2017

Routine Screening for Thyroid Peroxidase Antibodies During Pregnancy: Universal Versus targeted

Megan M. Gross
Bethel University

ROUTINE SCREENING FOR THYROID PEROXIDASE ANTIBODIES DURING PREGNANCY: UNIVERSAL VERSUS TARGETED

A MASTER'S PROJECT

SUBMITTED TO THE GRADUATE FACULTY

OF THE GRADUATE SCHOOL

BETHEL UNIVERSITY

BY

MEGAN M. GROSS

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SCIENCE IN NURSE-MIDWIFERY

MAY 2017

BETHEL UNIVERSITY

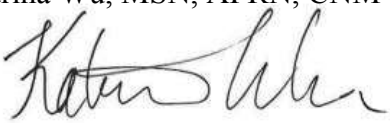
Routine Screening for Thyroid Peroxidase Antibodies During Pregnancy: Universal Versus Targeted

Megan M. Gross

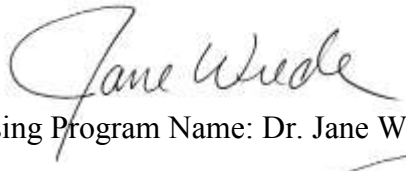
May 2017

Approvals

Project Advisor Name: Katrina Wu, MSN, APRN, CNM

Project Advisor Signature: 

Second Reader Name: Dr. Jane Wrede, PhD, APRN, CNM

Second Reader Signature: 

Director of Graduate Nursing Program Name: Dr. Jane Wrede, PhD, APRN, CNM

Director of Graduate Nursing Program Signature: 

Abstract

Background: There are currently no guidelines for screening for thyroid peroxidase antibodies (TPOAb) during pregnancy. Currently, there is some debate as to whether pregnant women should be screened for TPOAb, universally, or using a risk-based approach. In addition, there is conflicting evidence suggesting the implications of positive TPOAb testing during pregnancy and their effect on not only the pregnancy, but also the postpartum period and the fetus.

Purpose: To determine whether TPOAb should be screened for during the first trimester of pregnancy; and if so, to determine if a risk-based approach or universal screening method is more appropriate.

Results: Twenty-four studies were reviewed examining antepartum complications of positive TPOAb, postpartum complications of positive TPOAb, negative impact of TPOAb positivity on the fetus, cost effectiveness of screening for TPOAb during pregnancy, and risk factors identified for those more likely to have positive TPOAb levels.

Conclusion: There are enough risks associated with having positive TPOAb during pregnancy that they should be universally screened for during the first trimester of pregnancy. If all pregnant women are not universally screened for, then a risk-based approach should be implemented.

Implications for Research and Practice: Certified nurse-midwives should universally screen for TPOAb during pregnancy. They should also be aware of the costs of screening for TPOAb during pregnancy in their facility as well as which insurance covers the cost of these tests. They should also be aware of what to expect should complications arise in a pregnancy, postpartum, and fetal complications of a woman with positive TPOAb.

Keywords: thyroid peroxidase antibodies, TPOAb, first trimester, pregnancy screening, hypothyroidism, postpartum thyroiditis, Margaret Newman, theory of health as expanding consciousness

Table of Contents

Chapter One: Introduction

Studies have shown that thyroid dysfunction in pregnancy can lead to an increased risk for unfavorable pregnancy and newborn outcomes (Abbassi-Ghanavati, Casey, Spong, McIntire, Halvorson, & Cunningham, 2010). Abbassi-Ghanavati et al. (2010) explain that thyroid disease is more common in women, and the presence of thyroid antibodies (TPOAb) is an indicator for future thyroid problems. Pregnant women with positive TPOAb are at an increased risk for placental abruption, pregnancy loss, hypertension in pregnancy, preterm rupture of membranes, preterm delivery, postpartum thyroiditis, and postpartum depression, according to Abbassi-Ghanavati et al. (2010).

Statement of Purpose

The purpose of this paper is to examine studies about thyroid disease and learn the way that it impacts pregnancy and the newborn, as well as the postpartum experience of health. The specific focus of this paper will be on the screening for presence of TPOAb in pregnancy and how the presence of TPOAb impacts women and their offspring, specifically focusing on whether screening should be performed at all, should be performed with targeted screening, or should be performed universally in pregnancy. In connecting this topic to a theoretical framework, the paper will examine Margaret Newman's theory of health as expanding consciousness to address how the importance of screening for TPOAb during pregnancy will help women to evolve in their health journey as well as build relationships with their health care providers.

Evidence Demonstrating Need

Several researchers have found correlations between subclinical hypothyroid disease and increased incidence of risk to mother and baby during and after pregnancy (Bryant, Nelson,

McIntire, Casey, & Cunningham, 2015). There is disagreement between several different organizations including the Endocrine Society and the American Congress of Obstetrics and Gynecology (ACOG) about whether or not to routinely screen for thyroid disease during pregnancy, and whether screening should be targeted or universal.

ACOG released a practice bulletin in 2015 regarding thyroid disease in pregnancy and their conclusion was that they do not recommend the routine screening for thyroid disease in pregnancy (ACOG Practice Bulletin, 2015). Kilpatrick (2015) explained that the reason why ACOG does not recommend routine screening for thyroid disease in pregnancy is because the perceived neurological implications in the neonate of subclinical thyroid disease of the mother is just an association and not a causation. She also explained that there are not strong studies that show correlation between subclinical thyroid disease and adverse pregnancy outcomes. Finally, a study was published that showed no cognitive impairment in three-year-olds of mothers with thyroid disease who received treatment versus those that did not receive treatment (Kilpatrick, 2015).

The ACOG position statement does not solely address screening for TPOAb during pregnancy, which is the topic specific to this paper. Much of the research regarding TPOAb indicates that positive antibodies do show increased risks both during pregnancy and postpartum as well as increased risks to the neonate. It is difficult to completely apply the ACOG's position statement to this paper, because they only briefly mention thyroid autoantibodies (ACOG Practice Bulletin, 2015). Additionally, the ACOG position statement only references three studies, whereas the literature review matrix for this capstone includes over twenty studies. The ACOG position statement recommends not to universally screen women for thyroid disease,

however they also say that more evidence is needed in regards to this topic (ACOG Practice Bulletin, 2015).

Conversely, the Endocrine Society's guidelines to thyroid disease in pregnancy are to check for TPOAb in all women who are high risk for thyroid dysfunction (DeGroot et al., 2012). The Endocrine Society explained that there is not strong enough evidence at this time to either recommend or not recommend universal screening for TPOAb in all women in pregnancy. They do highlight the increased risks of TPOAb positive status including miscarriage, preterm labor, increased hypothyroidism, and postpartum thyroiditis. The Endocrine Society's guidelines incorporate a more thorough literature review than the ACOG's analysis of risks during pregnancy for women experiencing thyroid dysfunction (DeGroot et al., 2012).

Significance to Nurse-Midwifery

Approximately 10% of women test positive for TPOAb during the first trimester of pregnancy, and the risk of developing postpartum thyroiditis after testing positive for TPOAb ranges from 30 to just over 80% within one year postpartum (Bhattacharyya, R., Mukherjee, K., Das, A., Biwas, M.R., Basunia, S.R., & Mukherjee, A., 2015). Nahar, Naher, Habib, and Mollah (2013) also explain that positive TPOAb increase the risk for postpartum depression and future hypothyroidism by 30% each. Based on these findings, it would be worth further exploring if universal or risk based screening of TPOAb would be a beneficial way to identify these women sooner in order to identify and treat thyroid disease in a timely manner.

Theoretical Framework

Margaret Newman's theory of nursing postulates that every human is on a journey to expanding their consciousness through learning about their own health (Newman, 2011). Newman (2011) stresses that health is not the absence of disease, rather it is putting forth the

effort to learn more about oneself and connecting with others throughout their health journey. This theory applies to the research question of whether one should be screening for TPOAb in the first trimester of pregnancy, because gaining knowledge of a disease or pathology is a way of expanding consciousness.

Newman explains that as one becomes more aware of their pathologies, they are enabled to connect with the world around them and thus are able to develop further as human beings (Smith, 2011). In the event that universal screening for TPOAb during the first trimester of pregnancy was implemented, those with positive autoantibodies would become more aware of what is happening in their bodies. Having the knowledge of the presence of TPOAb would make it possible for women to understand that they are at an increased risk for complications like miscarriage, postpartum depression, and postpartum thyroiditis. This way, women would be better able to mentally prepare for these illnesses. Additionally, they would be able to work with their health care practitioners to have a plan for managing these conditions early to prevent complications.

One of Newman's intentions for health as expanding consciousness in practice is that it develops a partnership between the provider and patient in the journey to health (Jones, 2006). This applied to universal screening of TPOAb would have a similar effect. The combined knowledge between patient and nurse-midwife of positive TPOAb could lead to a collaborative partnership in improving health and disease prevention in the future. Throughout this partnership, a deeper level of caring would develop between nurse-midwife and patient which is another one of the goals of Newman's health as expanding consciousness. Jones (2006) explains that within Newman's theory, when partnership is developed, patient and nurse are able to uncover other health implications, which leads to a healthier state of being.

Newman emphasized that nursing, including advanced practice nursing, has to be in the moment, and care providers have to be fully engaged with their patients in order to reap the benefits of health as expanding consciousness (Jones, 2006). Taking this, universal screening for thyroid autoantibodies would be a way to engage fully with a patient initially through lab values, and then emotionally and educationally through explaining the implications of the lab values and what that means going forward.

Margaret Newman's nursing theory of health as expanding consciousness is one that can be applied to all aspects of health care. As it applies to testing for TPOAb universally in the first trimester of pregnancy, it allows for both the provider and patient to become closer, it allows for a collaborative relationship between patient and nurse-midwife, and finally it allows for patient insight, which can open up further information leading towards patients' overall health and wellbeing. Implementation of health as expanding consciousness into research regarding TPOAb can help to lead to better planning for the future of patients who have positive thyroid autoantibodies.

Summary

Screening for the presence of TPOAb in pregnant women is not currently done routinely, and there has been some disagreement about whether or not screening for antibodies should be performed for everyone or for a targeted population of individuals. Thyroid disease in pregnancy has been shown to have adverse effects on pregnancy, the health of the woman, and the neurophysical development of the newborn. TPOAb have been closely correlated with thyroid disease (Nahar et al., 2013). Nurse-midwives are not only responsible for caring for women during pregnancy, but also throughout the lifespan. Testing positive for TPOAb during pregnancy changes the outlook of health in a woman's lifespan, implicating the importance for

the nurse-midwife to provide comprehensive pregnancy care that potentially includes screening for thyroid diseases, which does not exclude screening for TPOAb.

Chapter II: Methods

This chapter is an overview of the processes used to critically appraise literature regarding the screening of thyroid peroxidase antibodies (TPOAb) in pregnant women. This chapter will discuss the search strategies used to ascertain information about research on this topic. It will also examine the criteria for including and excluding research in the literature review matrix. Lastly, the number and type of studies included in the literature review matrix is reviewed in this chapter.

