

1 **THE EFFECTS OF MATERNAL THYROID HORMONE FUNCTION ON EARLY PREGNANCY**

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Abstract

Purpose of review: It is unclear whether pregnancy outcomes are impacted by non-overt thyroid disease, and if detection and treatment of abnormalities improve outcomes. Consequently, there is an ongoing debate regarding universal thyroid screening in pregnancy. A lack of solid evidence has prompted researchers to evaluate the role of screening and to examine pregnancy outcomes in women with thyroid dysfunction. In addition, as in vitro fertilization (IVF) has developed into a commonly used procedure, its impact on thyroid function has also been investigated. The most current literature on these topics will be summarized in this review.

Recent findings: The multiple societies that have published guidelines on thyroid disease in pregnancy have developed different recommendations, with none definitively advocating for universal screening at this time. However, recent studies examining the role of screening have supported it from an economic and prevalence standpoint. Despite this, evidence has failed to consistently demonstrate that treatment of non-overt thyroid disorders improves maternal and fetal outcomes. Recent research does suggest that close monitoring for and treatment of thyroid dysfunction is warranted in women undergoing IVF.

Summary: Further research must be performed to determine whether treatment of non-overt thyroid disease during pregnancy impacts outcomes. Concrete evidence will likely influence the universal screening debate.

Keywords:

Thyroid, subclinical hypothyroidism, pregnancy, screening, infertility

INTRODUCTION

Pregnancy profoundly impacts thyroid function. During early gestation, high levels of human chorionic gonadotropin (hCG) cross-react with and stimulate the thyroid gland's thyrotropin (TSH) receptor leading to an increase in free thyroxine (T₄) and a decrease in TSH [1]. In addition, as estradiol (E₂) increases during early pregnancy, thyroxine-binding globulin (TBG) rises, and the thyroid gland must respond by producing more thyroid hormone. Adequate iodine is also required to maintain homeostasis [2]. However, iodine availability may be decreased due to the increase in renal clearance during pregnancy [3]. A functioning thyroid gland is important as the developing fetus relies on maternal thyroid hormone production during early gestation [3]. In addition, the thyroid is essential for helping meet maternal metabolic demands during pregnancy [4].

Previous studies have suggested that negative maternal and fetal outcomes can occur in pregnant women with thyroid dysfunction [1]. However, many questions remain unanswered regarding thyroid disease during early gestation. It is also unclear whether universal prenatal and antenatal screening should be performed. Therefore, the relationship between thyroid function and pregnancy outcomes continues to be investigated to determine optimal management during early pregnancy. The purpose of this paper is to review the current literature on the debate over universal thyroid screening, to analyze the most recent studies on maternal and fetal outcomes in women with overt and non-overt thyroid dysfunction, and to examine the latest research that has investigated the impact of thyroid function in women with infertility.

PRENATAL AND ANTENATAL SCREENING

Despite the fact that studies have examined the impact of maternal thyroid disease on pregnancy outcomes, previous evidence has not definitively demonstrated a benefit to detection and treatment of all thyroid disorders. It remains unclear whether thyroid screening should be universally performed before and during pregnancy. As demonstrated in Table 1 [5-8], professional societies do not uniformly agree on

screening in the prenatal and antenatal periods. Though some have previously advocated for universal screening of pregnant women [9], others recommend only screening high risk women, and some do not recommend screening at all. A number of recent studies address different angles of the universal screening topic.

Recent Evidence

A major concern with universal screening is cost. Although previous analyses have suggested that universal screening for thyroid dysfunction in pregnancy is cost-effective [10, 11], data from randomized, controlled trials (RCTs) that demonstrated a benefit of treatment for thyroid dysfunction was not available for these previous studies. Therefore, Dosiou et al. created a decision analytic model to evaluate cost-effectiveness of thyroid screening that included RCT data [12*]. Three strategies for screening of autoimmune thyroid disease in early pregnancy were compared: universal screening, high-risk screening, and no screening. The model demonstrated that both universal screening and risk-based screening were cost-effective when compared to no screening, with incremental cost-effectiveness ratios (ICERs) of \$7,138/QALY and \$6,753/QALY, respectively [12*]. This was the first study to show that universal screening was also cost-effective relative to risk-based screening, with an ICER of \$7,258/QALY [12*].

