The effects of maternal thyroid hormone function on early pregnancy

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Purpose of review
It is unclear whether pregnancy outcomes are impacted by nonovert thyroid disease, and whether 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 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 nonovert 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 nonovert thyroid disease during pregnancy impacts outcomes. Concrete evidence will likely influence the universal screening debate.

Keywords
infertility, pregnancy, screening, subclinical hypothyroidism, thyroid

INTRODUCTION
Pregnancy profoundly impacts thyroid function. During early gestation, high levels of human chorionic gonadotropin 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 review 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 nonovert thyroid dysfunction, and to examine the latest research that has investigated the impact of thyroid function in women with infertility.
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 nonovert 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.

PREGNATAL 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 [5,6,7**,8], professional societies do not uniformly agree on screening in the prenatal and antenatal periods. Although some have previously advocated for universal screening of pregnant women [9], others recommend screening only 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 were not available for these previous studies. Therefore, Dosiou et al. [12*] created a decision analytic model to evaluate cost-effectiveness of thyroid screening that included RCT data. 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 with no screening, with incremental cost-effectiveness ratios of $7138/QALY and $6753/QALY, respectively [12*]. This was the first study to show that universal screening was also cost-effective relative to risk-based screening, with an incremental cost-effectiveness ratio of $7258/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. [14] prospectively examined the risk factors associated with hypothyroidism among 1005 pregnant women. 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 (SCH) [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 [6,7**]. Given these guidelines, Potlukova et al. [15] performed a cross-sectional study to analyze whether age was a risk factor for autoimmune thyroid disease in pregnancy. Universal screening was performed on 5223 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 were 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 [6]. 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. [16] demonstrated that less than one quarter of women are being screened, despite a high prevalence of...
gestational hypothyroidism. However, the analysis by Dosiou et al. [12] suggested that universal screening is cost-effective, even if treating SCH is not beneficial. In addition, although high-risk screening is advocated by some, Goel et al. [14] and Potlukova et al. [15] reported that if only case-based screening is used, a proportion of women with thyroid dysfunction may be missed. 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 SCH, thyroid autoimmunity (TAI), and isolated hypothyroxinemia is less clear. Previous studies by Negro et al. [17–19] have demonstrated that women with TPOAb and SCH have increased pregnancy complications. 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 with 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 with the women with treated TPOAb (7%).

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**Table 1. Thyroid screening guidelines**

| Author (year) | Committee Opinion (2007) | Stagnaro-Green et al. (2011) | DeGroot et al. (2012) | Garber et al. (2012) |
|---------------|--------------------------|-----------------------------|----------------------|---------------------|
| **Definition of normal TSH in first trimester** | Not defined | Trimester-specific ranges should be applied. If unavailable: 0.1–2.5 mIU/l | 0.1–2.5 mIU/l | Upper limit should be based on trimester-specific ranges. If unavailable, upper limit of 2.5 mIU/l |
| **Universal preconception screening** | Not addressed | Not addressed | Not recommended | Not recommended |
| **High-risk preconception screening** | Not addressed | Insufficient evidence to recommend for or against | Recommended* | Recommended* |
| **Universal screening during pregnancy** | Not recommended | Insufficient evidence to recommend for or against | No consensus* | Not recommended |
| **High-risk screening during pregnancy** | Recommended* | Recommended* | Recommended* | Not addressed |
| **Screening for thyroid antibodies** | Not addressed | Insufficient evidence to recommend for or against all women for thyroid antibodies in the first trimester | Not recommended to screen for TPOAb before or during pregnancy | TPOAb should be considered when evaluating patients with SCH |

Sources: [5,6,7**, 8]. AACE, American Association of Clinical Endocrinologists; ACOG, American Congress of Obstetricians and Gynecologists; ATA, American Thyroid Association; SCH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone.

*High risk: Over age 30, family history of autoimmune thyroid disease or hypothyroidism, presence of goiter, thyroid antibodies, symptoms or signs of thyroid hypofunction, personal history of type 1 diabetes mellitus or autoimmune disorders, history of infertility, prior history of miscarriage or preterm delivery, history of prior therapeutic head or neck irradiation or prior thyroid surgery, currently receiving levothyroxine replacement, living in a region with presumed iodine deficiency.

