order to determine: 1) whether other pregnancy complications, in addition to those researched in this study, may be related to subclinical hypothyroidism, and 2) how subclinical hypothyroidism compares to overt (clinical) hypothyroidism in terms of these pregnancy complications.

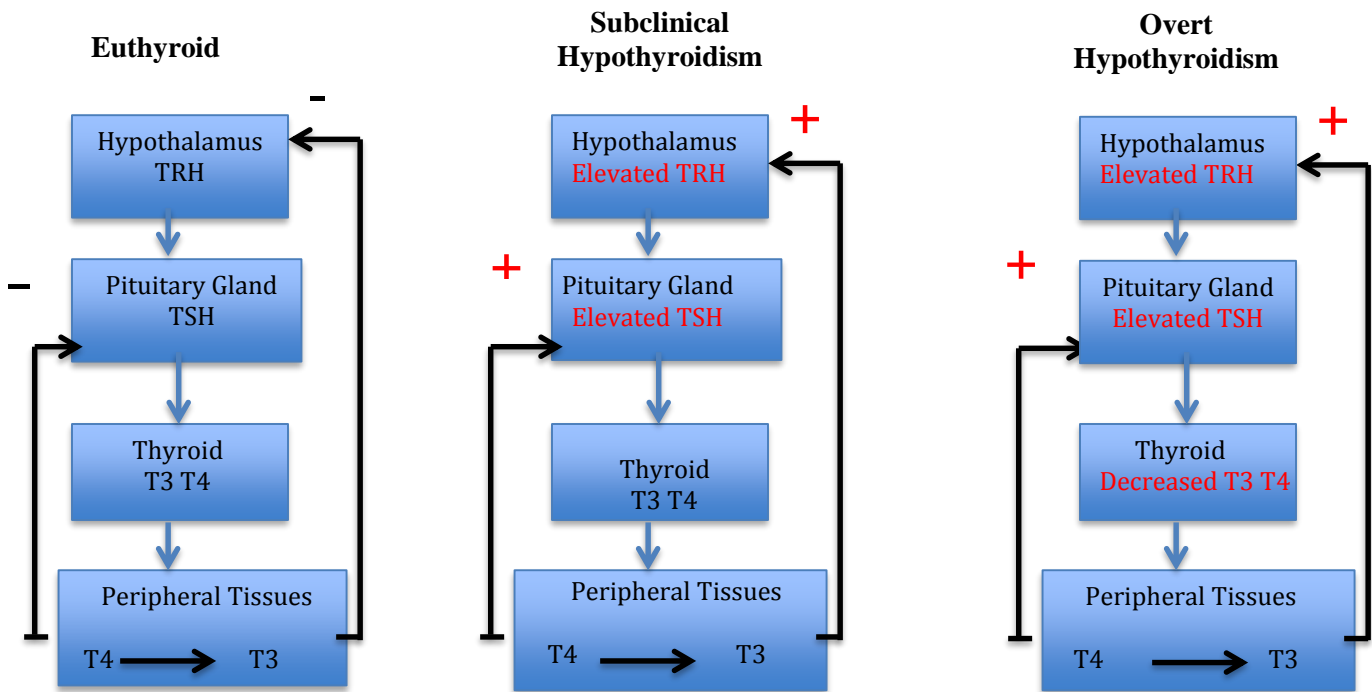
## **Introduction**

The thyroid gland is a small yet vital organ within the endocrine system. The thyroid is responsible for synthesizing and releasing hormones that regulate essential functions such as growth, metabolism, and temperature. The process of thyroid hormone production involves the hypothalamus, the pituitary gland, and the thyroid gland, which work in a feedback mechanism known as the hypothalamic-pituitary-thyroid (HPT) axis. The HPT axis begins in the hypothalamus of the brain where neuronal cell bodies in the paraventricular nucleus synthesize thyrotropin-releasing hormone (TRH). TRH is passed through the hypothalamic pituitary-portal system to the anterior pituitary to stimulate the synthesis and release of thyroid stimulating hormone (TSH) by thyrotrophs within the pars distalis. TSH is then released from the anterior pituitary where it acts on follicular cell receptors on the thyroid gland to stimulate the synthesis and production of triiodothyronine (T3) and tetraiodothyronine (T4) hormones<sup>45</sup>. Due to its longer half-life, the majority of thyroid hormones traveling in the blood are T4. To exert its effects when leaving the blood, T4 is then converted to T3 by the removal of an iodine atom<sup>4</sup>. When T3 and T4 reach a higher than normal concentration in the body, these hormones will act in a negative feedback manner. The negative feedback loop works by T3 and T4 signaling the hypothalamus and pituitary gland to stop the release of TRH and TSH, thus inhibiting further production of thyroid hormones in order to establish homeostasis<sup>45</sup>.

Thyroid complications are one of the most common endocrine disorders within the population. Approximately 20 million people living in the United States have some form of thyroid disorder-12 million of which are undiagnosed<sup>40</sup>. Remarkably, the majority of these affected individuals are women as opposed to men. Women are 5 to 8

times more likely to developed a thyroid disorder then men. Moreover, 1 in every 8 women will eventually be diagnosed with a thyroid disorder in her lifetime<sup>40</sup>.

Of the different types of thyroid disorders, hypothyroidism is the most common in women. Subclinical hypothyroidism (SCH) is defined as a high TSH concentration with a normal range of serum T4. Overt hypothyroidism (OH) is defined as a high TSH concentration with low serum T4 concentrations (Figure 1). The prevalence of SCH is higher than OH, affecting 4 to 8% of the US adult population<sup>38</sup>.