Although the American Congress of Obstetricians and Gynecologists (ACOG), the American Thyroid Association (ATA), and the Endocrine Society support the screening of high-risk women during pregnancy [5, 6**, 7**], a previous report demonstrated that approximately one third of pregnant women with subclinical or overt hypothyroidism would be missed with this method of screening [13]. Therefore, Goel et al. prospectively examined the risk factors associated with hypothyroidism among 1,005 pregnant women [14]. The overall prevalence of hypothyroidism was 6.3%, with 3.4% of the women being newly diagnosed [14]. Of the newly diagnosed women, 94% had subclinical hypothyroidism [14]. Risk factors were compared between the newly hypothyroid and euthyroid women. Although risk factors were more likely to be present in the hypothyroid group, only excessive weight gain was significantly more common

in the hypothyroid women [14]. Of the women with newly diagnosed hypothyroidism, 32% failed to have any of the risk factors that were assessed [14].

According to the ATA and Endocrine Society guidelines, women over 30 should be considered “high-risk” for thyroid dysfunction [6¹¹, 7¹²]. Given these guidelines, Potlukova et al. performed a cross-sectional study to analyze whether age was a risk factor for autoimmune thyroid disease in pregnancy [15]. Universal screening was performed on 5,223 pregnant women, and 5.6% of the women were diagnosed as hypothyroid [15]. There was no significant difference between the prevalence of hypothyroidism in women over 30 and those under 30 (5.5% and 5.8% respectively), although 64.3% of the women with hypothyroidism were at least 30 years old [15]. A logistic regression model demonstrated that there was no significant association between age and TSH suppression or elevation, presence of thyroid peroxidase antibodies (TPOAb), or an elevated TSH with TPOAb [15]. Risk factor data was also analyzed on 132 women that screened positive for hypothyroidism during pregnancy, and 86% of these women had at least one of the risk factors in the ATA guidelines, including age over 30 [6¹¹]. Only 55% of the women would have been identified by high-risk screening if age had not been used [15].

Interpretation

There continues to be a debate over thyroid screening in pregnant women. A recent study by Blatt et al. demonstrated that less than one quarter of women are being screened, despite a high prevalence of gestational hypothyroidism [16]. However, the analysis by Dosiou et al. suggested that universal screening is cost-effective, even if treating SCH is not beneficial [12¹³]. In addition, although high risk screening is advocated by some, Goel et al. and Potlukova et al. reported that if only case based screening is used, a proportion of women with thyroid dysfunction may be missed [14, 15]. These recent studies suggest that universal screening of pregnant women is warranted. However, outcomes of untreated thyroid dysfunction during pregnancy and the benefits of treatment must also be considered when determining whether screening should be performed.

PREGNANCY OUTCOMES

Both maternal and fetal outcomes of thyroid dysfunction during pregnancy have been evaluated in recent studies.

Maternal Outcomes

Although previous evidence has suggested that overt thyroid hypofunction during pregnancy can lead to negative maternal outcomes, [7**] the impact of subclinical hypothyroidism (SCH), thyroid autoimmunity (TAI), and isolated hypothyroxinemia is less clear. Previous studies by Negro et al. have demonstrated that women with TPOAb and SCH have increased pregnancy complications [17-19]. In a prospective study of 984 euthyroid pregnant women, 11.7% had TPOAb [17]. These women were randomized to treatment with levothyroxine (LT₄) or no treatment. There was a significantly higher rate of miscarriage (13.8%) in the untreated TPOAb group when compared to the women with treated TPOAb (3.5%) and the women without TPOAb (2.4%), $P < 0.05$ [17]. The women with untreated TPOAb also had a significantly higher rate of premature deliveries (22.4%) when compared to the women with treated TPOAb (7%) and the women without TPOAb (8.2%), $P < 0.01$ [17]. In another study, Negro et al. reported a post-hoc analysis of a previous prospective observational study of 4,637 women who were screened with TSH and TPOAb within the first 11 weeks of gestation [18]. In the post-hoc analysis [19], 4,123 women tested negative for TPOAb and were included in the study. Subclinical hypothyroidism (SCH), defined as TSH of 2.5–5.0 mIU/L, was diagnosed in 642 women, while the remaining 3,481 women were euthyroid [19]. The rate of spontaneous pregnancy loss was significantly higher in the women with SCH when compared to the euthyroid women, 6.1% vs. 3.6%, $P = 0.006$ [19]. Together, these studies suggest that women with untreated TAI and SCH may have increased miscarriage rates [17,19]. There may also be a relationship between TPOAb and preterm births. Other studies have also suggested that untreated thyroid dysfunction during pregnancy may increase the likelihood of poor maternal outcomes [20, 21]. However,