**High risk: autoimmune disease including type 1 diabetes mellitus, pernicious anemia, a first-degree relative with autoimmune thyroid disease, history of neck radiation to the thyroid gland, prior history of thyroid surgery or dysfunction, abnormal thyroid examination, psychiatric disorders, taking amiodarone or lithium. Also women with the following diagnoses: adrenal insufficiency, alopecia, unspecified anemia, cardiac dysrhythmia, changes in skin texture, congestive heart failure, constipation, dementia, dysmenorrhea, hypercholesterolemia, hypertension, mixed hyperlipidemia, malaise and fatigue, unspecified myopathy, prolonged QT interval, vitiligo, weight gain.

*Some committee members recommend screening all pregnant women. Others recommend neither for nor against screening all pregnant women, but support screening high-risk women at first visit.

*High risk: Symptomatic women and those with a personal history of thyroid disease or other medical conditions associated with thyroid disease.

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|-------------------------------------|
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| **Universal preconception screening** |
| Not addressed | Not addressed | Not recommended | Not recommended |
| **High-risk preconception screening** |
| Not addressed | Insufficient evidence to recommend for or against | Recommended* | Recommended* |
| **Universal screening during pregnancy** |
| Not recommended | Insufficient evidence to recommend for or against | No consensus* | Not recommended |
| **High-risk screening during pregnancy** |
| Recommended* | Recommended* | Recommended* | Not addressed |
| **Screening for thyroid antibodies** |
| Not addressed | Insufficient evidence to recommend for or against all women for thyroid antibodies in the first trimester | Not recommended to screen for TPOAb before or during pregnancy | TPOAb should be considered when evaluating patients with SCH |
and the women without TPOAb (8.2%), \(P < 0.01\) [17]. In another study, Negro et al. [18] reported a posthoc analysis of a previous prospective observational study of 4637 women who were screened with TSH and TPOAb within the first 11 weeks of gestation. In the posthoc analysis [19], 4123 women tested negative for TPOAb and were included in the study. SCH, defined as TSH of 2.5–5.0 mIU/l, was diagnosed in 642 women, whereas the remaining 3481 women were euthyroid [19]. The rate of spontaneous pregnancy loss was significantly higher in the women with SCH when compared with the euthyroid women, 6.1 versus 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 nonovert 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. [24] examined whether women with TPOAb had decreased miscarriage rates when treated with LT\(_4\), which was prescribed if the woman was found to have TPOAb and TSH was above 1 mIU/l. 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 has also been questioned. Yan et al. [25] performed an observational cohort study on women with recurrent miscarriage, defined as three or more miscarriages under 20 weeks gestation, to determine the prevalence of TPOAb and the value of empiric treatment with LT\(_4\) in women with TPOAb. There were 496 women with unexplained recurrent miscarriage and 220 women with explained recurrent miscarriage included in the study. There was no significant difference in terms of prevalence of TPOAb among the women with unexplained recurrent miscarriage (10.7%) and those with explained recurrent miscarriage (11.8%) [25]. Certain women with TPOAb and unexplained recurrent miscarriage were treated with LT\(_4\), whereas others received no treatment. Subsequent pregnancy outcomes were evaluated in women with unexplained recurrent miscarriage 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 recurrent miscarriage 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. [26] demonstrated that hypothyroidism during pregnancy negatively impacted a child’s neuropsychological development. Children born to mothers with untreated hypothyroidism had significantly lower intelligence quotient (IQ) scores than controls (\(P = 0.005\)), and 19% had IQ scores under 85 compared with 5% of controls [26]. Routine treatment of overt hypothyroidism during pregnancy is now recommended [6,7**]. However, treatment of nonovert 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. [27**] assessed whether universal thyroid screening and treatment in pregnancy improved childhood cognitive function in 21846 women. Women had TSH and free T\(_4\) measured in early pregnancy and were randomized to a screening group, wherein thyroid function was assayed immediately, or a control group, wherein serum samples were stored until delivery. Positive results were TSH above 97.5th percentile, free T\(_4\) below the 2.5th percentile, and 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\(_4\), whereas 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**].