Search Strategies

The goal of this literature appraisal is to determine whether or not universally testing for TPOAb in pregnant women is beneficial for their health both during pregnancy and in the future, or whether a targeted approach to screening for TPOAb during pregnancy should be taken. Initial searches were conducted regarding different types of thyroid dysfunction screenings and lab values that were evaluated in pregnant women, but it became evident that there was some discrepancy in the screening for TPOAb and how it affects women during pregnancy and postpartum.

Initial searches were performed in the Cumulative Index to Nursing and Allied Health Literature (CINAHL) including the search terms “TPO antibodies” and “pregnancy”. This search yielded 207 results from the years 2001 to 2016, of which many had to be disregarded due to not meeting criteria for the research question. Further searches were performed on the Google Scholar search engine including the search terms “screening” “thyroid antibodies” and “pregnancy”. This yielded 647 results from 2007 to 2016, of which many were disregarded due to relevance or not being an original research. Further searching was completed in the search engine Science Direct yielding 184 results from 2007 to 2017, of which many did not pertain to

the research question, and others were already included in the Matrix. The search engine PubMed was utilized with the terms “TPOAb”, “screening”, and “pregnancy, which yielded fifty-two results from 1998 to 2017. These articles were already included in the literature review matrix or irrelevant to the practice question. Finally, the search engine Scopus was utilized spanning the years 2001 to 2016, with the search terms “TPOAb”, “screening”, and “pregnancy”, which yielded thirty-seven results. Studies of relevance were included in the matrix and many were not included due to not pertaining to the practice question. Many of the studies in the literature review matrix were found in the different search engines. In addition to these search terms, reference sections in articles were evaluated for further research studies to be included in this critical appraisal.

Criteria for Including and Excluding Research Studies

Inclusion criteria for the literature review matrix included studies that addressed screening ranges and parameters for TPOAb during pregnancy. Also included in the matrix were studies that addressed risks of positive TPOAb during pregnancy, postpartum, and risks to the fetus. Finally, studies were included that addressed risk factors for thyroid dysfunction and TPOAb positivity as well as cost effectiveness of screening for TPOAb.

Research studies that were excluded from this critical appraisal included those that did not involve screening for TPOAb during pregnancy. Several studies addressed screening for thyroid stimulating hormone during pregnancy but not TPOAb, making them irrelevant to the practice question and therefore subject to exclusion from the literature appraisal. Other studies excluded from the literature appraisal included those that were deemed to be not of good quality according to the Johns Hopkins Nursing Evidence-Based Practice: Model and Guidelines

(Deerholt & Dang, 2012). Studies that were not included into the literature review matrix were not research studies, or were research studies that did not address TPOAb in pregnancy.

Criteria for Evaluating Research Studies

Evaluation criteria employed by the Johns Hopkins methods includes the level of evidence as well as the quality of that evidence (Deerholt & Dang, 2012). The highest level of quality is considered level I, and this includes randomized control trials and experimental studies. Level II includes quasi-experimental studies and studies that are a synthesis of other studies. Level III evidence includes non-experimental studies and qualitative studies. Quality is determined by whether the information in the study is generalizable, whether the sample size was sufficient, and whether they contain consistent recommendations. Good quality studies include reasonably consistent results and recommendations, as well as a fairly sufficient sample sizes. Studies of low quality do not meet the above listed criteria and were not included in this appraisal.

Number and Types of Studies Involved in Literature Review

The total number of studies included in the literature review matrix is twenty-four. Of these, eight are quasi-experimental studies, which are level II and considered to be of good quality. Eleven of the studies in the literature review matrix are observational studies including two retrospective studies, six prospective observational studies and three longitudinal studies. These range from level II to level III and range in quality from high quality to fair quality. The literature review matrix contains three studies that are prospective cohort studies that are all considered level II and good quality. One study in the literature review matrix is a secondary analysis of quantitative data, which is level III and of good quality. Finally, the literature review matrix includes one randomized control trial which is level I and of high quality.

The matrix is broken down into categories including citation, purpose of the study, sample, design type, measurement, results and conclusions, recommendations, and level and quality of each study. Studies that were not included into the literature review matrix were not original research studies, or were research studies that did not address TPOAb in pregnancy.

Summary

Screening for TPOAb during pregnancy is not currently routinely done. The literature review matrix compiled several types of studies addressing this screening and organizes the information provided in each study. The research was analyzed for level of research as well as the quality of the research. Inclusion and exclusion criteria for the literature review matrix were discussed as well as the criteria for evaluation of the studies.

Chapter III: Literature Review and Analysis

This chapter serves to provide an overview of the literature from the literature review matrix and an analysis of the findings of the studies included in the matrix. It will provide a discussion of the major areas in which positive thyroid peroxidase antibodies (TPOAb) affect pregnant and postpartum women and their offspring. Additionally, it will synthesize the data collected in the literature review matrix and synthesize the significant findings.

Synthesis of Literature Review Matrix

The literature review matrix's purpose is to organize the literature compiled and highlight themes among the research. There are twenty-four studies in the matrix and they all are organized using the following headings: citation, purpose, sample, design, measurement, results/conclusions, recommendations, and level/quality. The studies in the matrix are organized alphabetically.

Each study was appraised using Johns Hopkins research appraisal method and those that were not of a high level of research or those that were of poor quality were excluded from the matrix (Deerholt & Dang, 2012). Each study was appraised and then compared to the other studies in the matrix to synthesize information.

Synthesis of Significant Findings

The literature review matrix supports screening women for the presence of TPOAb during pregnancy, but differs in recommendations of whether to screen women universally or to perform targeted screening based on risk factors. The major themes that arose from researchers' findings included in the matrix are as follows: risks during pregnancy, risks during postpartum, cost analysis of screening for TPOAb, a comparison of screening parameters, risks to the offspring, and identification of salient risk factors should a targeted screening approach be taken.

Risks During Pregnancy

There were eight studies that addressed the risks of having positive TPOAb during pregnancy. This is an important factor to keep in mind when caring for pregnant women because it indicates that women need more thorough antenatal care if they have a TPOAb positive status.

In a robust study with a sample size of 17,298 pregnant women, Abbasi-Ghanavati et al. (2010) found that 1% of the population of TPOAb positive women experienced placental abruption during their pregnancy 0.3% of the TPOAb negative population. Nor et al. (2010) found in their small research study that in TPOAb positive women, 3.8% experienced placental abruption. Bryant, Nelson, McIntire, Casey, and Cunningham (2015) found that women in the over N= 23,000 women studied, those with unconfirmed hypothyroidism were more likely to have hypertension during pregnancy, which may explain the increased risk of placental abruption in the TPOAb positive population. Nor et al.'s research agrees with Bryant et al. and found that 7.7% of TPOAb positive women had hypertension in pregnancy and 15.4% of TPOAb positive women developed preeclampsia.

Ahmed, Eid, Orabi, and Ibrahim (2014) found that women with positive TPOAb were more likely to be high risk for having hypothyroidism during pregnancy in their relatively small but good quality study where $p < 0.05$. They found that it did not matter if they separated women into high and low risk groups; there was no change in whether elevated TPOAb would be linked to hypothyroidism. Pradhan, Anand, Singh, and Mehrotra (2013), also found an increased risk of hypothyroidism in TPOAb positive status in their study that included N= 2,479 pregnant women. Of the women studied, 7.91% were found to have hypothyroidism, and of those, 40% tested positive for TPOAb.

Another risk of testing positive for TPOAb during pregnancy is the increased risk of spontaneous abortion. Two studies addressed this concern. Pradhan et al. (2013) found that of women who tested positive for TPOAb, 17.86% of them experienced a spontaneous abortion in the first trimester versus 6.49% of the population that tested negative for TPOAb. Pradhan et al. (2013) found that of the TPOAb positive population, 10.71% experienced second trimester spontaneous abortion versus 1.3% of the TPOAb negative population in the second trimester. Bhattacharyya et al. (2015) also addressed the issue of spontaneous abortion and found that in their study of N= 400 pregnant women, 10.8% of the TPOAb positive population experienced SAB versus 4.8% of the TPOAb negative population.

Preterm delivery was identified by researchers to be more prevalent amongst the TPOAb positive population in two studies listed in the literature review matrix. Meena, Chopra, Jain, and Aggarwal (2016) found in their research population of N= 1,000 pregnant women that of the TPOAb positive subjects in their study, 12.5% of women experienced preterm delivery whereas of the women that did not test positive for TPOAb, only 2.5% had preterm delivery. Nor et al. (2010) also addressed the topic of preterm delivery and found that 11.5% of TPOAb positive women experienced this phenomenon, again their study was smaller in size.

One study addressed how TPOAb positivity and mood are related during pregnancy. Groer and Vaughan (2013) found that women who were TPOAb positive were more likely to score higher on a profile of mood states (POMS) questionnaire, as well as on scales for depression and mood disorders. Their study included N= 631 pregnant women and was considered to be of good quality.

Despite all these different findings, Bryant et al. (2015) concluded that overall pregnancy outcomes were similar in women who have positive TPOAb to women who tested negative for

TPOAb during the first trimester. However, the eight studies addressed in this section indicated that, in fact, TPOAb positivity does have an effect on pregnancy outcomes, as it has a correlation with increased risk of spontaneous abortion, hypertension during pregnancy, placental abruption, preterm delivery, preeclampsia, hypothyroidism during pregnancy, and mood disorders in pregnancy.

Risks Postpartum

Seven studies included in the literature review matrix addressed the risks that mothers face postpartum should they test positive for TPOAb during their pregnancy. These risks include postpartum thyroiditis, postpartum thyroid dysfunction in general, and postpartum depression. These are important topics to discuss, because all of them can affect how well a woman is able to take care of both herself and her infant.

Postpartum thyroiditis was addressed by five of the studies in the matrix. Bhattacharyya et al. (2015) found in the women that they studied, 81.25% of the women who tested positive for TPOAb experienced postpartum thyroiditis versus 4.7% of the general population. Ekinci et al. (2015) found in their smaller scale study of N=140 subjects, that pregnant women who had positive TPOAb were much more likely to experience postpartum thyroid dysfunction including postpartum thyroiditis, as well as Hashimoto's thyroiditis. Groer and Vaughan (2013) found that 64% of women with positive TPOAb developed postpartum thyroid dysfunction within six months of delivery. Mamede da Costa, Siero Netto, Coeli, Buescu, and Vaisman (2007) found that positive TPOAb status was as much as two thirds predictive for identifying women likely to develop postpartum thyroid dysfunction in their small study of 98 pregnant women. They identified 60% of TPOAb positive women to have postpartum thyroid dysfunction versus 4.55% of the TPOAb negative population. They also found that on average, thyroid stimulating

hormone (TSH) levels were more likely to be elevated at one year postpartum in women who tested positive for TPOAb in pregnancy. Meena et al. (2016) discovered through their research that 40% of women who tested positive for TPOAb developed hypothyroidism postpartum. Nor et al. (2010) found that by as few as eight weeks postpartum, 19.2% of TPOAb positive women developed postpartum thyroid dysfunction. Finally, Springer, Potlukova, Limanova, and Zima (2012) found in their sizable study of N= 7,530 pregnant women that 40% of TPOAb positive women experienced some sort of thyroid dysfunction within one year postpartum ($p>0.20$).