not all have confirmed that non-overt thyroid disorders are consistently associated with adverse outcomes [22, 23].

Recent evidence

In a retrospective descriptive study of 96 women with TPOAb (49 treated and 47 untreated) and 441 women without TPOAb, Lepoutre et al. examined whether women with TPOAb had decreased miscarriage rates when treated with LT₄, which was prescribed if the woman was found to have TPOAb and TSH was above 1mIU/L [24]. There was a significant difference in the miscarriage rate between the women with treated (0%) and untreated TPOAb (16%) ($P=0.02$) [24]. There was no significant difference in the miscarriage rate between women with untreated TPOAb (16%) and those without TPOAb (8%), ($P=0.17$) [24].

The impact of thyroid dysfunction in women with recurrent miscarriage (RM) has also been questioned. Yan et al. performed an observational cohort study on women with RM, defined as three or more miscarriages under 20 weeks gestation, to determine the prevalence of TPOAb and the value of empiric treatment with LT₄ in women with TPOAb [25]. There were 496 women with unexplained RM and 220 women with explained RM included in the study. There was no significant difference in terms of prevalence of TPOAb among the women with unexplained RM (10.7%) and those with explained RM (11.8%) [25]. Certain women with TPOAb and unexplained RM were treated with LT₄, whereas others received no treatment. Subsequent pregnancy outcomes were evaluated in women with unexplained RM who conceived after evaluation. Live birth rates were not significantly different among the groups: treated TPOAb (53%), untreated TPOAb (58%), and without TPOAb (64%) [25]. In the women with unexplained RM and TPOAb, there was no significant difference in TPOAb titers when women who had a miscarriage were compared with those who had a live birth [25].

Fetal Outcomes

A previous retrospective study by Haddow et al. demonstrated that hypothyroidism during pregnancy negatively impacted a child's neuropsychological development [26]. Children born to mothers with untreated hypothyroidism had significantly lower IQ scores than controls ($P=0.005$) and 19% had IQ scores under 85 compared to 5% of controls [26]. Routine treatment of overt hypothyroidism during pregnancy is now recommended [6**, 7**]. However, treatment of non-overt thyroid dysfunction during pregnancy is not universally supported. There is a debate whether isolated hypothyroxinemia affects fetal development, and at this time the ATA does not recommend treatment in pregnancy [6**]. The relationship between SCH and neurocognitive development in the fetus is also not well understood. Due to a lack of randomized controlled studies, the ATA does not recommend for or against LT_4 treatment in women with SCH and TPOAb. However, treatment of women with SCH and TPOAb is recommended [6**]. The Endocrine Society recommends LT_4 treatment in all women with SCH [7**].

Recent evidence

In a randomized, controlled trial Lazarus et al. assessed whether universal thyroid screening and treatment in pregnancy improved childhood cognitive function in 21,846 women [27**]. Women had TSH and free T_4 measured in early pregnancy and were randomized to a screening group, where thyroid function was assayed immediately, or a control group, where serum samples were stored until delivery. Positive results were TSH above 97.5th percentile, free T_4 below the 2.5th percentile, or both. The rate of positive results was 4.6% in the screening group versus 5.0% in the control group [27**]. Approximately 5% of the women had both a high TSH and a low free T_4 , while the remainder had only one positive test [27**]. All women in the screening group who tested positive were treated with LT_4 to maintain a TSH of 0.1-1.0 mIU/L [27**]. In women with positive screens, the IQs of their children at 3 years of age were assessed. The mean standardized IQ at age 3 was not significantly different between the control group (100.0) and the screening group (99.2), $P=0.40$ [27]. Among the children in the screening group, 12.1% had an IQ under 85 versus 14.1% of the control group, $P=0.39$ [27**].