Julvez et al. [28] also examined the association between thyroid function in pregnant women and cognitive function in their children. Using a population-based birth cohort, 1761 mother and child pairs were analyzed. Thyroid function testing was performed in early pregnancy and neurodevelopment of the children was assessed at a median of 14 months. The women with free \( T_4 \) levels under the 5th percentile had children with significantly poorer mental scores than women with free \( T_4 \) above the cutoff point \( \beta = -3.4, 95\% \) confidence interval (CI) \(-6.7 \) to \(-0.2 \) [28]. The children of women with a previous diagnosis of thyroid dysfunction who were not treated in early pregnancy also had lower mental scores when compared with children born to women without thyroid disease \( \beta = -5.5, 95\% \) CI \(-8.9 \) to \(-2.0 \) [28]. Increased TSH levels alone were not significantly associated with mental scores [28].

Hyperthyroidism during pregnancy can also result in negative outcomes. If not properly treated, hyperthyroidism can lead to intrauterine growth restriction, low birth weight, preterm delivery, preeclampsia, maternal congestive heart failure, and fetal demise [6]. Therefore, it is recommended that women with hyperthyroidism due to Graves’ disease or thyroid nodules be medically treated with antithyroid drugs (ATDs) to maintain free \( T_4 \) at or just above the upper limit of the nonpregnant reference range [7**]. Propylthiouracil (PTU) and methimazole (MMI) are ATDs that have historically been used during pregnancy. However, reports have suggested that MMI use during pregnancy is associated with congenital anomalies [29]. Yoshihara et al. [29] performed a retrospective study of 6744 hyperthyroid women to determine whether those who used ATD during the first trimester had an increased rate of major malformations in their children when compared with women who did not use any medication. The rate of malformations was significantly higher in the MMI group (4.1%) when compared with the control group (2.1%) \( P = 0.002 \) [29]. There was no significant difference between the rate of malformations in the PTU group (1.9%) and the control group \( P = 0.709 \) [29].

**Interpretation**

This recent evidence must be evaluated and synthesized to determine whether thyroid dysfunction alters pregnancy outcomes and whether treatment is beneficial. A systematic review with meta-analysis by Vissenberg et al. [30] examined treatment of various thyroid disorders during the preconception period and early gestation. This study determined that when women with clinical hyperthyroidism were treated with ATD, there was a decreased risk of preterm delivery [relative risk (RR) 0.23, 95% CI 0.1 to 0.52, \( P = 0.0004 \)], preeclampsia (RR 0.23, 95% CI 0.06 to 0.89, \( P = 0.03 \)), and low birthweight infants (RR 0.38, 95% CI 0.22 to 0.66, \( P = 0.0005 \)) [30]. When overt hypothyroidism was treated with \( LT_4 \), the risk of miscarriage (RR 0.18, 95% CI 0.08 to 0.39, \( P < 0.01 \)) and preterm delivery (RR 0.41, 95% CI 0.24 to 0.68, \( P < 0.01 \)) was decreased [30].

This meta-analysis also determined that when women with TAI were treated with \( LT_4 \) there was a nonsignificant decrease in miscarriage rate (RR 0.58, 95% CI 0.32 to 1.06, \( P = 0.07 \)), but a significant reduction in preterm birth (RR 0.31, 95% CI 0.11 to 0.90, \( P = 0.03 \)) [30]. The authors concluded that there was insufficient evidence that TAI should be treated with \( LT_4 \) [30]. Recent studies evaluating the impact of TAI also do not provide strong evidence regarding treatment. Although Lepoutre et al. [24] reported that miscarriage rates were significantly decreased when women with TPOAb were treated with \( LT_4 \), Yan et al. [25] did not find a significant improvement in live birth rate when women with recurrent miscarriage and TPOAb were treated.

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

The study by Yoshihara et al. [29] reported that PTU used during pregnancy was associated with a lower risk of congenital anomalies than MMI. 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 IVF. Controlled ovarian hyperstimulation (COH) leads to rises in \( E_2 \) and subsequent
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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. [31*] performed a prospective cohort study to examine how thyroid function changes in women undergoing COH and in early pregnancy. Women underwent COH, oocyte retrieval, and embryo transfer. 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 1 week after human chorionic gonadotropin was administered [31*]. During or after COH, 44.0% of women (22/50) with an initial TSH 2.5 mIU/l or less 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 2 weeks after a positive pregnancy test [31*].