**Figure 1.** Hypothalamic-Pituitary-Thyroid axis of patients that are euthyroid (left), or have subclinical hypothyroidism (center) or overt hypothyroidism (right).

Symptoms of hypothyroidism include fatigue, weight gain, decreased heart rate, dry hair and skin, sensitivity to cold, and potential swelling of the thyroid gland (goiter)<sup>43</sup>. If untreated, hypothyroidism can lead to cardiac dysfunction, neuropsychiatric symptoms and increase in low-density lipoprotein (LDL) cholesterol<sup>38</sup>. Because

hypothyroidism is relatively common and undiagnosed in women, there is increased concern that these thyroid disorders may consequently affect pregnancies.

During pregnancy, the fetus relies heavily on its mother to synthesize essential hormones. As a result, hormone levels in the mother fluctuate greatly. For instance, the maternal thyroid gland must produce twice as much thyroid hormone during pregnancy in order to supply enough thyroid hormones for both the mother as well as the developing fetus<sup>24</sup>. However, if a pregnant woman has an undiagnosed thyroid disorder, she may not be able to provide an adequate amount of hormones, which is essential for both her and her fetus. Ultimately, an insufficient amount of thyroid hormones may lead to severe pregnancy complications<sup>18</sup>. Many studies have demonstrated the detrimental affects of OH and decreased levels of T3 and T4 on pregnancy<sup>1, 2, 29</sup>.

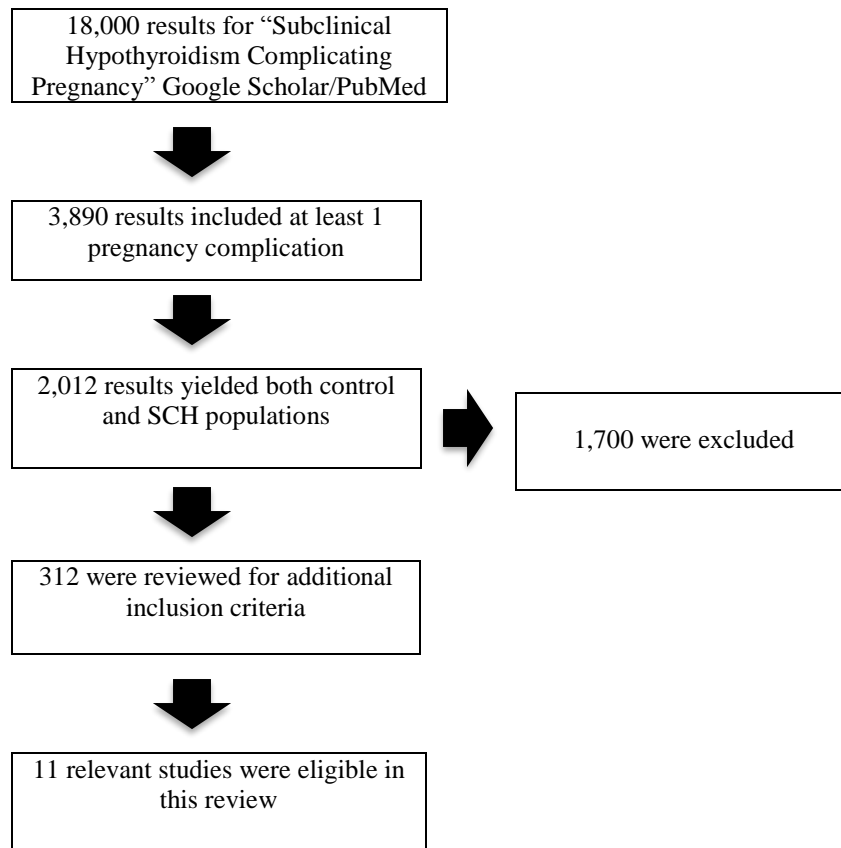
Even though the maternal thyroid is crucial for a fetus, universal screening for thyroid disorders has yet to be established<sup>11</sup>. The American College of Obstetricians and Gynecologists and the clinical practice guidelines of the Endocrine Society recommend to only screen for women who are presenting symptoms or have a history of thyroid diseases<sup>13</sup>. Though it is well understood that OH can cause pregnancy complications, there is not a high enough prevalence of OH in the United States to justify screening. Women diagnosed with OH are often times infertile and unable to conceive which decreases the prevalence of pregnant women with OH even further<sup>37</sup>. In SCH, these women are able to maintain a normal range of thyroid hormones, and are thus not believed to be at risk for pregnancy complications. Thus universal screening for SCH has also yet to be established.

While several studies have demonstrated the risk of OH in women who are able to conceive<sup>1, 2, 29</sup>, fewer studies have been carried out regarding SCH. Due to a higher incidence of women with SCH versus OH, the aim of this systemic review was to determine whether an increased maternal TSH level and normal serum T4 levels, as seen in SCH, could also be associated with pregnancy complications. In this study, a meta-analysis was performed on 11 different studies to generate an overall effect size for each complication. Results were then used to make a recommendation for universal thyroid screening in pregnancies.

## **Methods**

### *Inclusion Criteria*

Research for potential studies used in this systematic review and meta-analysis began on February 1, 2015 and ended on September 1, 2015. Keywords, “subclinical hypothyroidism” and “pregnancy” were used to find studies in the PubMed and Google Scholar databases. Search criteria included: 1) total sample size of at least 300 people; 2) results included at least one of following complications- placental abruption, premature delivery, low birth weight, intrauterine growth restriction, fetal distress, and/or fetal and neonatal demise; 3) studies were reported in English; 4) Levothyroxine treatment was not administered; 5) SCH was defined as an increased TSH level with a normal concentration of FT4. Any study that defined SCH as high TSH without measuring FT4 was excluded, as well as studies that failed to meet any other criteria. Figure 3 below describes the methods used in order to find eligible studies that met these criteria.