Groer and Vaughan (2013) determined that TPOAb positive women were more likely to have postpartum depression following a pregnancy where they tested positive for TPOAb (Chronbach's alpha 0.839). They expressly stressed that these women have no other reasons for experiencing postpartum depression such as stressors or other demographic factors at the time.

The studies compiled in the literature review matrix that address postpartum risks related to testing positive for TPOAb indicated that there is an increased risk for thyroid dysfunction within one year postpartum. According to the matrix, women with positive TPOAb are also at an increased risk for postpartum depression if they have tested positive for TPOAb, however most researchers did not address this subject.

Cost Analysis

It is important to address cost analysis when deciding whether and how to screen for TPOAb. Additionally, when addressing cost effectiveness, it is important to identify locations where screening is cost effective versus where it might be less cost effective. Six of the studies in the literature review matrix addressed the topic of cost effectiveness of universal screening for TPOAb in pregnancy.

There are varying opinions about whether or not it is cost effective to universally screen for TPOAb during pregnancy. Abbassi-Ghanavati et al. (2010) concluded in their study that it is not cost effective to universally screen for TPOAb in pregnancy, however they believe that it might be plausible to screen for TPOAb in the future if there were further studies performed to prove its cost effectiveness. Conversly, Dosiou, Sanders, Araki, and Crapo (2008) point out that in the United States it only costs an average of $102 to screen for thyroid stimulating hormone (TSH) and $212 to screen for TPOAb. They believe that their high quality study enables them to conclude that these low costs implicate that universally screening for TPOAb, as well as TSH during pregnancy, is justified (Dosiou et al., 2008).

Nazarpour et al. (2016) have a stance neutral to the other two that have been discussed. They state that universal screening is a cost effective procedure, however there have not been enough studies performed at this time to fully endorse universal screening. Of note, Nazarpour et al. performed their large study in Iran where nutritional deficiencies differ from the United States, namely the amount of iodine consumed, which needs to be considered when addressing this topic. Nor et al. (2010) seemingly agree with Nazarpour et al. and say that in well developed countries, universal screening is more affordable so they recommend universally screening all women, however in developing countries this might not be the case. Yang et al. (2014) concluded from their study of N= 3,882 pregnant women, that since the price of testing for thyroid dysfunction including TPOAb is relatively low, universal screening for thyroid dysfunction during pregnancy is a cost effective option, and better than screening only targeted risk factors for thyroid dysfunction. Finally, Dhaifalah, Salet, Kangova and Cuckle (2017) believe that adding screening for thyroid disease on to other first trimester screening tests is probably beneficial, however further research is needed until it can be recommended overall.

Their recommendation is strong, as their sample size included N= 10,052 pregnant women ($p > 0.0001$).

Comparison of Screening Parameters

Ten of the studies addressed the accuracy of screening for TPOAb and thyroid dysfunction in general during pregnancy. Some researchers pointed out trends in other thyroid related markers whereas others focused on setting parameters for normal lab values for thyroid function during pregnancy. Some researchers addressed the differences in thyroid serum levels depending upon the ethnic background of the individuals being screened. Finally, some researchers focused on when is the best and most accurate time to screen for thyroid disease during pregnancy.

Four groups of researchers are in agreement that average TSH levels are higher in pregnant women who test positive for TPOAb. Nahar et al. (2013) found in their research study of 200 women in Bangladesh, that if TPOAb values were greater than 12IU/ml, then pregnant women's TSH was more likely to be higher ($p<0.05$ and a confidence interval of 95%). Quinn, Reyes-Mendez, Nicholson, Compean and Tavera (2014) also found that TSH levels were more likely to be higher in TPOAb positive pregnant women when studying 660 pregnant women versus 104 non-pregnant women in Mexico. Springer, Potlukova, Mimanova, and Zima (2012) found that in pregnant women with positive TPOAb, free thyroxine (fT4) levels were more likely to be lower, however no other researchers found that to be the case in their studies. Sarkhail, Mehran, Tahamasbinejad, Tohidi and Azizi (2016) found that 23% of women with positive TPOAb had either hypothyroidism or subclinical hypothyroidism in at least one trimester during pregnancy in their good-sized study of N= 466 Iranian women.

Screening parameters and the best time to screen pregnant women for TPOAb were addressed by two of the studies. Ekinci et al. (2015) found that the accuracy of screening for TPOAb in pregnancy was much higher in the first trimester and the amount of positive TPOAb tests in the second trimester decreased by 96% in the second trimester and 97% in the third trimester of pregnancy. Sarkhail et al. (2016) found in their study that in pregnant women with thyroid dysfunction, 45.5% tested positive for TPOAb in the first trimester but that number dropped to 41.2% of women in the second trimester and 25% of women in the third trimester.

Five of the groups of researchers compiled in the literature review matrix addressed parameters for TPOAb and thyroid function during pregnancy both due to the fact of women being pregnant and in an altered body state and looking into differences in racial background and how that affects thyroid serum levels. Hollowell et al. (2001) set out to determine reference ranges in general for thyroid serum markers in their study of N= 631 women during pregnancy and postpartum, and pointed out that generally White and Mexican Americans have higher levels of TSH than do Black Americans. Hollowell et al. also pointed out that it is important to be aware of the possible iodine deficiency in people of certain cultural backgrounds or people from certain geographical locations. Quinn et al. (2014) stressed that narrower reference ranges should be used in pregnant women of Mexican descent as well as emphasizing that pregnancy for all women should have specific reference ranges for thyroid function testing. Nahar et al. (2013) set the reference range for TPOAb to be levels greater than 12IU/ml whereas Springer, Potlukova, Limanova and Zima set the parameters for TPOAb positivity at 143 IU/ml. Finally, Springer, Bartos, and Zima (2014) emphasized after their study of N= 229 pregnant women, that parameters for TPOAb should be set lower in pregnancy than they would be in a non-pregnant

state ($p<0.05$). All of these parameters are important for practitioners to keep in mind when screening pregnant women for thyroid dysfunction.

Risks to the Offspring

Positive TPOAb status in women has been shown in some studies to affect offspring. Four of the studies in the literature review matrix addressed the effects that positive TPOAb during pregnancy has on the pregnant mother's offspring. They not only focused on issues that can arise at birth, but also long-term effects of positive TPOAb in the mother.

Nor et al. (2010) found that in pregnant women with positive TPOAb, 15.4% had babies with IUGR. Meena et al. (2016), however, discovered no difference in incidence of IUGR in babies of mothers with positive TPOAb. Pradhan et al. indicated that 17.86% of infants had malformations if their mother was positive for TPOAb versus only 6.4% of babies born with malformations in TPOAb negative mothers. Sarkhail et al. (2016) stated that TPOAb positivity in the first trimester is the most likely time for the fetus to be affected, since that is when much of development takes place. Wasserman et al. (2007) performed a study with a sample size of N= 1,859 children whose mothers who tested positive for TPOAb during pregnancy and found that 7.5% of these children had sensorineural hearing loss versus only 1.3% of the total population ($p>0.20$).

Though there has been little research done on the effects of positive TPOAb in pregnancy on the offspring, the research that has been completed does indicate that the children of affected mothers are more likely to suffer negative effects during the pregnancy, immediately at birth, as well as later in life. When addressing effects of TPOAb positivity on the offspring, it would be prudent to consider the implications that preterm delivery and placental abruption have upon the

affected newborns. See the section above on risks during pregnancy for the corresponding risks in the literature.

Risk Factors

If universal screening for TPOAb during pregnancy is not the most cost effective option in a particular setting, then targeted screening is another option to explore. Six of the studies in the literature review matrix address risk factors for thyroid dysfunction during pregnancy. This section will discuss the risk factors identified.

Yang et al. (2014) found that TPOAb positivity was only slightly higher in the population that they deemed high-risk versus the population that was deemed low-risk. The risks that Yang et al. (2014) identified were based on patient history, physical exam at presenting appointment, and any other implications of thyroid dysfunction such as symptomatic identifiers including fatigue, weight gain, and hair loss. Springer, Potlukova, Limanova, and Zima (2012) identified four risk factors for women more likely to have positive TPOAb and overall thyroid dysfunction including age greater than thirty, family history of thyroid dysfunction, personal history of thyroid dysfunction, and the presence of a goiter upon examination. They found that 11.5% of women with these markers were positive for TPOAb. Pradhan et al. (2013) found that 40% of women with hypothyroidism had positive TPOAb. Nazarpour et al. (2016) identified risk factors including age greater than thirty, family history of thyroid disease, and history of spontaneous abortion. When Nazarpour et al. (2016) separated their subjects into high and low risk categories, 39.6% of the high risk group were found to have thyroid disorders versus 27.4% of the low risk group. Mamede da Costa et al. (2007) identified increased risk factors for developing thyroid dysfunction were family history of thyroid disease and the presence of a goiter upon physical

examination. Finally, Bryant et al. (2015) pointed out in their article that age greater than thirty-five increases risk for hypothyroidism.

Compiling all of the risk factors addressed by the studies, the main risk factors identified for thyroid dysfunction during pregnancy and postpartum include being greater than thirty years of age, family history of thyroid disease, personal history of thyroid dysfunction, and presence of a goiter upon examination.

Summary

There is not a consensus for how to approach screening for TPOAb during pregnancy among medical societies, however themes have arisen in the literature review matrix, which may help providers to decide whether they should screen for TPOAb at all, use a targeted screening for pregnant individuals, or universally screen all pregnant women. These themes include understanding the risks of thyroid disease during and after pregnancy for both the woman and her offspring, the cost analysis of screening for TPOAb, parameters for testing for thyroid dysfunction in pregnancy, and the risk factors that should be focused on if targeted screening is chosen as the preferred method. Despite everything compiled in the literature review matrix, overarching opinion is that more research is needed in regards to whether TPOAb should be screened for, and if so, should a universal or targeted screening approach be utilized.

Chapter IV: Discussion, Implications, and Conclusion

This chapter will contain a critical appraisal of the literature that has been discussed in previous chapters. It will also include a synthesis of literature, the current trends in practice along with a discussion of the gaps in research, the implications for future research and practice, and application and integration of the theoretical framework discussed in chapter one. This critical appraisal of literature will help to elucidate the recommendations for thyroid antibodies (TPOAb) screening in pregnancy, whether that means to not screen for them at all, to perform targeted screening for at risk women, or to universally screen for TPOAb in the first trimester.

Literature Synthesis

The research question that was the basis for all of the research collection was whether or not nurse-midwives and all obstetrical providers should be screening women for TPOAb during the first trimester of pregnancy in order to improve outcomes during pregnancy and postpartum.

