Treatment of thyroid disorders before conception and in early pregnancy: a systematic review

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BACKGROUND: Thyroid disorders are associated with pregnancy complications. Universal screening is currently not recommended because of a lack of evidence on the effectiveness of treatment. Women with hyperthyroidism and hypothyroidism evidently require treatment but this is less clear for women with subclinical hypothyroidism and thyroid autoimmunity. Therefore, we conducted a systematic review to provide a comprehensive overview on the available treatment interventions.

METHODS: Relevant studies were identified by searching Medline, EMBASE and Cochrane Controlled Trials Register, published until December 2011.

RESULTS: From a total of 7334 primary selected titles, 22 articles were included for the systematic review and 11 were appropriate for meta-analyses. Eight studies reported on hyperthyroidism. Propylthiouracil (PTU) and methimazole reduce the risk for preterm delivery [risk ratio (RR): 0.23, confidence interval (CI): 0.1–0.52], pre-eclampsia (RR: 0.23, CI: 0.06–0.89) and low birthweight (RR: 0.38, CI: 0.22–0.66). The nine studies that reported on clinical hypothyroidism showed that levothyroxine is effective in reducing the risk for miscarriage (RR: 0.19, CI: 0.08–0.39) and preterm delivery (RR: 0.41, CI: 0.24–0.68). For treatment of subclinical hypothyroidism, current evidence is insufficient. The five studies available on thyroid autoimmunity showed a not significant reduction in miscarriage (RR: 0.58, CI: 0.32–1.06), but significant reduction in preterm birth by treatment with levothyroxine (RR: 0.31, CI: 0.11–0.90).

CONCLUSION: For hyperthyroidism, methimazole and PTU are effective in preventing pregnancy complications. For clinical hypothyroidism, treatment with levothyroxine is recommended. For subclinical hypothyroidism and thyroid autoimmunity, evidence is insufficient to recommend treatment with levothyroxine. The overall lack of evidence precludes a recommendation for universal screening and is only justified in a research setting.

Key words: hypothyroidism / hyperthyroidism / thyroid autoimmunity / adverse pregnancy outcome / levothyroxine
Introduction

Thyroid disease affects 2–3% of pregnant women and is associated with adverse pregnancy outcomes (Abalovich et al., 2007; Fitzpatrick and Russell, 2010; van den Boogaard et al., 2011). Thyroid disorders can be divided into (sub)clinical hyperthyroidism, (sub)clinical hypothyroidism and/or thyroid autoimmunity.

Hyperthyroidism is found in 0.1–0.4% of pregnant women and is most commonly caused by Graves’ disease (Bahn et al., 2011). Graves’ disease in pregnancy is associated with miscarriage, pre-eclampsia, preterm birth, placental abruption and fetal hyperthyroidism (Zimmerman, 1999; Earl et al., 2010). According to the Endocrine Society Clinical Practice Guideline (ESCPG) and the American Thyroid Association (ATA), the treatment of choice is with propylthiouracil (PTU) (Abalovich et al., 2007; Stagnaro-Green et al., 2011). Treatment with methimazole (MMI) has been associated with a higher risk of congenital disorders, such as aplasia cutis and choanal atresia (Di et al., 2001; Clementi et al., 2010). It is advised by ATA to switch to MMI treatment after the first 12 weeks because of reports of hepatotoxicity in children of mothers treated with PTU (Cooper and Rivkees, 2009; Rivkees and Mattison, 2009). A recent Cochrane review could not identify any randomized controlled trial (RCT) comparing treatment interventions in pregnant women with hyperthyroidism (Earl et al., 2010).

The prevalence of clinical hypothyroidism is 0.3–0.5% in pregnant women (Abalovich et al., 2007). Hypothyroidism in women of reproductive age is most commonly caused by an autoimmune thyroiditis and Hashimoto’s disease (Abalovich et al., 2007). Hypothyroidism in pregnancy is associated with miscarriage, placental abruption, neonatal intensive care unit (NICU) admission and lower intelligence scores (Haddow et al., 1999; Li et al., 2010; van den Boogaard et al., 2011). Treatment with levothyroxine is therefore recommended and considered safe in pregnancy (Abalovich et al., 2007). The prevalence of subclinical hypothyroidism, defined biochemically by the combination of elevated serum thyroid-stimulating hormone (TSH) level and a free thyroxine level within the reference range, is 3–5% (Abalovich et al., 2007). There is a strong association with pre-eclampsia and perinatal mortality and lower intelligence scores in the offspring (Haddow et al., 1999; Klein et al., 2001; Li et al., 2010; van den Boogaard et al., 2011). The ESCPG ‘Management of Thyroid dysfunction during Pregnancy and post-partum’ advises hormone replacement therapy in pregnant women with subclinical hypothyroidism and reports the evidence as fair for pregnancy outcomes but poor for neurological outcome (Abalovich et al., 2007). A recent Cochrane review could not find an RCT on levothyroxine treatment for women with clinical or subclinical hypothyroidism on the effect of pregnancy outcomes (Reid et al., 2010). Given this poor evidence, it is advised in the guidelines from the ATA to treat subclinically hypothyroid women only when thyroid antibodies are detected as well (Stagnaro-Green et al., 2011).