186

187 Julvez et al. also examined the association between thyroid function in pregnant women and cognitive
188 function in their children [28]. Using a population-based birth cohort, 1,761 mother and child pairs were
189 analyzed. Thyroid function testing was performed in early pregnancy and neurodevelopment of the
190 children was assessed at a median of 14 months. The women with free T₄ levels under the 5th percentile
191 had children with significantly poorer mental scores than women with free T₄ above the cutoff point ($\beta = -$
192 3.4, 95% CI -6.7 to -0.2) [28]. The children of women with a previous diagnosis of thyroid dysfunction who
193 were not treated in early pregnancy also had lower mental scores when compared with children born to
194 women without thyroid disease ($\beta = -5.5$, 95% CI -8.9 to -2.0) [28]. Increased TSH levels alone were not
195 significantly associated with mental scores [28].

196

197 Hyperthyroidism during pregnancy can also result in negative outcomes. If not properly treated,
198 hyperthyroidism can lead to intrauterine growth restriction, low birth weight, preterm delivery,
199 preeclampsia, maternal congestive heart failure, and fetal demise [6**]. Therefore, it is recommended that
200 women with hyperthyroidism due to Graves' disease or thyroid nodules be medically treated with
201 antithyroid drugs (ATD) to maintain free T₄ at or just above the upper limit of the non-pregnant reference
202 range [7**]. Propylthiouracil (PTU) and methimazole (MMI) are ATD that have historically been used
203 during pregnancy. However, reports have suggested that MMI use during pregnancy is associated with
204 congenital anomalies [29]. Yoshihara et al. performed a retrospective study of 6,744 hyperthyroid women
205 to determine if those who used ATD during the first trimester had an increased rate of major
206 malformations in their children when compared to women who did not use any medication [29]. The rate
207 of malformations was significantly higher in the MMI group (4.1%) when compared to the control group
208 (2.1%) ($P=0.002$) [29]. There was no significant difference between the rate of malformations in the PTU
209 group (1.9%) and the control group ($P=0.709$) [29].

210

211 **Interpretation**

This recent evidence must be evaluated and synthesized to determine if thyroid dysfunction alters pregnancy outcomes and whether treatment is beneficial. A systematic review with meta-analysis by Vissenberg et al. examined treatment of various thyroid disorders during the preconception period and early gestation [30]. This study determined that when women with clinical hyperthyroidism were treated with ATD, there was a decreased risk of preterm delivery (RR 0.23, CI: 0.1-0.52, P=0.0004), pre-eclampsia (RR 0.23, CI: 0.06-0.89, P=0.03), and low birthweight infants (RR 0.38, CI: 0.22-0.66, P=0.0005) [30]. When overt hypothyroidism was treated with LT₄, the risk of miscarriage (RR 0.18, CI: 0.08-0.39, P<0.01) and preterm delivery (RR 0.41, CI: 0.24-0.68, P<0.01) was decreased [30].

This meta-analysis also determined that when women with TAI were treated with LT₄ there was a non-significant decrease in miscarriage rate (RR: 0.58, CI 0.32-1.06, P=0.07), but a significant reduction in preterm birth (RR: 0.31, CI: 0.11-0.90, P=0.03) [30]. The authors concluded that there was insufficient evidence that TAI should be treated with LT₄ [30]. Recent studies evaluating the impact of TAI also do not provide strong evidence regarding treatment. Although Lepoutre et al. reported that miscarriage rates were significantly decreased when women with TPOAb were treated with LT₄, [24] Yan et al. did not find a significant improvement in live birth rate when women with RM and TPOAb were treated [25].