Current trends and gaps in research

Cost effectiveness. Current trends in screening for TPOAb are varied. Some practitioners do not screen for them at all. Some practitioners believe that they should routinely screen everyone during pregnancy because of the cost effectiveness of the testing in the United States (Dosiou, Sanders, Araki, & Crapo, 2008). The aforementioned researchers indicated in their study that the testing is inexpensive and therefore, should be utilized. Other researchers agree with this and suggest universally screening all pregnant women for TPOAb because it is inexpensive (Yang et al., 2014). Conversely Abbassi-Ghanavati et al. (2010) state that the cost is not worth universal screening for TPOAb in pregnancy, however they believed that further research was needed in regards to this topic. While one group of researchers reported that cost is less likely to be an issue in developed countries, however in developing countries universal

screening might not be a reasonable guideline to follow (Nor et al., 2010). There is still more research needed in regards to whether or not it is cost effective to screen for TPOAb universally during the first trimester of pregnancy, however in developed countries it appears that universal screening would be a cost effective choice.

Timing and accuracy of screening. It is generally agreed upon by all researchers that accuracy of screening for TPOAb in pregnancy decreases after the end of the first trimester (Ekinci et al., 2015; Sarkhail, Mehran, Tahamasbinejad, Tohidi, & Azizi, 2016). It is recommended that to obtain the most accurate results, women should be screened for TPOAb in the first trimester of pregnancy in order to assess for thyroid disease that might affect pregnancy.

Risks during pregnancy. Several researchers focused on the risks to pregnancy in women who were positive for TPOAb. Risk of first trimester spontaneous abortion was found to be higher in pregnant women with positive TPOAb by Bhattacharyya et al. (2015) and Pradhan, Anand, Singh, and Mehrota (2013). The presence of TPOAb in women with recurrent pregnancy loss could be the answer to the question of why someone has had multiple spontaneous abortions. Two groups of researchers found that there was an increased risk of hypertensive disorder during pregnancy in women with positive TPOAb including pregnancy induced hypertension and preeclampsia (Bryant, Nelson, McIntyre, Casey, & Cunningham, 2015; Nor et al., 2010). The risks associated with pregnancy induced hypertension, as well as preeclampsia, can contribute to placental insufficiency as well as placental abruption, which Abbassi-Ghanavati et al. (2010) and Nor et al. (2010) mentioned to also be correlated with presence of TPOAb in pregnant women. It was also found that women with positive TPOAb were more at risk for experiencing preterm labor and birth (Meena, Chopra, Jain, & Aggarwal, 2016; Nor et al., 2010). Women with positive TPOAb were also more likely to experience hypothyroidism during

pregnancy in addition to mood disorders during pregnancy including anxiety and depression (Ahmed, Eid, Orabi, Ibrahim, 2014; Groer & Vaughan, 2013). Contrary to most studies, some researchers reported that the overall outcomes of pregnancy were comparable to women negative for TPOAb (Bryant et al., 2015). From these findings, it can be concluded that further research is needed to discover the relationship between TPOAb and these increased risk factors during pregnancy.

Postpartum risks. Women with positive TPOAb during pregnancy were found by several researchers to be more likely to experience postpartum thyroid disease within one year of pregnancy (Bhattacharyya et al, 2015; Ekinci et al., 2015; Groer & Vaughan, 2013; Mamede da Costa, Siero Netto, Coeli, Buescu, & Vaisman, 2007; Meena et al., 2016; Nor et al., 2010; Springer, Potlukova, Limanova, & Zima, 2012). Women with positive TPOAb are also at an increased risk for postpartum depression (Groer & Vaughan, 2013). Further investigation is needed regarding postpartum risks of TPOAb during pregnancy, because some of the researchers only followed women for eight weeks postpartum whereas others followed women for twelve months postpartum. Those that followed women for a longer amount of time had more subjects with positive TPOAb that developed postpartum thyroid disease than those that only followed women for eight weeks (81.2% versus 19.2% of women) (Mame da Costa et al, 2007; Springer et al., 2012).

Potential risks to the fetus/newborn. Positive TPOAb are more likely to affect the fetus during the first trimester, which is the most vital time for embrologic and fetal development (Sarkhail et al., 2016). This means that fetuses of mothers with positive TPOAb are more likely to be born with malformations versus those that were born to mothers who were negative for TPOAb (Pradhan et al., 2013). Additionally, one group of researchers found that babies were

more likely to be born with intrauterine growth restriction if their mothers were positive for TPOAb (Nor et al., 2010). One study indicated that children were more likely to suffer from sensorineural hearing loss when born to mothers positive for TPOAb (Wasserman et al., 2007). Conversely one group of researchers found there to be no difference in fetal outcomes after a TPOAb positive pregnancy (Meena et al., 2016). More research is needed on how positive TPOAb results affect not only fetal development but also long term implications for babies born to mothers positive for TPOAb.

Risk factors for targeted screening. Many researchers agreed that risk factors for women to have positive TPOAb during pregnancy includes having personal history of thyroid disease including the presence of a goiter on physical exam, as well as family history of thyroid disease, and being aged thirty or greater (Bryant et al. 2015; Mamede da Costa et al., 2007; Nazarpour et al., 2016; Pradhan et al., 2013; Springer et al., 2012). They are all in agreement with the risk factors although some specify over the age of thirty while others do not list age as a risk factor until the age of thirty-five has been reached.

Recommendations for Future Research

There are some areas regarding screening for TPOAb during pregnancy that need further research. One area is a more thorough appraisal of whether or not screening for TPOAb is cost effective, and in addition to that whether universal screening is more cost effective than just targeted screening, or not screening for them at all. The cost effectiveness needs to be compared against the potential damage and associated costs that thyroid disease would have on pregnancy, postpartum, and on the fetus. Dosiou et al. (2008) reported that in the U.S. the damage of thyroid disease is more expensive than screening each woman universally. Abbassi et al. (2010) also performed their research in the U.S., but came to a different conclusion. This implicates that

further research is needed regarding overall cost effectiveness of universal screening, targeted screening, and the cost of the personal and financial hardship once thyroid disease develops. Research also needs to be performed on cost effectiveness of screening versus personal damages from untreated thyroid disease postpartum as well as pregnancy related issues caused by TPOAb.

Further research is also needed in regards to risks to the fetus, as there are some disagreements in literature about whether a mother's positive TPOAb has negative implications for the fetus. Small sample sizes and limited research on implications to the fetus are two other reasons why further research is needed on this topic. Especially in looking for trends between races to try and identify more at risk groups.

Finally further research is needed in how positive TPOAb affect pregnancy outcomes so that a plan can be set in place for prevention or early disease detection for potential negative pregnancy outcomes such as spontaneous abortion, hypertensive disorders, and preterm labor.

Implications for Practice

Nurse-midwives are enabled to take information from the literature analyzed and apply it to practice in several ways. First, they can research common insurance companies in their area and their willingness to cover screening for TPOAb and other thyroid markers during pregnancy in order to screen for thyroid issues in the most cost effective way. Nurse-midwives should also be aware of the cost of each individual blood test through their hospital system or lab so they are aware of the cost that screening inflicts upon their patients and insurance companies. This may differ between systems and labs because Dosiou et al. (2008) and Yang et al. (2014) found screening for thyroid disease to be low cost, whereas Abbassi et al. (2010) found it to be too expensive to be utilized for every pregnant patient. Nurse-midwives should also educate their

patients about the labs that they are planning on drawing so that they can check into the cost with their individual insurance policies.

Nurse-midwives can also utilize the information collected in the literature synthesis and apply it to women who have a history of pregnancy issues including pregnancy-induced hypertension, history of preterm delivery, the birth of a baby diagnosed with intrauterine growth restriction, history of spontaneous abortion during the first or second trimester, or history of previous postpartum thyroiditis, and screen them for TPOAb in subsequent pregnancies. This is in part, a targeted screening based on risk factors found in the literature (as described by Bryant et al, Mamede da Costa et al., Nazarpour et al., Pradhan et al., and Springer et al.)

Screening for TPOAb during pregnancy is a prudent test for providers to perform for their pregnant patients in the first trimester. Helping to elucidate why some problems during pregnancy may occur, as well as prepare to meet problems early on during pregnancy or the postpartum period is beneficial for patients, especially since in the United States screening for TPOAb is a relatively low cost lab option. Anticipating a host of complications with a patient with positive TPOAb during pregnancy and in the postpartum period provides more thorough patient care. Additionally, knowing that the presence of TPOAb during pregnancy could lead to fetal malformation, level II ultrasounds could be set up for patients to catch any potential issues with the fetus. Though further research is needed on the topic, there are many positive factors to screening for TPOAb during the first trimester of pregnancy universally for all women. If this is not plausible, then a targeted screening approach should be undertaken.

Application and Integration of Margaret Newman's Theory of Nursing

Margaret Newman's theory of expanding consciousness is applicable to screening for TPOAb during the first trimester of pregnancy because the ultimate goal of Newman's theory is

to learn more about individual health in order to be more aware of health problems and therefore take care of oneself by being aware of personal health implications (Newman, 2011). Newman continually stresses that her theory of health is not focused on the absence of disease, rather the awareness of what is within the body and how to address potential issues.

The benefits of screening for TPOAb during the first trimester of pregnancy align with Newman's theory of expanding consciousness because it elucidates future problems that the mother and fetus could encounter. Having this awareness is consciousness expanded of health for both the patient and the nurse-midwife. With this knowledge, they can work together in order to achieve the healthiest and safest pregnancy possible as well as be keenly aware of risks that may develop later on in the pregnancy.

Conclusion

This literature review compiled research from twenty-four studies and utilized the Johns Hopkins Research Evidence Appraisal Tool in order to analyze the quality and level of research. This tool and the matrix indicate that the main topics that come to light when looking into research regarding screening for TPOAb during pregnancy include risks during pregnancy, postpartum risks, risks to the fetus, cost effectiveness of screening for TPOAb, and risk factors for targeted screening for TPOAb. The most common risks during pregnancies with positive TPOAb are hypertensive disorders, spontaneous abortion during first and second trimester, thyroid disorder, placental abruption, preterm labor, and mood disorders in pregnancy. Risks postpartum include postpartum thyroid disease, which is the most common risk, as well as postpartum depression. Risks to the fetus include fetal malformation, intrauterine growth restriction, and sensorineural hearing loss. Cost-effectiveness includes the financial benefits of screening universally as well as a discussion of where, globally, it is most cost effective to screen

for TPOAb in pregnancy. Finally, risk factors highlighted in the event that targeted screening for TPOAb is chosen include history personal or family of thyroid disease, presence of a goiter, and age over thirty. Screening for TPOAb during pregnancy comply with Newman's theory of health as expanding consciousness because when found, both patient and provider become more aware of that individual's health and are able to address potential issues more proactively. Nurse-midwives can provide better care for their pregnant patients if they screen universally for TPOAb during pregnancy because they are then better able to anticipate issues that may arise for women if they have positive TPOAb. In this way, nurse-midwives can more closely monitor women during pregnancy for the pregnancy risks, as well as anticipate postpartum thyroid disease and diagnose it earlier in the postpartum period.