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

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

In a meta-analysis, Velkeniers et al. [35*] examined whether pregnancy outcomes in infertile women with SCH and TAI undergoing IVF were affected by treatment with LT4. Three RCTs of 220 women wherein LT4 treatment was compared with no treatment or placebo were included. Delivery rate in women treated with LT4 was significantly higher (pooled RR 2.76, 95% CI 1.20 to 6.44, P = 0.018) [35*]. Treatment with LT4 also resulted in significantly lower miscarriage rates (pooled RR 0.45, 95% CI 0.24 to 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. [31*] demonstrated that COH significantly impacts thyroid function. 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. [35*] reported that women with SCH and TAI had improved pregnancy outcomes after IVF when treated with LT4. Overall, this evidence suggests that thyroid monitoring may be warranted in women undergoing IVF and that treatment for nonovert 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 nonovert 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.

Acknowledgements

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

REFERENCES AND RECOMMENDED READING

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

** of special interest

& of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 339–340).

1. Stagnaro-Green A, Pearce E. Thyroid disorders in pregnancy. Nat Rev Endocrinol 2012; 8:650–658.
2. Krassas GE, Poppe K, Glinser D. Thyroid function and human reproductive health. Endocr Rev 2010; 31:702–755.
3. Casey BM, Leveno KJ. Thyroid disease in pregnancy. Obstet Gynecol 2006; 108:1283–1292.
4. Glinser D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997; 18:404–433.
5. ACOG Committee Opinion No. 381. Subclinical hypothyroidism in pregnancy. Obstet Gynecol 2007; 110:899–906.
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; 21:1081–1125.
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; 97:2543–2565.
8. Updated evidence-based guidelines for the diagnosis and treatment of thyroid dysfunction before, during, or after pregnancy.
9. 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; 22:1200–1235.
10. 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 2008; 15:24–28.
11. Thung SF, Funai EF, Grobman WA. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am J Obstet Gynecol 2009; 200:267e1–267e7.
12. Dosiou C, Sanders GD, Araki SS, Crapo LM. Screening pregnant women for autoimmune thyroid disease: a cost-effectiveness analysis. Eur J Endocrinol 2008; 158:841–851.
13. Vaidya B, Anthony S, Blouss M, et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? J Clin Endocrinol Metab 2007; 92:203–207.
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, Jiska J, et al. Is age a risk factor for hypothyroidism in pregnancy? An analysis of 5223 pregnant women. J Clin Endocrinol Metab 2012; 97:1945–1952.
16. Blatt AJ, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. J Clin Endocrinol Metab 2012; 97:777–784.
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; 91:2587–2591.
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; 95:1699–1707.
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–E48.
20. Abalovich M, Gutierrez S, Alcaraz G, et al. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002; 12:63–69.
21. Casey BM, Dashe J, Spong CY, et al. Cost-effectiveness of universal and risk-based screening in pregnancy for subclinical hypothyroidism. Obstet Gynecol 2005; 105:239–245.
22. Casey BM, Dashe J, Spong CY, et al. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol 2007; 109:1129–1135.
23. Clevy-Goldman J, Malone FD, Lambert-Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 2008; 112:85–89.
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; 74:265–273.
25. Yan J, Sripada S, Saravos EL, et al. Thyroid peroxidase antibody in women with unexplained recurrent miscarriage: prevalence, prognostic value, and response to empirical thyroxine therapy. Fertil Steril 2012; 98:378–382.
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; 341:549–555.
27. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012; 366:493–501.
28. Julvez J, Alvarez-Pedrerol M, Rebagliato M, et al. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology 2013; 24:150–157.
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; 97:2396–2403.
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; 18:350–373.
31. Gracia CR, Morse CB, Chan G, et al. Thyroid function during controlled ovarian hyperstimulation as part of in vitro fertilization. Fertil Steril 2012; 98:586–591.
32. A prospective cohort study that monitored multiple serum thyroid hormones at frequent intervals during COH and early gestation to evaluate how and when thyroid function is altered in women undergoing IVF.
33. 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; 95:1650–1654.
34. 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; 22:831–836.
35. 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; 9:121–125.
36. 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 2013; 19:251–258; doi: 10.1093/humupd/dms052.
37. A meta-analysis that examined the benefits of treating SCH and TAI in infertile women undergoing assisted reproductive technology.