**Figure 2.**Flow chart describing the method for incorporating relevant studies for this review

### *Assessment of Pregnancy Complications*

Placental abruption is the premature separation from uterine lining of a normally implanted placenta prior to delivery<sup>5, 13, 14</sup>. Previous research has demonstrated that placental abruption can lead to additional pregnancy risks such as premature birth, low birth weight, intrauterine restriction and stillbirth<sup>5</sup>.

Premature delivery is defined as birth before 34-37 weeks of gestation and very premature birth is defined as birth before 34 weeks of gestation<sup>9, 12-14, 19, 20, 25, 29, 30, 37</sup>. In the present study, premature and very premature birth were classified together as one complication and defined as premature if birth occurred before 37 weeks. Prematurity is a

significant risk as it can cause chronic lung disease, developmental delay, growth reduction, hearing impairment, neonatal infections, respiratory distress syndrome, intraventricular hemorrhage and more<sup>42</sup>.

Low birth weight is classified as neonatal weight less than 2500 gm after birth<sup>2, 12-14, 20, 37</sup>. This complication can lead to an increased threat of infant mortality and childhood morbidity<sup>22</sup>.

Intrauterine growth restriction is a decreased in growth rate of a fetus during gestation. Intrauterine growth restriction occurs when a fetus' developmental rate is less than 10<sup>th</sup> percentile of its gestational age<sup>2, 9, 12, 13, 29</sup>. This complication poses a significant threat as it can lead to fetal hypoxia and perinatal mortality<sup>21</sup>.

Of the studies included, only one gave a description of fetal distress. In this study, fetal distress was defined as fetal heart rate less than 120 beats per minute or greater than 160 bpm, presence of meconium (fetal feces), signs of abnormal fetal movement, and fetal scalp pH less than 7.22<sup>13</sup>. In another study entitled *What is Fetal Distress*<sup>26</sup>, the authors claim that fetal distress is due to the onset of asphyxia where the fetus is deprived of oxygen due to insufficient uterine or umbilical blood flow. This stress can lead to irregular fetal heart rate patterns such as late decelerations, variable decelerations, or prolonged bradycardia<sup>26</sup> (slow heart rate). Fetal distress can cause neonatal encephalopathy, where the brain's function or structure is impaired, as well as impaired development of the central nervous system<sup>2, 32, 37</sup>.

For the purpose of this present study, fetal and neonatal demise were defined as a terminated pregnancy at any duration during gestation. Death during the first 28 days of life was also included in order to account for neonatal demise. There are several ways of

classifying terminated pregnancy including fetal demise, miscarriage, spontaneous abortion, stillbirth, and neonatal demise. These terms were thus classified together as one complication.

### *Defining Subclinical Hypothyroidism*

The diagnosis of SCH varied within the several studies included in this project. For this reason, guidelines according to the American Thyroid Association were used to establish a single reference range. The American Thyroid Association recommends the specific reference range for TSH levels during each trimester should be 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester, and 0.3–3.0 mIU/L in the third trimester<sup>35</sup>. The first trimester is marked by a decreased level of TSH due to the increase in human chorionic gonadotropin (hCG) secretion from the placenta, which binds to TSH receptors in the brain. As hCG levels decrease throughout the pregnancy, TSH increases<sup>35</sup>.

When diagnosing SCH, free tetraiodothyronine (FT4) are measured instead of T4. T4 hormones are bound to albumin and thyroid binding globulin (TBG) in the blood, which prevents them from entering target tissues. FT4, however, is free to enter and exert its effects<sup>4</sup>. When measuring FT4 during the duration of a pregnancy, FT4 appears to have an inverse affect with TSH. Trimester specific levels of FT4 are as follows: 1.13±0.23 ng/dL in the first trimester, 0.92±0.30 ng/dL in the second trimester, and 0.86±0.21 ng/dL in the third trimester<sup>35</sup>.

Overall, the American Thyroid Association states that SCH during pregnancy may be defined as a serum TSH between 2.5 and 10 mIU/L with a normal FT4 concentration<sup>35</sup>. The average interval of FT4 in each trimester is between 0.6 and 1.3

ng/dl. Because the studies used in this current project ranged in the time of SCH screening from 13 to 40 weeks, this range of FT4 was used to define this disease in all three trimesters.

### *Data Analysis*

Listed in Table 1 and 2 of the appendix are the 11 studies that were included in this project. The combined number of women with SCH from each number was 2,272. Nationality ranged worldwide across eight different countries. Age of participants among total population sizes also varied between 20 to 40 years of age. Each study was carried out as a prospective cohort in which subclinical hypothyroid and euthyroid (control) participants were followed throughout their pregnancies. In these prospective cohorts, a correlation between euthyroid (control) and hypothyroid (tested) populations were determined and effects sizes were reported.

Effect sizes are reported as either an odds ratio (OR) or risk ratio (RR), which allows the comparison between an exposure and outcome. An OR determines the odds that an outcome will occur for a given exposure as compared to the odds of the outcome occurring in the absence of that exposure. Relative risk is the probability of an event occurring in an exposed population as compared to the probability of the same event occurring in a non-exposed group. Because some studies in this project reported OR while others gave RR, both effect sizes were used.

If the effect sizes were not reported, which was true for four studies<sup>2, 14, 20, 15</sup>, the effect sizes were calculated from the raw data using a 2x2 contingency table<sup>46</sup> (Figure 3).