References

Abbassi-Ghanavati, M., Casey, B.M., Spong, C.Y., McIntire, D.D., Halvorson, L.M.& Cunningham, G.F. (2010). Pregnancy outcomes in women with thyroid peroxidase antibodies. *Obstetrics and Gynecology, 116*(2), 381-386. Doi: 10.1097/AOG.0b013e3181e904e5

Ahmed, I.Z., Eid, Y.M., Orabi, H.E., & Ibrahim, H.R. (2014). Comparison of universal and targeted screening for thyroid dysfunction in Egyptian women. *European Journal of Endocrinol-ogy, 171*(2), 285-291. doi: 10.1530/EJE-14-0100

American College of Obstetrics and Gynecologists. (2015). *ACOG practice bulletin no. 148.* Washington, DC: College Publications

Bhattacharyya, R., Mukherjee, K., Das, A., Biwas, M.R., Basunia, S.R., & Mukherjee, A. (2015). Anti-thyroid peroxidase antibody positivity during early pregnancy is associated with pregnancy complications and maternal morbidity in later life. *Journal of Natural Science, Biology and Medicine, 6*(2), 402-405. doi: 10.4103/0976-9668.160021

Bryant, S.N., Nelson, D.B., McIntire, D.D., Casey, B.M., & Cunningham, F.G. (2015). An analysis of population-based prenatal screening for overt hypothyroid-ism. *American Journal of Obstetrics and Gynecology, 213*(4), 565.e1-565.e6. doi: 10.1016/j.ajog.2015.06.0601

Costeria, M.J., Oliveira, P., Ares, S., Roque, S., Morreale de Escobar, G., & Palha, J.A. (2010). Parameters of thyroid function throughout and after pregnancy in an iodine-deficient population. *Thyroid, 20*(9), 995-1001. doi: 10.1089/thy.2009.0356

Deerholt, S., & Dang, D. (2012). *Johns Hopkins nursing evidence-based practice: Models and guidelines* (Second edition.). Indianapolis, IN: Sigma Theta Tau International.

De Groot, L., Abalovich, M., Alexander, E.K., Amino, N., Barbour, L., Cobin, R., Cresswell, E., Lazarus, J., Luton, D., Mandel, S., Mestman, J., Rovet, J., & Sullivan, S. (2012). Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism, 97*(8), 2543-2565. Doi: 10.1210/jc.2011-2803

Dhaifalah, I., Salek, T., Langova, D., & Cuckle, H. (2017). Routine first trimester screening for maternal thyroid disease. *Journal of Fetal Medicine,* 1-5. Doi: 10.1007/s40556-017-0112-8

Dosiou, C. Sanders, G.D., Araki, S.S., & Crapo, L.M. (2008). Screening pregnant women for autoimmune thyroid disease: a cost-effective analysis. *European Journal of Endocrinology, 158,* 841-851. doi: 10.1530/EJE-07-0882

Ekinci, E.I., Chiu, W.L., Lu, Z.K., Sikaris, K., Churilov, L., Bittar, I., Lam, Q., Crinis, N., & Houlihan, C.A. (2015). A longitudinal study of thyroid autoantibodies in pregnancy: the importance of test timing. *Clinical Endocrinology, 82*(4), 604-610. Doi: 10.1111/cen.12571

Groer, M.W., &Vaughan, J.H. (2013). Positive thyroid peroxidase antibody titer is associated with dysphoric moods during pregnancy and postpartum. *Journal of Obstetric, Gynecologic, & Neonatal Nursing: Clinical Scholarship for the Care of Women, Childbearing Families, & Newborns, 42*(1), E26-E32. Doi: 10.1111/j.1552-6909.2012.01425.x

Hollowell, J.G., Staehling, N.W., Flanders, D., Hannon, W.H., Gunter, E.W., Spencer, C.A., &Braverman, L.E. (2001). Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National health and nutrition examination survey (NHANES III). *The Journal of Clinical Endocrino-logy and Metabolism, 87*(2), 489-499. Retrieved from: http://press.endocrine.org/doi/full/10.1210/jcem.87.2.8182

Jones, D.A. (2006). Health as expanding consciousness. *Nursing Science Quarterly, 19*(4), 330-332. Doi: 10.1177/0894318406293136

Kilpatrick, S.J. (2015). ACOG guidelines at a glance thyroid disease in pregnancy. *Contemporary OB/GYN*. Retrieved from: http://contemporaryobgyn.modernmedicine.com/contemporary-obgyn/news/acog-guidelines-glance-thyroid-disease-pregnancy?page=full

Mamede da Costa, S., Siero Netto, L., Coeli, C.M., Buescu, A., & Vaisman, M. (2007). Value of combined clinical information and thyroid peroxidase antibodies in pregnancy for prediction of postpartum thyroid dysfunction. *American Journal of Reproductive Endocrinology, 58*(4), 344-349. Doi: 10.1111/j.1600-0897.2007.00508.x

Meena, M., Chopra, S., Jain, V., & Aggarwal, N. (2016). The effect of anti-thyroid peroxidase antibodies on pregnancy outcomes in euthyroid women. *Journal of Clinical Diagnostic Research, 10*(9), QC04-QC07. Doi: 10.7860/JCDR/2016/19009.8403

Moleti, M., Presti, V.P.L., Mattina, F., Mancuso, A., De Vivo, A., Giorgianni, G., Di Bella, B., Trimarchi, F., & Vermiglio, F. (2009). Gestational thyroid function abnormalities in conditions of mild iodine deficiency: Early screening versus continuous monitoring of maternal thyroid status. *European Journal of Endocrinology, 160*(4), 611-617. doi: 10.1530/EJE-08-0709

Nahar, U.N., Naher, Z.U., Habib, A., & Mollah, F.H. (2013). Assessment of thyroid peroxidase antibody and thyroid stimulating hormone in the first trimester. *Bangladesh Journal of Medical Science, 12*(2), 164-170. Doi: 10.3329/bjms.v.12i2.14945

Nazarpour, S., Ramezani Tehrani, F., Simbar, M., Tohidi, M., AlaviMajd, H., & & Azizi, F. (2016). Comparison of universal screening with targeted high-risk case finding for diagnosis of thyroid disorders. *European Journal of Endocrinology, 174*(1), 77-83. Doi: 10.1530/EJE-15-0750

Newman, M. (2011, November 14). Health as expanding consciousness. *Nursing Theories a companion to nursing theories and models.* Retrieved from: http://currentnursing.com/nursing_theory/Newman_Health_As_Expanding_Consciousness.html

Nor, A.M.I., Bakin, Y.D., Mustafa, N., Wahab, N.A., Johari, M.J.M., Kamarudin, N.A., & Jamil, M.A. (2010). Thyroid autoantibodies and associated complications during pregnancy. *Journal of Obstetrics & Gynaecology, 30*(7), 675-678. Doi: 10.3109/01443615.2010.503908

Pradhan, M., Anand, B., Singh, N., & Mehrotra, M. (2013). Thyroid peroxidase antibody in hypothyroidism: Its effect on pregnancy. *The Journal of Maternal-Fetal and Neonatal Medicine, 26*(6), 581-583. Doi: 10.3109/1476758.2012.745498

Quinn, F.A., Reyes-Mendez, M.A., Nicholson, L., Compean, L.P., & Tavera, M.L. (2014). Thyroid function and thyroid autoimmunity in apparently healthy pregnant and non-pregnant Mexican women. *Clinical Chemistry & Laboratory Medicine, 52*(9), 1305-1311. Doi: 10.1515/cclm-2014-0350

Sarkhail, P., Mehran, L., Tahamasbinejad, Z., Tohidi, M., & Azizi, F. (2016). Maternal thyroid function and autoimmunity in 3 trimesters of pregnancy and their offspring's thyroid function. *Hormone and Metabolic Research, 48*(1), 20-26. Doi: 10.1055/s-003501555878

Silvio, R., Swapp, K.J., La'ulu, S.L., Hansen-Suchy, K., & Roberts, W.L. (2008). Method specific second-trimester reference intervals for thyroid-stimulating hormone and free thyroxine. *Clinical Biochemistry, 42*(7-8), 750-753. doi: 10.1016/j.clinbiochem.2008.12.004

Smith, M.C. (2011). Integrative review of research related to Margaret Newman's theory of health as expanding consciousness. *Nursing Science Quarterly, 24*(3), 256-272. Doi: 10.1177/0894318411409421

Springer, D. Bartos, V., & Zima, T. (2014). Reference intervals for thyroid markers in early pregnancy

determined by seven different analytical systems. *Scandinavian Journal of Clinical & Laboratory Investigation, 74*(2), 95-101. doi: 10.3109/00365513.2013.860617

Springer, D., Potlukova, E., Limanova, Z., & Zima, T. (2012). Recomm-endations on prenatal screening and the connections to other diseases such as thyroid dysfunction. *Clinical Chemistry and Laboratory Medicine, 50*(7), 1211-1220. doi: 10.1515/cclm-2011-0598

Wasserman, E.E., Nelson, K., Rose, N.R., Eaton, W., Pillion, J.P., Seaberg, E., Talor, M.V., Burek, L., Duggan, A., & Yolken, R.H. (2007). Maternal thyroid autoantibodies during the third trimester and hearing deficits in children: An epidemio-logical assessment. *American Journal of Epidemiology, 167*(6), 701-710. http://doi-org.ezproxy.b

Yang, H., Shao, M., Chen, L., Chen, Q., Yu, L., Cai, L., Lin, Z., Zhang, C., & Lu, X. (2014). Screening strategies for thyroid disorders in the first and second trimester of pregnancy in China. *PLoS ONE, 9*(6), 1-7. Doi: 10.1371/journal.pone.0099611

Appendix

Literature Review Matrix

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Abbassi-Ghanavati, M., Casey, B.M., Spong, C.Y., McIntire, D.D., Halvorson, L.M.& Cunningham, G.F. (2010). Pregnancy outcomes in women with thyroid peroxidase antibodies. *Obstetrics and Gynecology, 116*(2), 381-386. Doi: 10.1097/AOG.0b013e3181e904e5	To compare pregnancy outcomes between women who are positive for thyroid antibodies with those that are negative.	17,298 pregnant women from November 2000-April 2003.	Prospective Observational Study Serum samples taken once from women during the first 20 weeks of their pregnancy. Women with overt hypo-thyroidism were not included in the analysis.	TSH, FT4, TPOAb using Immulite 2000 Analyzer Perinatal outcomes records were obtained through accessing the records from the computer database at Parkland Hospital. Pearson's chi square and Student's t test were used for comparing the groups.	1,012 (6%) of the women were positive for TPOAb. 10 (1%) of the TPOAb positive women experienced placental abruption vs. 0.3% of the negative population. Other pregnancy complications were not found to be more statistically significant in TPOAb positive women other than the incidence of placental abruption, which is four times more	This study indicates that universal screening for TPOAb is not justifiable. Further studies should be performed to prove an intervention preventing pregnancy risk prior to universally screening for TPOAb.	Level II Good Quality

					likely in TPOAb positive women.		