The meta-analysis by Vissenberg et al. also reported that there was insufficient evidence to determine whether treatment of SCH was beneficial [30]. Similarly, recent studies have not demonstrated consistent findings in women with non-overt thyroid disease. The randomized trial by Lazarus et al. did not discover a significant decrease in the IQ of children born to women with untreated reduced thyroid function [27**]. In contrast, Julvez et al. reported poorer mental scores in children born to mothers with hypothyroxinemia and untreated thyroid dysfunction [28]. Further randomized studies are needed to determine the impact of reduced thyroid function on pregnancy outcomes.

The study by Yoshihara et al. reported that PTU used during pregnancy was associated with a lower risk of congenital anomalies than MMI [29]. However, a report by the U.S. Food and Drug Administration (FDA) suggests that PTU may be associated with severe liver injury [6**, 7**]. As a result, PTU continues to be recommended by the ATA and the Endocrine Society for the treatment of hyperthyroidism in the first trimester, but both groups suggest switching to MMI later in pregnancy [6**, 7**].

INFERTILITY

Thyroid function can be affected in infertile women undergoing In Vitro Fertilization (IVF). Controlled ovarian hyperstimulation (COH) leads to rises in E₂ and subsequent elevations in TBG which can impact the hypothalamic-pituitary-thyroid axis. Consequently, the distribution of thyroid hormones may be impaired in women undergoing COH [2]. In addition, infertile women have an increased prevalence of TAI, and this may also impact thyroid function in those undergoing IVF [2].

Recent Evidence

As thyroid dysfunction during pregnancy may be associated with negative outcomes, understanding the changes during COH is essential [31*]. Gracia et al. performed a prospective cohort study to examine how thyroid function changes in women undergoing COH and in early pregnancy [31*]. Women underwent COH, oocyte retrieval, and embryo transfer (ET). Testing for TSH, free T₄, E₂, TBG, and TPOAb was performed six times throughout the process. The final analysis included 57 women, 15.8% of whom were treated for hypothyroidism. All hormone levels changed significantly over time. Baseline TSH was 1.42 mIU/L and increased with stimulation to a peak of 2.44 mIU/L one week after hCG was administered [31*]. During or after COH, 44.0% of women (22/50) with an initial TSH ≤ 2.5 mIU/L had an increase in TSH to above 2.5 mIU/L [31*]. In addition, there was a significant interaction between pregnancy and time in regards to TSH as TSH fell in women who did not become pregnant, but remained elevated in pregnant women two weeks after a positive pregnancy test [31*].

262

263 The impact on IVF outcomes in women with thyroid dysfunction has also been investigated. A previous
264 study by Kim et al. demonstrated that in women with SCH who underwent IVF, those treated with LT₄ had
265 significantly higher live birth rates and lower miscarriage rates than untreated women [32]. However,
266 there is limited data on the impact of treated overt hypothyroidism on COH and IVF. Scoccia et al.
267 performed a retrospective cohort study to assess outcomes after IVF in women with treated
268 hypothyroidism and euthyroid women [33]. Of the 240 women included in the analysis, 8.8% were
269 hypothyroid and were treated with LT₄ to maintain their TSH under 4.0 mIU/L. COH, oocyte retrieval, and
270 ET were performed per protocol. The women with hypothyroidism had significantly lower implantation and
271 clinical pregnancy rates when compared to the euthyroid women [33]. The live birth rate was also
272 significantly lower in the hypothyroid group (14.3%) when compared to the euthyroid group (37.3%),
273 $P=0.035$ [33].

274

275 The role of TAI in women undergoing IVF has also been investigated. Some studies have demonstrated
276 an association between antithyroid antibodies and miscarriage in IVF patients, while others have not.
277 According to the Endocrine Society, a conclusion regarding whether women with TAI and infertility who
278 undergo IVF are at increased risk of miscarriage is unable to be drawn [7**]. In a retrospective analysis by
279 Zhong et al. 766 infertile women underwent IVF/ICSI, 90 of whom had antithyroid antibodies [34]. The
280 women with antithyroid antibodies had a significantly lower rate of fertilization, implantation rate, and
281 pregnancy rate than the women without antibodies [34]. The miscarriage rate was significantly higher in
282 the antithyroid antibody group, 26.9% versus 11.8% ($P=0.002$) [34].