In three studies<sup>12, 13, 19</sup>, effect sizes were reported for only certain complications. For the complications that were not reported, these effect sizes were also calculated by raw data.

	Events	Non-Events	N
Tested	A	B	n1
Control	C	D	n2

$$\text{Risk Ratio} = \frac{A/n1}{C/n2}$$

$$\text{Odds Ratio} = AD/BC$$

**Figure 3.** 2x2 Contingency Table for calculation of odds ratio and risk ratio.

From the effect sizes, confidence intervals were generated and used to calculate the standard errors for each pregnancy complication. Confidence intervals measure the precision of the effect size within that study. Smaller confidence intervals are more precise and typically indicate the result of a larger sample size. Thus, smaller confidence intervals are assigned a higher weight in the meta-analysis.

The effect sizes and standard errors were used to run a meta-analysis and the results were plotted on a forest plot for each complication. A summary effect was generated using R software (version 3.2.2) and meta-package, which reported the weighted mean of the individual effects.

The two types of summary effects reported in a meta-analysis are the fixed effect model and the random effect model. The fixed effect model is used in cases where every study included in the meta-analysis is functionally equivalent. The goal is to then

generate a summary effect for an identical population. This model assumes common effect sizes between studies and variation is thus only accounted for within studies. The random effect model is used when generalizing results from studies that have been conducted by independent researchers with different population sizes. Random effect takes into account the variation within each study plus the variation between studies.

In this meta-analysis, results from 11 independent studies were included and therefore the random effect model was used to generate a forest plot. The p-value of between study significance as well as the test for heterogeneity were also reported. A p-value of less than 0.05 was used to indicate significant difference between studies. Heterogeneity refers to variation between studies, which was reported as  $I^2$ . A higher  $I^2$  percentage was reflective of higher heterogeneity between studies.

## **Results**

The summary effects from each study were computed for six pregnancy complications and the data were organized onto separate forest plots. The vertical line through the value of 1 indicates the reference line, or the line of no effect. An effect size equal to 1 implies that there is no relation or difference in risk between SCH and the pregnancy complication. An effect size greater than 1 implies that that SCH is positively related, or more likely to occur, in that pregnancy complication. If the effect size value is less than 1, then SCH is negatively related, or less likely to occur for that pregnancy complication. The size of the boxes indicates the weight, which is calculated by taking the inverse of the variance for that particular study. Therefore the study with the lowest variation, which is also commonly due to a larger population size, is assigned the highest weight. A large population size is also indicative of a smaller confidence interval, which

again reflects a smaller variance and is represented by a horizontal line through the effect size. At the end of the forest plot, depicted in red, is the summary effect. Both fixed and random effects are reported, however, only the random effects are displayed on the forest plots. As mentioned previously, a random effect size is more appropriate to use for this meta-analysis due to the fact that independent researchers with different population sizes conducted each study. The red dotted line runs through the summary effect value in order to better interpret the trend between studies.

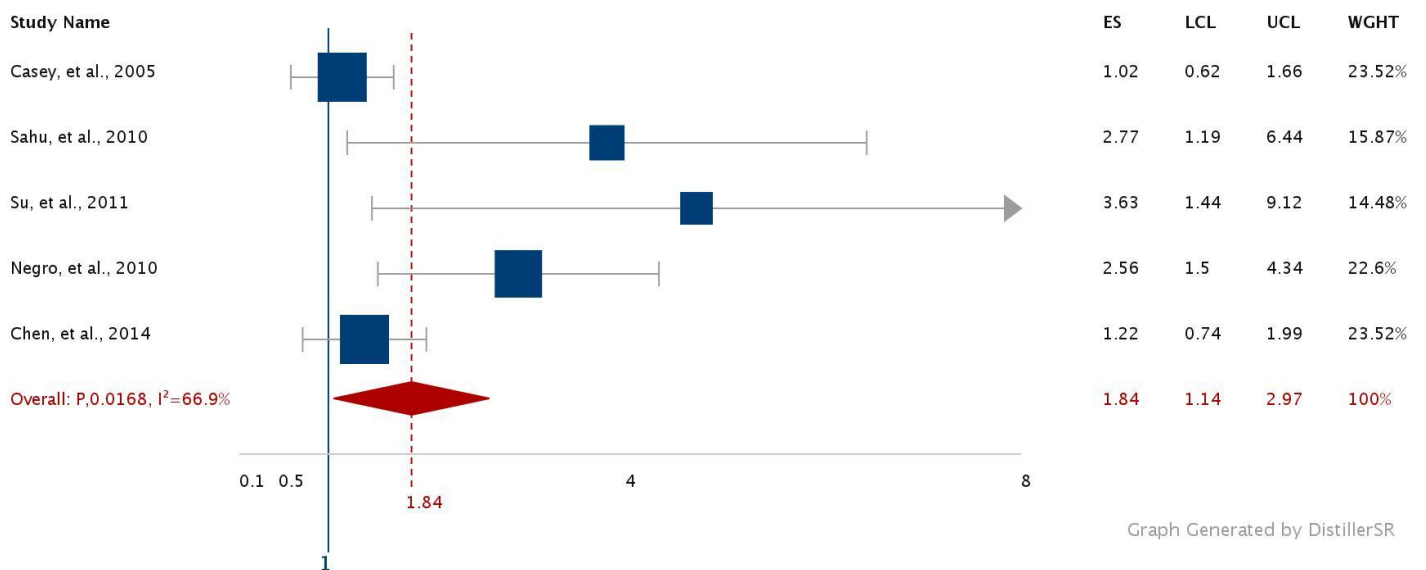
Of the six complications measured, four were positively related with SCH: fetal distress, intrauterine growth restriction, placental abruption, and fetal/neonatal demise. Low birth weight had a random effect size of 1.16 (fixed effect = 1.21) and a non-significant p value of 0.57. This random effect size is only slightly above 1 and therefore was not regarded as a statistically significant, positive relation. The random effect size for premature delivery was 0.98 (fixed effect = 0.79) with an insignificant p value of 0.97. The random summary effect for premature birth was almost exactly the null value indicating that the SCH group and the euthyroid group were at the same odds or risk of having a preterm birth.