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Ahmed, I.Z., Eid, Y.M., Orabi, H.E., & Ibrahim, H.R. (2014). Comparison of universal and targeted screening for thyroid dysfunction in Egyptian women. *European Journal of Endocrinol-ogy, 171*(2), 285-291. doi: 10.1530/EJE-14-0100	To compare testing of thyroid function in pregnant women assessing for the prevalence of hypothyroidis m. Comparison between testing everyone or only testing people with risk factors for effectively identifying hypothyroidis m	168 pregnant women that attended an outpatient OB clinic in Cairo, Egypt	Quasi-experimental study Patient history interview Thyroid function tests including: TSH, Free T4, Free T3, and anti-thyroid peroxidase.	Pearson's correlation of $p<0.05$ Student's t test X2 test to compare qualitative variables	104 women were found to be low risk 64 were found to be high risk No difference was found between low and high risk groups of clinical or subclinical hypothyroid with TSH or fT3 Elevated TPO and fT4 were more prevalent in the high risk group 75 total patients had hypothyroidism with no statistical significance between being high and low risk.	Categorizing women into high or low risk groups causes missed diagnosis of hypothyroidism; so pregnant women should be universally tested for hypothyroidism.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Bhattacharyya, R., Mukherjee, K., Das, A., Biwas, M.R., Basunia, S.R., & Mukherjee, A. (2015). Anti-thyroid peroxidase antibody positivity during early pregnancy is associated with pregnancy complications and maternal morbidity in later life. *Journal of Natural Science, Biology and Medicine, 6*(2), 402-405. doi: 10.4103/0976-9668.160021	To ascertain if assessing for thyroid autoantibodies in the first trimester of pregnancy has an affect on the outcome of pregnancy or postpartum thyroid disease.	400 pregnant women (8-12 weeks gestation) from April 2011-October 2012	Prospective cohort study Participants found to have abnormal thyroid function at 12 weeks postpartum were followed up every 8 weeks up to 12 months postpartum.	FT4, FT3, TSH, and TPOAb measured at first antepartum visit and then repeated 12 weeks postpartum.	46 (11.5%) of the mothers tested positive for TPOAb. 11.34% of euthyroid mothers tested positive for TPOAb and 14.28% of subclinical hypothyroid mothers tested positive for TPOAb. Average TSH levels were higher in TPOAb positive mothers. 10.87% of TPOAb mothers suffered from SAB. Vs 4.8% of TPOAb negative mothers. PPTD developed	Women who test positive for TPOAb in the first trimester should be monitored closely as they are at a higher risk for SAB and preterm delivery as well as increased risk of developing postpartum thyroiditis.	Level II Good Quality

					in 4.7% of the women and of those women, 81.25% were positive for TPOAb.		