283

284 In a meta-analysis, Velkeniers et al. examined whether pregnancy outcomes in infertile women with SCH
285 and TAI undergoing IVF were affected by treatment with LT₄ [35*]. Three RCTs of 220 women where LT₄
286 treatment was compared with no treatment or placebo were included. Delivery rate in women treated
287 with LT₄ was significantly higher (pooled RR 2.76, 95% CI 1.20-6.44, $P=0.018$) [35*]. Treatment with LT₄

also resulted in significantly lower miscarriage rates (pooled RR 0.45, 95% CI 0.24-0.82, $P=0.010$) [35*]. There was no significant benefit of LT₄ treatment on number of retrieved or mature oocytes, number of embryos transferred, number of embryos cryopreserved, or clinical pregnancy rate [35*].

Interpretation

The study by Gracia et al. demonstrated that COH significantly impacts thyroid function [31*]. Therefore, evaluation of thyroid function seems warranted in women undergoing IVF, especially in individuals with preexisting thyroid disorders. Other recent studies have supported this notion as IVF pregnancy rates were significantly lower in women with treated hypothyroidism [33] and in women with TAI [34]. In addition, the meta-analysis by Velkeniers et al. reported that women with SCH and TAI had improved pregnancy outcomes after IVF when treated with LT₄ [35*]. Overall, this evidence suggests that thyroid monitoring may be warranted in women undergoing IVF and that treatment for non-overt thyroid dysfunction can potentially improve pregnancy outcomes.

CONCLUSION

Although pregnancy clearly impacts the thyroid, studies have continued to examine whether adverse pregnancy outcomes result from non-overt thyroid dysfunction during early pregnancy. Recent evidence has demonstrated that the effects on maternal and fetal outcomes are still unclear. However, it does appear based on the current literature that women undergoing IVF may benefit from thyroid monitoring and treatment. Given that many unanswered questions remain, thyroid disease in early pregnancy should be studied in large, prospective RCTs. Until stronger evidence becomes available, the topic of universal thyroid screening will continue to be debated.

REFERENCES

Papers of particular interest, published within the annual period of review have been highlighted as:

- Of special interest

- Of outstanding interest

- [1] Stagnaro-Green A, Pearce E. Thyroid disorders in pregnancy. *Nat Rev Endocrinol* 2012;8:650-8.
- [2] Krassas GE, Poppe K, Glinioer D. Thyroid function and human reproductive health. *Endocr Rev* 2010;31:702-55.
- [3] Casey BM, Leveno KJ. Thyroid disease in pregnancy. *Obstet Gynecol* 2006;108:1283-92.
- [4] Glinioer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997;18:404-33.
- [5] ACOG Committee Opinion No. 381. Subclinical hypothyroidism in pregnancy. *Obstet Gynecol* 2007;110:959-60.
- [6] Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21:1081-125.
 - Extensive recommendations, based on a thorough review of the literature, from a task force of international experts regarding thyroid dysfunction during pregnancy.
- [7] De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543-65.
 - Updated evidence-based guidelines for the diagnosis and treatment of thyroid dysfunction before, during, or after pregnancy.
- [8] Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid* 2012;22:1200-35.
- [9] Gharib H, Tuttle RM, Baskin HJ, et al. Consensus Statement #1: Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. *Thyroid* 2005;15:24-8.
- [10] Thung SF, Funai EF, Grobman WA. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. *Am J Obstet Gynecol* 2009;200:267e1-7.
- [11] Dosiou C, Sanders GD, Araki SS, Crapo LM. Screening pregnant women for autoimmune thyroid disease: a cost-effectiveness analysis. *Eur J Endocrinol* 2008;158:841-51.
- [12] Dosiou C, Barnes J, Schwartz A, et al. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J Clin Endocrinol Metab* 2012;97:1536-46.
 - A cost-effective analysis that included data from randomized controlled trials and compared universal thyroid screening with high-risk screening and no screening during pregnancy.
- [13] Vaidya B, Anthony S, Bilous M, et al. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 2007;92:203-7.
- [14] Goel P, Kaur J, Saha PK, et al. Prevalence, associated risk factors and effects of hypothyroidism in pregnancy: a study from north India. *Gynecol Obstet Invest* 2012;74:89-94.
- [15] Potlukova E, Potluka O, Jiskra J, et al. Is age a risk factor for hypothyroidism in pregnancy? An analysis of 5223 pregnant women. *J Clin Endocrinol Metab* 2012;97:1945-52.
- [16] Blatt AJ, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. *J Clin Endocrinol Metab* 2012;97:777-84.