Five studies were included in the analysis of fetal distress (Figure 4). After weighing the individual effect sizes for fetal distress, the random effect summary was 1.84, which implies that women with SCH were 1.84 times more likely to develop fetal distress than the control group (fixed effect = 1.64). The confidence interval was 1.14-2.97 meaning that there is 95% confidence that the true random effect summary fell within this range. Due to the fact that the confidence interval did not include the null value of 1, the p value was significant (p value = 0.012). The heterogeneity p value

(0.016) was also significant indicating that at least one study was significantly different from the rest, which furthers the reason to use a random effect summary value as compared to the fixed effect. This point is also illustrated by an  $I^2$  percentage of 66.9% heterogeneity.

As depicted on the forest plot in figure 4, it can be inferred that Chen, et al., and Casey, et al., had much smaller confidence intervals as opposed to the other studies. This difference may be explained by their sample sizes that were several thousand times larger. Chen, et al., and Casey, et al., also adjusted for several variables whereas the remaining studies did not report any adjustment.

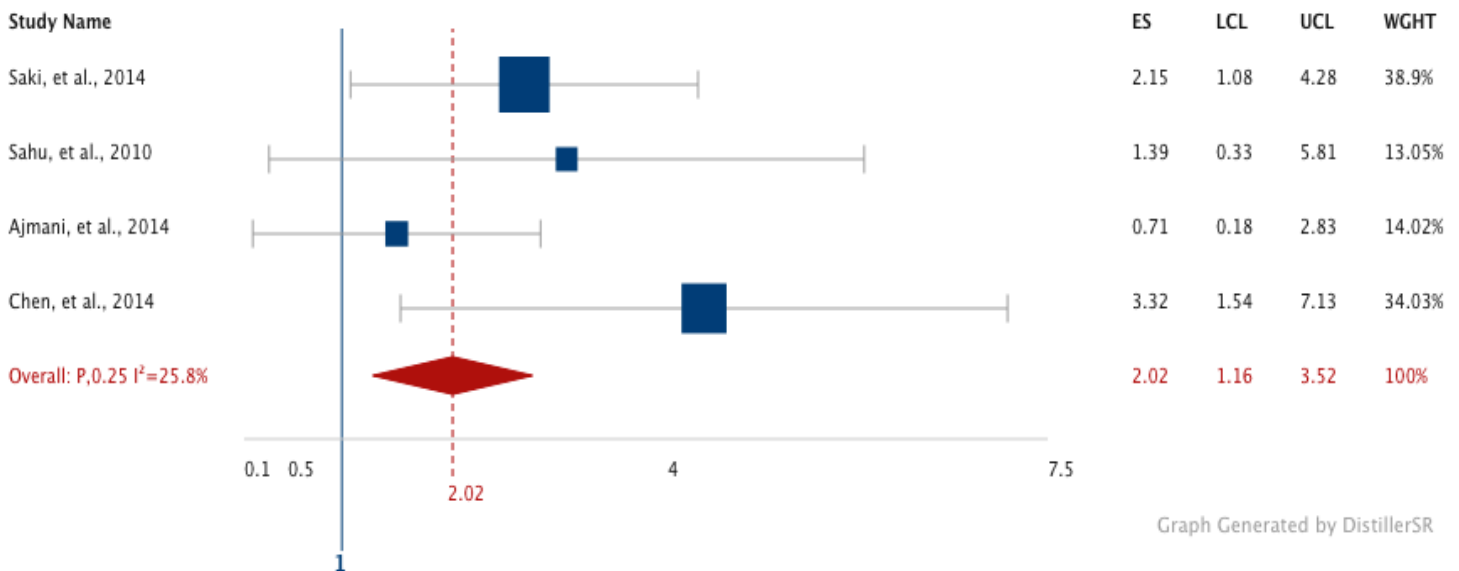
#### Fetal Distress



**Figure 4.** Individual effect sizes and summary estimates of the association between SCH and fetal distress

For intrauterine growth restriction (Figure 5), the random effect summary was 2.023 (fixed effect = 2.13) therefore making the SCH group over two times more likely of developing IUGR. Due to the fact that the confidence interval did not include the value of 1, the p value was again significant (0.013). Though the effect size was large, indicating a positive relation, only four studies measured intrauterine growth restriction. However, three of the four included studies reported an effect size greater than 1 indicating a positive relation between SCH and intrauterine growth restriction. As seen in red in the forest plot in figure 5, the test for heterogeneity p value was not significant. However, the  $I^2$  value still reflected heterogeneity between the included studies.