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Bryant, S.N., Nelson, D.B., McIntire, D.D., Casey, B.M., & Cunningham, F.G. (2015). An analysis of population-based prenatal screening for overt hypothyroid-ism. *American Journal of Obstetrics and Gynecology, 213*(4), 565.e1-565.e6. doi: 10.1016/j.ajog.2015.06.0601	To analyze the outcomes of pregnancies of individuals diagnosed with hypothyroi-dism that were identified in population-based screening.	Sample taken from 26,518 women prenatally at Parkland Hospital from Nov. 2000-April 2003.	Secondary Analysis of Quantitative data. Serum thyroid panel levels taken at initial prenatal visit. Thresholds: TSH >3.0 mU/L fT4 <0.9 ng/dL	Chart review completed by nurses to ascertain demographic data pregnancy and birth outcomes (including cesarean delivery, newborn weight, and hypertension after 20 weeks of pregnancy) 2 tailed probability value of <0.05 deemed significant.	47 women had overt hypothyroidism 183 women had positive screenings for hypothyroidism but were unconfirmed. 25% of women with overt hypothyroidism were over the age of 35. Women that screened positive but had unconfirmed hypothyroidism were found more likely to develop pregnancy-related hypertension. Pregnancy outcomes were similar in women that screened positive for hypothyroidism, but were not confirmed (no treatment) to those that received treatment to those who have euthyroid.	This study suggests that universally screening for thyroid dysfunction prenatally is an option for helping to diagnose and treat some hypothyroid disorders. However, since they found the same incidence of hypothyroid that they were already getting before they started the universal screening process they cannot recommend that universal screening is the best option.	Level III Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Costeria, M.J., Oliveira, P., Ares, S., Roque, S., Morreale de Escobar, G., & Palha, J.A. (2010). Parameters of thyroid function throughout and after pregnancy in an iodine-deficient population. *Thyroid, 20*(9), 995-1001. doi: 10.1089/thy.2009.0356	To define the parameters of normal thyroid hormone function during pregnancy and up to one year postpartum in a mild to moderate iodine insufficient population.	118 pregnant women who were negative for thyroid antibodies in Portugal between January 2003 to December 2005	Quasi-experimental study Food intake questionnaire Serum collected in each trimester of pregnancy, intrapartum, and postpartum at 3 days, 3 months, and 1 year after delivery measuring total T4, free T4, total T3, free T3, TSH, Tg, anti—TPO and Anti-Tg antibodies using DYNOtest	Statistical analyses performed with the SPSS 15 software and values were considered reliable if $p<0.05$.	FT4 levels during pregnancy were always lower than postpartum. TT4, TT3, and TBG were higher during pregnancy than after delivery (by 25%). FT4, FT3, and TSH levels changed significantly between all trimesters. TT4 changed significantly between second and third trimesters.	Since TSH is usually lower during the first trimester of pregnancy, the TSH cutoff of 2.5 mIU/L might be too high to catch all of those with subclinical hypothyroidism. This needs to be studied on a larger population. More knowledge is necessary about iodine insufficiency.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Dhaifalah, I., Salek, T., Langova, D., & Cuckle, H. (2017). Routine first trimester screening for maternal thyroid disease. *Journal of Fetal Medicine,* 1-5. Doi: 10.1007/s40556-017-0112-8	To determine how much screening for thyroid disease in the first trimester of pregnancy applies a burden to endocrinology as well as the effectiveness of combining screening for thyroid disease with other screening tests in the first trimester.	10,052 Pregnant women in the first trimester from November 2009-September 2015 in the Czech Republic. (2 phases, the first phase ended in March 2013).	Quasi-experimental Study In phase one, TPOAb, TSH and fT4 were screened for. In phase 2, fT4 was left out.	TPOAb considered positive if greated than 5.6 IU/ml. TSH range 0.35-4.94mU/L, fT4 range 9.0-19.1 pmol/L. Symptomatic thyroid disease sufferers prior to pregnancy were excluded from the study. *P*> 0.0001, chi square test	1190 women (11.8%) were considered to be outside of the range and sent for endocrinology referral. 338 women (3.4%) of women had positive TPOAb.	It may be beneficial to routinely screen pregnant women for thyroid disease in the first trimester when other screening tests are performed, however further research is needed.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Dosiou, C. Sanders, G.D., Araki, S.S., & Crapo, L.M. (2008). Screening pregnant women for autoimmune thyroid disease: a cost-effective analysis. *European Journal of Endocrinology, 158,* 841-851. doi: 10.1530/EJE-07-0882	To determine when it is cost effective to screen pregnant women for thyroid disease.	Women in the US in their first trimester of pregnancy between the ages of 15 to 45 with no history of thyroid disease.	Randomized control trial with the following groups 1. No screening 2. Screening TSH only 3. Screening for TPOAb and then further screening for TSH if Ab were positive.	Markov health transition tree was utilized to see trends in overall costs and savings.	Overall it is cost saving to screen TSH in early pregnancy (overall savings of $102 per patient). Screening for TPOAb overall was also cost effective ($212 per patient). It is cost effective to screen for thyroid disease because the overall damage of undiagnosed thyroid disease costs more than does the screening.	Screen pregnant women in the first trimester for either TSH or TPOAb to rule out thyroid disease.	Level I High Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Ekinci, E.I., Chiu, W.L., Lu, Z.K., Sikaris, K., Churilov, L., Bittar, I., Lam, Q., Crinis, N., & Houlihan, C.A. (2015). A longitudinal study of thyroid autoantibodies in pregnancy: the importance of test timing. *Clinical Endocrinology, 82*(4), 604-610. Doi: 10.1111/cen.12571	To ascertain the best time during pregnancy in which to test for TPOAb and TgAb to help detect hypothyroidism and PPTD	140 women in Melbourne Australia less than 13 weeks pregnant.	Longitudinal Study TPOAb, TgAb, TSH and FT4 measured at 1st, 2nd, and 3rd trimester as well as postpartum.	Longitudinal random-effect logistic regression measured the relationship between time and whether TPOAb status was positive or negative.	13 (9.29%) positive for TPOAb and 15 (10.71%) positive for TgAb during the first trimester Odds of having a positive TPOAb test in 2nd trimester were decreased by 96% and in the 3rd trimester by 97%. Odds of having a positive TgAb test in the 2nd and 3rd trimesters were 99% decreased. 13 out of 83 women (16%) had PPTD by 20 weeks postpartum 32% were TPOAb positive versus 5.1% who were TPOAb negative. It was higher in women who had TPOAb or TgAb positivity.	TPOAb and TgAb decreased between 12-25 weeks gestation so it should be tested for in early pregnancy. If negative thyroid antibody tests are found at the second or third trimester, it does not mean that the women will not have thyroid problems.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Groer, M.W., &Vaughan, J.H. (2013). Positive thyroid peroxidase antibody titer is associated with dysphoric moods during pregnancy and postpartum. *Journal of Obstetric, Gynecologic, & Neonatal Nursing: Clinical Scholarship for the Care of Women, Childbearing Families, & Newborns, 42*(1), E26-E32. Doi: 10.1111/j.1552-6909.2012.01425.x	To observe women's moods who tested positive for TPOAb during pregnancy and postpartum.	631 pregnant women then 63 who screened TPOAb positive and a convenience sample of 72 TPOAb negative women.	Longitudinal, correlational, two-group, observational study. The women followed up with blood tests monthly for six months postpartum.	TPOAb serum testing Demographic Profile of Mood States or POMS questionnaire. Perceived Stress Scale. Thyroid Symptom Checklist	Cronbach's alpha for the PSS-0.839 POMS 0.91 During pregnancy, TPOAb positive women scored higher on the POMS scale including depression and other dysphoric moods. 64% of TPOAb positive women developed PPTD within 6 months postpartum. Postpartum depression and high POMS scores were more common among TPOAb positive women	Routine TPOAb screening might help to predict and prevent postpartum depression since dysphoric moods are more common among women who test positive for TPOAb.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Hollowell, J.G., Staehling, N.W., Flanders, D., Hannon, W.H., Gunter, E.W., Spencer, C.A., &Braverman, L.E. (2001). Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National health and nutrition examination survey (NHANES III). *The Journal of Clinical Endocrino-logy and Metabolism, 87*(2), 489-499. Retrieved from: http://press.endocrine.org/doi/full/10.1210/jcem.87.2.8182	To find a reference range for TSH, fT4, and TPO Ab for the general population.	17,353 people over the age of 12 years old who participated in the NHANES III and had thyroid studies without preexisting thyroid disorders.	Retrospective study fT4 using immunoassay reference range 57.9nmol/L to 169.9 nmol/L TSH reference range 0.39-4.6 mlU/L TPO Ab normal range less than <0.5 IU/mL and TgAb normal range, 1.0 IU/mL	Calculation of prevalence, prevalence distance, and prevalence ratios while using a logistic regression.	4.6% of the population studied had hypothyroidism. Mean TSH for population was 1.4 mIU/L. White study participants had a higher TSH than Black participants. Mean fT4 for population was 112.3 +/- 0.7nmol/L TPO Ab were present in 13% of the population and TgAb were present in 11.3 % of the population.	Keep in mind that Whites and Mexican Americans have higher TSH levels than Blacks. TSH levels in the Black population needs further research. Early detection is important, especially in women who have higher TSH levels. The iodine nutrition of the general population needs to continue to be monitored as it may affect thyroid function.	Level III High Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/Quality
Mamede da Costa, S., Siero Netto, L., Coeli, C.M., Buescu, A., & Vaisman, M. (2007). Value of combined clinical information and thyroid peroxidase antibodies in pregnancy for prediction of postpartum thyroid dysfunction. *American Journal of Reproductive Endocrinology*, *58*(4), 344-349. Doi: 10.1111/j.1600-0897.2007.00508.x	To determine if TPOAb positivity in early pregnancy is a predictor for PPTD within 1 year of giving birth.	98 Pregnant women from March 2000 to June 2003.	Concurrent Cohort Study TPOAb , TSH, and FT4 levels tested at 9-12 weeks gestation, 6 months postpartum, and 12 months postpartum. Patients answered a symptoms and family history questionnaire and underwent examination by a physician.	95% CI of 4.1-16.3 for TSH and 60%, 95.5%, and 60% for positive TPOAb.	10 women (10.2%) were positive for TPOAb. At 12 months postpartum, TSH levels were slightly higher in women who were positive for TPOAb. 6 out of 10 TPOAb women developed PPTD (60%) vs. 4 out of 88 (4.55%). Women were at higher risk for PPTD if they had family history of thyroid dysfunction and if they presented at initial appointment with a goiter.	Screen all pregnant women for TPOAb and follow up with TSH and FT4 in all trimesters in TPOAb positive women. This is because women with TPOAb positivity are at higher risk for pregnancy complications and loss as well as PPTD.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Meena, M., Chopra, S., Jain, V., & Aggarwal, N. (2016). The effect of anti-thyroid peroxidase antibodies on pregnancy outcomes in euthyroid women. *Journal of Clinical Diagnostic Research, 10*(9), QC04-QC07. Doi: 10.7860/JCDR/2016/19009.8403	To determine the risk of the presence of TPOAb in a euthyroid woman during pregnancy.	1000 Pregnant women who presented to an outpatient clinic in India from December 2012-December 2013. Euthyroid women with positive TPOAb were separated and then studied throughout the rest of the study (40/1000) and studied against 40 women in a control group with all normal serum results.	Prospective Study. Serum samples taken during the first 20 weeks of pregnancy and then the women with positive TPOAb but otherwise normal thyroid function were followed through pregnancy.	Statistically analyzed with SPSS software for standard deviation, mean, distribution, range, and Student's t-test.	16/40 (40%) of TPOAb positive women developed hypothyroidism postpartum. 5/40 (12.5%) of TPOAb women experienced preterm delivery vs. 1/40(2.5%) of the control group.	It may be beneficial to screen for TPOAb during pregnancy to diagnose a population as at risk for further problems in the future. A larger, more diverse population should be studied to see if the conclusions are similar.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Moleti, M., Presti, V.P.L., Mattina, F., Mancuso, A., De Vivo, A., Giorgianni, G., Di Bella, B., Trimarchi, F., & Vermiglio, F. (2009). Gestational thyroid function abnormalities in conditions of mild iodine deficiency: Early screening versus continuous monitoring of maternal thyroid status. *European Journal of Endocrinol-ogy, 160*(4), 611-617. doi: 10.1530/EJE-08-0709	To determine whether it is beneficial to assess thyroid function in early pregnancy to test for iodine deficiency and thyroid under-functioning	220 pregnant women living in North Eastern Sicily which is a region known to have iodine deficiency.	Observational study Levels taken in first, second, and third trimesters	Circulating TSH, fT4, TPO-Ab, and Tg-Ab using kits from Roche Diagnostics. Inter and Intra-assay coefficients of <5%	Overt and subclinical hypothyroid affected 26 out of the 220 women tested. 15/26 (57.7%) of women were identified in the first trimester. Of the women left, 6 were identified in the early second trimester and 5 were identified in the late second trimester. 82 out of 220 women received iodine supplementation during pregnancy for low levels of fT4, all of these women's fT4 levels normalized within 4 weeks of birth.	The study suggests that women of childbearing age should take iodine supplements since iodine deficiency is the lead cause of thyroid dysfunction in pregnancy. They suggest that for areas known to have iodine deficiency, targeted screening times for thyroid dysfunction should be addressed using a cost-based analysis.	Level III Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Nahar, U.N., Naher, Z.U., Habib, A., & Mollah, F.H. (2013). Assessment of thyroid peroxidase antibody and thyroid stimulating hormone in the first trimester. *Bangladesh Journal of Medical Science, 12*(2), 164-170. Doi: 10.3329/bjms.v.12i2.14945	To assess the level of TPOAb in women in their first trimester of pregnancy as well as their general thyroid status and to see how they relate to one another in pregnancy.	200 pregnant women from Bangladesh in their first trimester of un-complicated pregnancies.	Cross-sectional quantitative study First trimester serum samples of TSH and TPOAb collected.	TPOAb level and TSH level. Analyzed using SPSS Chi-square test, Z test, and Spearman's correlation coefficient. 95% confidence limit ($p < 0.05$)	Positive for TPOAb (cutoff value of > 12IU/mL) 43/200 women or 21.5%. Mean TSH 2.12 mIU/mL +/- 1.68 mIU/mL Women with TSH >2.5 60/200 or 30% R value of positive TPOAb with increase in TSH level was 0.466 with a p value of <0.01	Screening for TPOAb in the first trimester of pregnancy should be encouraged due to the risks involved with TPOAb positivity.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Nazarpour, S., Ramezani Tehrani, F., Simbar, M., Tohidi, M., AlaviMajd, H., & & Azizi, F. (2016). Comparison of universal screening with targeted high-risk case finding for diagnosis of thyroid disorders. *European Journal of Endocrinology, 174*(1), 77-83. Doi: 10.1530/EJE-15-0750	Compare the effectiveness of universal screening vs. targeted screening in pregnant women for finding thyroid dysfunction.	1480 pregnant Iranian women in their first trimester between September 2013-September 2014.	Cross-sectional prospective study. Patients were separated into low and high-risk groups based on lab tests and physical exams.	A comprehensive questionnaire that included a checklist of risk factors for thyroid disease. Physical exams including palpation of the thyroid, height, weight, and blood pressure. TSH, FT4, & TPOAb.	Normal thyroid function 974 (65.8%). Thyroid disorder 506 (34.2%). 445 (30.1%) had hypothyroidism 132 (8.9%) were positive for TPOAb and of those 34 (2.3% of total population) were euthyroid. Three most prevalent risk factors identified for thyroid dysfunction included age greater than 30 years (30.7%), family history of thyroid disorder (11.4%), and history of SAB (16.5%). Thyroid disorders were identified in 39.6% of high-risk group and 27.4% of low-risk group.	In this study, one third of the women that experienced thyroid dysfunction were not included in the high-risk group. It is reasonable to screen all women for thyroid dysfunction in pregnancy because of its low cost and high availability.	Level II Good Quality

					Hyperthyroidism cases were identified as 8 in the high-risk group and 2 in the low-risk group.		

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Nor, A.M.I., Bakin, Y.D., Mustafa, N., Wahab, N.A., Johari, M.J.M., Kamarudin, N.A., & Jamil, M.A. (2010). Thyroid autoantibodies and associated complications during pregnancy. *Journal of Obstetrics & Gynaecology, 30*(7), 675-678. Doi: 10.3109/01443615.2010.503908	To determine the complications that may arise in women who have thyroid disease with positive thyroid autoantibodies during pregnancy.	49 pregnant women with thyroid disease in Malaysia.	Prospective Observational Study TPOAb, FT4, FT3, and TSH were taken via serum once during each trimester of pregnancy.	TPOAb FT4, FT3, TSH X2 test difference statistically significant if $p<0.05$	19 (61%) of the women with Grave's Disease and 7 (39%) of the women with hypothyroidism had positive thyroid antibodies. Of women with positive antibodies: 7.7% developed hypertension, 15.4% developed preeclampsia, 15.4% had infants with IUGR, 3.8 % had placental abruption, 11.5% had preterm delivery, 7.7% developed postpartum hemorrhage, and 19.2% had PPTD by 8 weeks.	Cost may be an issue for routine screening of thyroid antibodies in pregnancy, but in well-developed countries it is less likely do be a problem than in developing countries. In women with thyroid antibodies, closer monitoring is required because of the increased risk of pregnancy complication and postpartum thyroid dysfunction.	Level II Fair Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Pradhan, M., Anand, B., Singh, N., & Mehrotra, M. (2013). Thyroid peroxidase antibody in hypothyroidism: Its effect on pregnancy. *The Journal of Maternal-Fetal and Neonatal Medicine, 26*(6), 581-583. Doi: 10.3109/14767058.2012.745498	To find out the importance of finding TPOAb in pregnant women and their effect on the outcome of pregnancy.	2479 pregnant women from the Sanjay Gandhi Post Graduate Institute of Medical Sciences antenatal clinic in India from July 2009-June 2011.	Prospective Study Women with hypo-thyroidism during pregnancy were compared with women who did not have hypo-thyroidism during pregnancy.	TSH and FT4 at first antenatal visit and then those diagnosed with hypothyroidism either before or during pregnancy had a TPOAb level drawn as well.	196 women (7.91%) were found to have hypothyroidism. 56 (40%) of those women were TPOAb positive. 10 (17.86%) of the TPOAb positive women suffered 1st trimester SAB vs. 5 (6.49%). 6 (10.71%) of TPOAb positive women suffered 2nd trimester SAB vs. 1 (1.3%). 10 (17.86%) of the infants of TPOAb women suffered from malformations vs 5 (6.49%) of the TPOAb negative women.	Women who have hypothyroidism and are TPOAb positive should be treated with levothyroxine during pregnancy. TPOAb positive women need to be monitored more closely than TPOAb negative women.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Quinn, F.A., Reyes-Mendez, M.A., Nicholson, L., Compean, L.P., & Tavera, M.L. (2014). Thyroid function and thyroid autoimmunity in apparently healthy pregnant and non-pregnant Mexican women. *Clinical Chemistry & Laboratory Medicine, 52*(9), 1305-1311. Doi: 10.1515/cclm-2014-0350	To determine reference intervals for thyroid function tests in women of Mexican heritage.	660 pregnant and 104 non-pregnant Mexican women who were negative for TPOAb and had a TSH <4.94 mIU/L.	Quasi-experimental design Samples were collected from August 2010 to July 2011.	TSH, FT4, TT4, FT3, TT3, TPOAb, and TgAb using ARCHITECT analyzer. Tests used to determine differences: Student's t, Mann-Whitney, and Kruskal_Wallis tests. Two tailed p-value of $p<0.05$.	Pregnant women with positive TPOAb 89 or 13.5% Non-pregnant women with TPOAb 15 or 14.4%. Women with positive TPOAb had a higher average TSH. TSH: Non-pregnant- 0.52-3.77 mIU/L 1st tri- 0.04-3.46 mIU/L 2nd tri- 0.6-4.22 mIU/L 3rd tri- 0.51-4.53 mIU/L FT4: Non-pregnant- 10.68-17.63 pmol/L 1st tri- 9.65-17.89 pmol/L 2nd tri- 9.52-16.73 pmol/L 3rd tri- 8.37-14.41 pmol/L TT4: Non-pregnant- 4.45-10.86 ug/dL 1st tri- 5.86-13.37 ug/dL 2nd tri- 7.08-14.18 ug/dL 3rd tri- 6.55-13.35 ug/dL FT3: Non-pregnant- 1.7-3.26 pg/mL 1st tri- 2.21-4.03 pg/mL	Narrower reference intervals may need to be used in women of Mexican descent. Pregnancy specific reference intervals should be used when evaluating thyroid function.	Level II Good Quality