- [17] Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006;91:2587-91.
- [18] Negro R, Schwartz A, Gismondi R, et al. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 2010;95:1699-707.
- [19] Negro R, Schwartz A, Gismondi R, et al. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab* 2010;95:E44-8.
- [20] Abalovich M, Gutierrez S, Alcaraz G, et al. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2002;12:63-8.
- [21] Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005;105:239-45.
- [22] Casey BM, Dashe JS, Spong CY, et al. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstet Gynecol* 2007;109:1129-35.
- [23] Cleary-Goldman J, Malone FD, Lambert-Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 2008;112:85-92.
- [24] Lepoutre T, Debieve F, Gruson D, Daumerie C. Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. *Gynecol Obstet Invest* 2012;74:265-73.
- [25] Yan J, Sripada S, Saravelos SH, et al. Thyroid peroxidase antibody in women with unexplained recurrent miscarriage: prevalence, prognostic value, and response to empirical thyroxine therapy. *Fertil Steril* 2012;98:378-82.
- [26] Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;341:549-55.
- [27] Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012;366:493-501.
- A randomized, controlled trial that compared cognitive function in children born to women who were screened and treated for thyroid dysfunction during pregnancy with those born to mothers with untreated thyroid abnormalities.
- [28] Julvez J, Alvarez-Pedrerol M, Rebagliato M, et al. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. *Epidemiology* 2013;24:150-7.
- [29] Yoshihara A, Noh J, Yamaguchi T, et al. Treatment of graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *J Clin Endocrinol Metab* 2012;97:2396-403.
- [30] Vissenberg R, van den Boogaard E, van Wely M, et al. Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 2012;18:360-73.
- [31] Gracia CR, Morse CB, Chan G, et al. Thyroid function during controlled ovarian hyperstimulation as part of in vitro fertilization. *Fertil Steril* 2012;97:585-91.
- A prospective cohort study that monitored multiple serum thyroid hormones at frequent intervals during controlled ovarian hyperstimulation and early gestation to evaluate how and when thyroid function is altered in women undergoing IVF.
- [32] Kim CH, Ahn JW, Kang SP, et al. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril* 2011;95:1650-4.
- [33] Scoccia B, Demir H, Kang Y, et al. In vitro fertilization pregnancy rates in levothyroxine-treated women with hypothyroidism compared to women without thyroid dysfunction disorders. *Thyroid* 2012;22:631-6.
- [34] Zhong YP, Ying Y, Wu HT, et al. Relationship between antithyroid antibody and pregnancy outcome following in vitro fertilization and embryo transfer. *Int J Med Sci* 2012;9:121-5.
- [35] Velkeniers B, Van Meerhaeghe A, Poppe K, et al. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. *Hum Reprod Update*, In Press, DOI: 10.1093/humupd/dms052.

408 •A meta-analysis that examined the benefits of treating subclinical hypothyroidism and thyroid
409 autoimmunity in infertile women undergoing assisted reproductive technology.

410

411

Key points:

- Although screening of high-risk pregnant women is supported by some professional societies, there is a debate regarding universal prenatal and antenatal screening for thyroid dysfunction because studies have not consistently demonstrated that outcomes are improved with screening.
- Current evidence does not strongly support treatment of non-overt thyroid dysfunction and thyroid autoimmunity during pregnancy, but further studies are needed to determine optimal management of women with these conditions.
- Because controlled ovarian hyperstimulation affects thyroid gland function, close monitoring is warranted in individuals undergoing IVF, as these women may benefit from treatment of thyroid dysfunction.

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425 None

426

427 **Conflicts of interest:**

428 The authors have no conflicts of interest to declare.

429 **Table legends:**

430 Table 1.

431 Heading: Thyroid screening guidelines

432 Sources: [5-8]