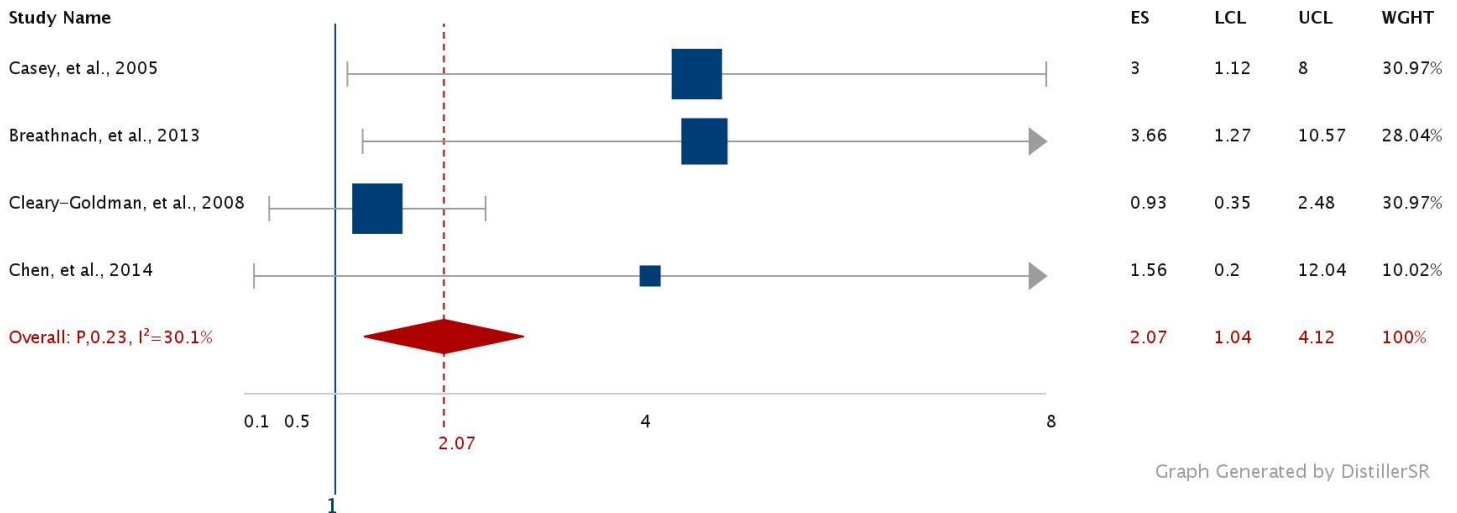
### Intrauterine Growth Restriction



**Figure 5.** Individual effect sizes and summary estimates of the association between SCH and intrauterine growth restriction

The random effect summary for placental abruption was 2.072 (fixed effect = 2.071) with a significant p value of 0.038. Again, this pregnancy complication was almost two times more likely for the SCH group as compared to the euthyroid group (Figure 6). Even though only four studies included this complication as well, three were in agreement with an association between SCH and placental abruption. The heterogeneity p value was 0.23, which doesn't meet the cut off for significance, however, the  $I^2$  percentage of 30.1% reflects some variation between these studies. Cleary-Goldman, et al., was a slight outlier in this meta-analysis, however this may be explained by the fact that they adjusted for previous birth complications that decreased a large amount of variation within their study.