					2nd tri- 2.44-4.15 pg/mL 3rd tri- 2.14-3.61 pg/mL TT3: Non-pregnant: 0.63-1.68 ng/mL 1st tri- 0.82-2.05 ng/mL 2nd tri- 1.15-2.2 ng/mL 3rd tri- 1.09-1.94 ng/mL		

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Sarkhail, P., Mehran, L., Tahamasbinejad, Z., Tohidi, M., & Azizi, F. (2016). Maternal thyroid function and autoimmunity in 3 trimesters of pregnancy and their offspring's thyroid function. *Hormone and Metabolic Research, 48*(1), 20-26. Doi: 10.1055/s-003501555878	To evaluate thyroid dysfunction and autoimmunity during pregnancy and how it affects offspring.	466 pregnant Iranian women during all three trimesters of pregnancy from November 2004 to November 2006	Quasi-experimental study Measurements taken at <14 weeks, 14-27 weeks, >28 weeks, from cord blood, from 10 day old newborns, and in infants at 2, 4, and 6 months of age.	TT4 and TT3 measured using RIA method, TSH measured using IRMA. TPOAb and TgAb measured using IEMA	10 (8%) of the mothers had subclinical hyperthyroidism and 18 (15%) had subclinical hypothyroidism in at least one trimester. Positive thyroid antibodies in women with thyroid dysfunction were 45.5% in 1st trimester, 41.2% in 2nd trimester, and 25% in 3rd trimester. No correlation was found between the presence of antibodies and thyroid function tests during pregnancy. In cord blood, 7 samples were positive for	TPOAb presence in pregnancy is closely related to thyroid dysfunction whereas TgAb is not as closely correlated with dysfunction. Maternal antibodies have the most profound effect on the neonate in the first trimester of pregnancy, but more information is needed on the effect of TgAb on the fetus.	Level II Good Quality

					TPOAb, 6 were of euthyroid mothers that had TPOAb positive results during pregnancy. 3 samples were positive for high TgAb one was of euthyroid mother, one was of mother with subclinical hypothyroidism in the first trimester and and one was subclinical hypothyroidism in the second trimester but both normalized in the third trimester.		

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Silvio, R., Swapp, K.J., La'ulu, S.L., Hansen-Suchy, K., & Roberts, W.L. (2008). Method specific second-trimester reference intervals for thyroid-stimulating hormone and free thyroxine. *Clinical Biochemistry, 42*(7-8), 750-753. doi: 10.1016/j.clinbiochem.2008.12.004	To define a reference interval for TSH and FT4 in the second trimester of pregnancy.	3102 residual samples from around the United States of women 14-20 weeks gestation	Quasi-experimental study Serum samples compared between Modular E17 Analyzer and Elecsys Regents for testing thyroid hormones. Results were analyzed on Analyse it software	TPOAb TgAb TSH FT4 Total T4 Free triiodothryr-onine And total triiodothryr-onine using ARCHITECT i2000SR	14% of the samples were positive for either TPOAb or TgAb. When the antibody positive samples were excluded, the reference range for TSH was 0.18-4.07mIU/L (2,660) with a 95% confidence interval. Reference range for FT4 in those with normal TSH and no antibodies was 9.5-15.8 pmol/L (2,528). Thyroid antibodies may play a role in thyroid hormone levels during the second trimester of pregnancy.	In order to appropriately interpret results of TSH and FT4, the way that they are tested needs to be calibrated so that the appropriate reference ranges are being used and further studies must be performed with this equipment to determine these exact intervals.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Springer, D. Bartos, V., & Zima, T. (2014). Reference intervals for thyroid markers in early pregnancy determined by seven different analytical systems. *Scandinavian Journal of Clinical & Laboratory Investigation, 74*(2), 95-101. doi: 10.3109/00365513.2013.860617	To identify normal parameters for TSH, fT4 and TPO antibody levels during the first trimester of pregnancy	229 pregnant women 9-12 weeks gestation	Quasi experimental study TSH, FT4, and TPOAb using ADVIA Centaur Siemens automated immunoassay analyser.	Statistical analysis considered to be statistically significant at $p<0.05$ level.	TSH levels were found to be slightly higher in pregnancy. TPO Ab levels were found to be slightly lower in early pregnancy.	No change needs to be made for parameters for fT4 in early pregnancy, but TSH parameters should be slightly increased and TPOAb should be slightly lowered for early pregnancy.	Level II Good Quality

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Springer, D., Potlukova, E., Limanova, Z., & Zima, T. (2012). Recomm-endations on prenatal screening and the connections to other diseases such as thyroid dysfunction. *Clinical Chemistry and Laboratory Medicine, 50*(7), 1211-1220. doi: 10.1515/cclm-2011-0598	To take note of the prevalence of thyroid dysfunction during pregnancy in asymptomatic Czech women and to identify reference ranges for TSH, FT4 and TPOAb during pregnancy.	7530 pregnant Czech women between 9-11 weeks gestation. From 2006-2008.	Quasi-experimental study	Statistical analysis found to be significant when $p<0.05$	Reference interval for TSH in the first trimester should be between 0.06-3.67 mU/L Limit for TPOAb positivity was 143 kU/L Reference interval for FT4 was the same as a nonpregnant adult population of 9.8-23.0 pmol/L 1250 women had markers out of the reference intervals and followed up with endocrinology. 5.1% of them had increased TSH, 2.9% had decreased TSH. 11.5% were positive for TPOAb. FT4 was lower in TPOAb positive women than in the general population. Four risk factors identified: age greater than 30 years, family history of thyroid dysfunction,	Case sensitive screening of thyroid dysfunction in those women with family history of thyroid disease, personal history of diabetes, and history of having thyroid dysfunction. Women positive for TPOAb should be closely monitored.	Level II Good Quality

					personal history of thyroid dysfunction, and goiter. Of the 11.5% of women positive for TPOAb, 40% of them suffered from thyroid dysfunction greater than 1 year postpartum.		

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Wasserman, E.E., Nelson, K., Rose, N.R., Eaton, W., Pillion, J.P., Seaberg, E., Talor, M.V., Burek, L., Duggan, A., & Yolken, R.H. (2007). Maternal thyroid autoantibodies during the third trimester and hearing deficits in children: An epidemio-logical assessment. *American Journal of Epidemiology, 167*(6), 701-710. http://doi-org.ezproxy.b	To assess immunoassays in the third trimester of pregnancy to see if TPOAb affected future sensorineural hearing loss (SNHL) in the offspring of TPOAb positive women.	1859 frozen serum samples stored at -20 degrees Celsius. Serums drawn from pregnant women in Baltimore, MD between 1959-1965.	Observational cohort study. Serum samples taken from women during pregnancy were analyzed later and then follow-up with the offspring was conducted.	Frozen serum samples tested for TPOAb in the third trimester of pregnancy using QUANTA Lite TPO. Range was considered statistically significant if greater than or equal to 62.5 IU/ml, and then greater than or equal to 31.25IU/ml to increase sensitivity. Audiology examination at 8 years of age in offspring, which used bone and air conduction methods. *P* >0.20 Student's t and Whitney-Wilcoxon tests	74 (4.3%) of children had SNHL in primary case definition and when parameters were expanded 103 (7.5%). Of the 22 children of mothers with positive TPOAb at >62.5, 5 (22.7%) had SNHL versus those that tested positive at >31.25 6 (18.8%) had SNHL. Overall incidence of SNHL in the entire population was 1.3%	Additional studies on how TPOAb affects children are needed. Screen mothers in early pregnancy for TPOAb and fT4 and if positive, follow an algorithm to continue testing for TPOAb even if TSH values remain normal.	Level II Good Quality

ethel.edu/10.1093/aje/kwm342							

Citation	Purpose	Sample	Design	Measurement	Results/ Conclusions	Recommendations	Level/ Quality
Yang, H., Shao, M., Chen, L., Chen, Q., Yu, L., Cai, L., Lin, Z., Zhang, C., & Lu, X. (2014). Screening strategies for thyroid disorders in the first and second trimester of pregnancy in China. *PLoS ONE, 9*(6), 1-7. Doi: 10.1371/journal.pone.0099611	To determine if using targeted case finding is the best way to find women with thyroid disorders during the first and second trimesters of pregnancy.	3,882 Chinese women	Prospective Cohort Study Women were divided into groups of high risk and non-high risk based on history, physical, or any other implications of thyroid dysfunction.	Fasting TSH, FT4, and TPO Ab taken during the first and second trimester of pregnancy.	TPOAb positivity was higher in the high-risk group than the non-high risk group. 118 (10.1%) of the total population was positive. 30 (11.7%) of the high-risk women vs 88 (9.6%) of the non-high-risk women. Overt hypo or hyperthyroidism was more likely in those placed in the high-risk group.	Since it is easy to test for and relatively inexpensive, universal screening for TSH, FT4, and TPOAb is a better option than just screening high-risk women.	Level II Good Quality