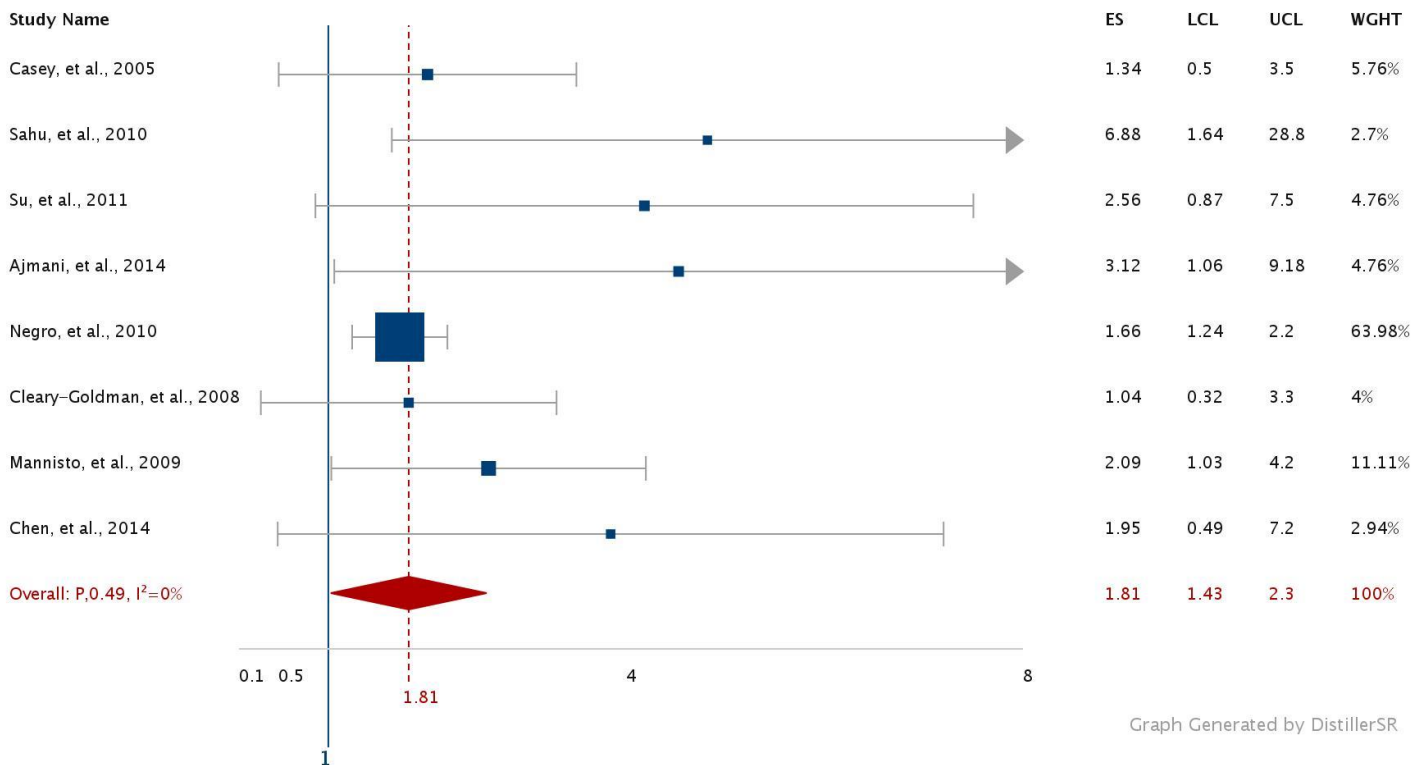
### Placental Abruption



**Figure 6.** Individual effect sizes and summary estimates of the association between SCH and placental abruption

Finally, fetal and neonatal demise had a random effect summary of 1.81 and a significant p value of 0.001 (Figure 7). The fixed affect value was identical in this meta-analysis (1.81) and the  $I^2$  was 0%. Though these studies were not identical, as they had different population sizes, a 0% heterogeneity could be explained by the fact that they each had the same standard error and therefore were very similar. All eight individual studies reported effect values above the null value for fetal and neonatal demise, which suggests a strong relation between SCH and fetal and neonatal demise. An outlier in this meta-analysis was in the Negro, et al., however, this study did not report their covariates and it is unclear as to why their confidence interval is much smaller in comparison to the other studies.

### Fetal and Neonatal Death



**Figure 7.** Individual effect sizes and summary estimates of the association between SCH and fetal and neonatal demise

## **Discussion**

### *Physiological Rational*

The present meta-analysis, indicates that SCH may be positively related to pregnancy complications. Four of the pregnancy complications were significantly associated with SCH, and every pregnancy complication was more closely associated with SCH versus euthyroid groups. The physiological reason behind why an elevated level of TSH and normal levels of T3 and T4 are associated with these complications is not well understood. However, below are three plausible explanations for these results.

Several studies have demonstrated that an increase in TSH concentration can cause high blood pressure<sup>7, 15, 44</sup>. Hypertension in pregnant women can pose a threat to her developing child as it may lead to decreased blood flow and oxygen to the placenta. In several studies<sup>3, 5, 10</sup>, complications, such as fetal demise, placental abruption, and others have been shown to be the result of maternal high blood pressure. Therefore, there may be a cascade of events in which SCH induces high blood pressure in women who are then at a higher risk of several different complications during pregnancy.

Another explanation is derived from the negative feedback loop of the HPT axis. As mentioned previously, T3 and T4 work to shut off the production of TRH and TSH in the brain. However, if thyroid hormones are not working properly, these hormones can cause an increase in production of TRH, which acts tropically on TSH to increase its production. TRH not only works to increase the production of TSH, however, it also increases levels of prolactin released from the pituitary gland, which can lead to hyperprolactinemia, or the overproduction of prolactin.

Hyperprolactinemia is often seen in patients diagnosed with SCH<sup>27</sup>. High TRH levels, resulting in an increase in prolactin concentrations, have also been shown to be associated with miscarriages<sup>17, 23</sup>. Elevated levels of prolactin can lead to a decrease in progesterone, which is crucial to maintain a pregnancy. Without progesterone, the corpus luteum is unable to survive, which then results in a miscarriage<sup>8</sup>. Therefore, women with elevated levels of TSH and prolactin are at a higher risk of having a prematurely terminated pregnancy than those who are not.

A final explanation as to why SCH can cause pregnancy complications may be due to the consequences of an underlying autoimmune disease. Hypothyroidism is often the result of an autoimmune disorder known as Hashimoto's disease. In the latter disease, antibodies such as thyroid peroxidase antibodies (anti-TPO) destroy the enzymes responsible for synthesizing thyroid hormones. Although it is unclear whether these antibodies can cross the placenta and cause complications, certain studies<sup>34, 39</sup> have suggested that these auto reactive antibodies can be harmful to a developing fetus.

### *Limitations*

Throughout the course of the present meta-analysis, certain limitations impacted the results. For instance, within each study there was a difference in the reported conditions such as the diagnostic criteria of SCH, the timing of SCH screening as well as their adjusted variables. In the studies investigated, normal TSH levels ranged between > 2.5-5.5 mIU/L. This range is potentially problematic, as studies focusing on the higher end of TSH concentrations may have missed complications in women they defined as euthyroid. Timing of screening may have also impacted the results. Screening for SCH ranged throughout the entire gestational period. Some studies that diagnosed SCH during

the first trimester, did not focus on women who may have developed the disorder later in their pregnancy. The present meta-analysis, therefore, did not adjust for timing of diagnosis. The adjusted variables ranged from delivery gestation age, maternal age, body mass index, exposure to smoking, parity, ethnicity, maternal height, and neonatal sex. However, consistency was not met between studies. Another variation was the range in ethnicity. Ethnic discrepancies were not taken in account when generating the results, which may have also had an impact. Since only two studies used in this meta-analysis were conducted in the United States, it is difficult to advocate for or against universal screening in North America. A final limitation was the size of available studies used in the meta-analysis. Due to the fact that SCH complicating pregnancies is a relatively new concept, little research has thus far been conducted on this matter.

#### *Recommendations for Future Research*

Debate regarding whether to screen for thyroid diseases is ongoing, as experts involved in producing guidelines on thyroid diseases during pregnancy have not reached a consensus. Those in favor of screening claim that, due to the inexpensive cost of screening and treating thyroid diseases, many women may be spared from experiencing pregnancy complications<sup>24</sup>. Those against screening do not believe these disorders meet the criteria for universal screening. According to the US Preventative Services Task Force, criteria used to initiate new population screening includes: 1) the diagnosis of the disease should be prevalent or important enough to justify screening; 2) clear evidence of negative outcomes associated with the diagnosis; 3) an intervention that should improve the outcome; and 4) screening should be cost effective<sup>11</sup>. Though OH has

been shown to cause complications during pregnancy, the prevalence of OH is only 0.02%. For this reason, the current stance on the matter is not to include women with SCH, for lack of a high enough prevalence of this disease to implement universal screening<sup>11</sup>.

According to the results of this meta-analysis, there may be reasons to believe that high TSH and normal T4 concentrations in the blood, as seen in patients with SCH, can result in pregnancy complications. For this reason, the prevalence of SCH should be included in the case for universal screening as it occurs in 4-8% of the US adult population<sup>38</sup>. Additional research needs to be done to determine the associations of SCH and pregnancies specifically in the United States population. Preceding these studies, additional research should be conducted to determine whether treatment of thyroid diseases alleviates this issue. If future research also demonstrated a correlation between SCH and pregnancy complications, and viable treatment options are available, then the four recommended criteria would be met for implementations of universal screening for thyroid disorders.

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## Appendix

**Table 1.** Demographics and measured birth defects between 11 studies included in the meta-analysis

<b>Study</b>	<b>Country</b>	<b>Mean Age ± SD</b>	<b>Time of Screening (weeks)</b>	<b>Measured Birth Defects</b>
Casey, et al., 2005	United States	26.9 ± 5.9	< 20	Preterm delivery, very preterm delivery, placental abruption, neonatal/fetal demise, fetal distress, LBW
Saki, et al. 2014	Iran	25.8 ± 3.5	15-28	IUGR, preterm delivery
Sahu, et al. 2010	India	27.2 ± 4.1	13-26	Fetal distress, premature delivery, IUGR, fetal/neonatal demise
Su, et al., 2011	China	20-42	20	Spontaneous abortion, fetal death, neonatal death, fetal distress, preterm delivery, LBW
Ajmani, et al. 2014	India	24.51 ± 4.71	13-26	LBW, preterm delivery
Breathnach, et al., 2013	Australia/New Zealand	27 ± 5	13-27	Premature delivery, IUGR, placental abruption
Korevaar, et al, 2013	Netherlands	29.7 ± 5	13.2	Premature delivery
Negro, et al., 2010	Italy	28.7 ± 5	1-12	Fetal/neonatal demise, premature delivery
Cleary-Goldman, et al., 2008	United States	29.8 ± 5.7	1-27	Fetal/neonatal demise, placental abruption, LBW
Mannisto, et al., 2009	Finland	28.6 ± 5.8	1-12	LBW, premature delivery, fetal/neonatal demise
Chen, et al., 2014	China	26.33 ± 0.24	1-40	LBW, fetal/neonatal demise, premature delivery, placental abruption, fetal distress, IUGR

**Table 2.** Characteristics of studies assessing SCH and pregnancy complications

<b>Study</b>	<b>Euthyroid Sample Size</b>	<b>SCH Sample Size</b>	<b>Effect Size</b>	<b>SCH Criteria</b>	<b>Covariates</b>
Casey, et al., 2005	15689	404	RR	Elevated TSH levels (2.74-5.09 mU/L). Normal free thyroxine (>0.680ng/dL)	Maternal age, race, and placental abruption
Saki, et al. 2014	497	66	RR	Elevated TSH levels (3-10mIU/L) Normal free thyroxine	Delivery gestation age, maternal body mass index, age of mother, and occurrence of preeclampsia.
Sahu, et al. 2010	552	41	RR	Elevated TSH >5.5 mIU/L. Normal T4	Not reported
Su, et al., 2011	845	41	OR	TSH greater than the 95th percentile and a fT4 between the fifth and 95th percentiles	Maternal age, parity, and BMI.
Ajmani, et al. 2014	347	36	RR (calculated)	TSH>3.0 IU/l with normal levels of FT4 (0.8-2.0 ng/dl).	Not reported
Breathnach, et al., 2013	870	16	RR (calculated)	TSH values at or above the 98 <sup>th</sup> percentile (>4.1 mU/L) with a normal free thyroxine above 2nd percentile	Not reported
Korevaar, et al, 2013	4970	188	OR	TSH >4.04 mU/L and normal FT4 (2.5th-97.5th percentiles)	maternal smoking status,BMI, gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height, and child sex
Negro, et al., 2010	3481	642	RR (calculated)	TSH between 2.5-5.0 mIU/L Normal T4 levels	Not reported

Cleary-Goldman, et al., 2008	10021	243	RR (calculated)	TSH levels above the 97.5th percentile and FT4 between the 2.5th and 97.5th percentiles	Age, prior pregnancy, body mass index, and study site.
Mannisto, et al., 2009	4719	224	RR (calculated)	TSH (mIU/liter) > 3.6 and TT4 (pmol/liter) 11.96-20.5	Maternal age and parity.
Chen, et al., 2014	7641	371	OR	TSH exceeding trimester specific range with normal FT4: first trimester, TSH 0.09–3.47 mIU/L and FT4 6.00–12.25 ng/L; second trimester, TSH 0.20–3.81 mIU/L and FT4 4.30–9.74 ng/L; and third trimester, TSH 0.67–4.99 mIU/L and FT4 4.56–8.50 ng/L.	Maternal age, parity, gestational age at delivery, and exposure to husband's smoking