Thyroid autoimmunity is defined as the presence of thyroid antibodies against thyperoxidase (TPO-Ab) and/or thyroglobulin (Tg-Ab) in combination with a normal thyroid function or euthyroid state. This has an incidence of ~8–14% among women of fertile age (Krassas et al., 2010). The presence of thyroid autoantibodies in euthyroid women is associated with a significant risk for unexplained subfertility, miscarriage, recurrent miscarriage, preterm birth and maternal postpartum thyroiditis (Thangaratinam et al., 2011; van den Boogaard et al., 2011). Women with thyroid autoimmunity who are euthyroid in the early stage of pregnancy are at risk of developing hypothyroidism in the course of pregnancy and should be monitored (Abalovich et al., 2007; Stagnaro-Green et al., 2011). A systematic review and meta-analysis restricted to thyroid autoimmunity showed that levothyroxine lowers the risk for miscarriage and preterm birth but this was based only on two very small studies (Negro et al., 2005; Negro et al., 2006; Thangaratinam et al., 2011). The effects of treatment with levothyroxine on other pregnancy complications or subfertility, or the effect of other treatment interventions on pregnancy outcomes, were not studied in this review.

The high prevalence of thyroid autoimmunity and subclinical hypothyroidism makes it an important health problem. These conditions are not diagnosed without an active screening strategy because they present without any symptoms. The ESCPG guideline supports selective screening in patients who are at increased risk for thyroid disease (Abalovich et al., 2007). Universal screening of thyroid function in pregnancy is under debate and is currently not recommended because of lack of evidence on the effect of treatment interventions, especially for subclinical hypothyroidism and thyroid autoimmunity.

We therefore conducted a systematic review of the literature to present an overview on treatment interventions and their effects on pregnancy complications in women with thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy.

Methods

Relevant studies were identified by searching Medline, EMBASE and the Cochrane Controlled Trials Register, published until December 2011. Search criteria used were related to thyroid function, thyroid autoimmunity, pregnancy outcome and any form of pharmacological intervention used to treat (sub)clinical hypothyroidism, (sub)clinical hyperthyroidism or thyroid autoimmunity.

The diagnosis of clinical or subclinical hypothyroidism was based on high TSH concentrations and a decreased free thyroxine or free thyroxine within the reference range in case of subclinical hypothyroidism. The diagnosis of hyperthyroidism was based on a decreased TSH with an increased TSH concentrations and a decreased free thyroxine or free thyroxine within the reference range in case of subclinical hyperthyroidism (Canaris et al., 2000). Worldwide accepted reference intervals for thyroid hormones or thyroid antibodies in pregnant women are not available. We therefore included all cut-off levels for TSH, free thyroxine and/or TPO-Ab as described for the diagnosis of (sub)clinical hypothyroidism, clinical hyperthyroidism and thyroid autoimmunity.

The data limit was specified for the availability of reliable free thyroxine assays, which excluded articles published before 1975 (Ball et al., 1989). Search criteria used were relevant to thyroid function, thyroid autoimmunity, pregnancy outcomes and treatment interventions. Specifically, the following search terms were used: thyroid*, hyperthy*, hypothy*, tpo*, tsh, thyrotropin receptor antibod*, thyroid stimulating immunoglobulin*, thyrotropin-binding inhib*, thyroxine, thyrotropin, thyroid microsomal antibodies, fertility, infertility, abortion*, miscarriag*, pregnan*, obstetric*, gestation*, preterm deliver*, premature deliver*, intrauterine growth retardation*, fetal growth restriction*, intrauterine growth restriction* and child development*. Mesh terms used were: thyroid gland, thyroid diseases, immunoglobulins, thyroid-stimulating, thyrotropin, thyroxine,
fertility, infertility, pregnancy, pregnancy outcome, pregnancy complications, fetal growth retardation, drug therapy, placebos, antithyroid agents, iodine, MMI, selenium, PTU, triiodothyronine, thiocyanates, adrenergic beta-antagonists and child development. There were no language limitations for this search. RCTs, cohort studies and case–control studies were included.

Titles and subsequently abstracts of the articles were screened independently by two reviewers (R.V., E.B.). Included articles for full text evaluation were compared during a consensus meeting. In case of disagreement, a third reviewer (P.B., M.G.) was consulted for the decision on inclusion or exclusion for full text evaluation. Articles that did not contribute to the answer of our research questions after full text evaluation were excluded. Only articles that described at least 10 patients were eligible. Articles that reported treatment of thyroid disorders after 20 weeks of gestation were excluded. After consensus, the remaining articles were included for critical appraisal and assessed by two reviewers independently (R.V., E.B.). Articles were judged on scientific quality according to the CONSORT and STROBE statement (von et al., 2007; Schulz et al., 2010). Levels of evidence were attributed according to the Oxford Centre for Evidence-based Medicine (Oxford Centre for Evidence-based Medicine, 2009). Articles in foreign languages were translated and included if eligible, except for articles in Chinese, Japanese and Russian.

In order to reach a consistent presentation of the data, all individual study results were translated into a risk ratio (RR) and 95% confidence interval (CI).

In the case of adequate clinical and statistical homogeneity, with the same outcome measure, treatment intervention and control group were described and articles were included in the meta-analysis. Summarized relative RRs were calculated using random effect models. Software of Review Manager 5 (available from Cochrane) was used to perform the meta-analyses.

Results

In Fig. 1, the selection process after the search is represented. Two hundred and fifty-four articles were selected for critical appraisal, all dealing with pregnancy outcome, post-partum period and/or neonatal outcome. Of the 22 included articles in this systematic review, 8 reported on clinical hyperthyroidism (Momotani et al., 1984; Phuapradit et al., 1993; Millar et al., 1994; Wing et al., 1994; Momotani et al., 1997; Di et al., 2001; Rosenfeld et al., 2009; Chen et al., 2011), 9 reported on (sub)clinical hypothyroidism (Leung et al., 1993; Abalovich et al., 2002; Blazer et al., 2003; Idris et al., 2005; Matalon et al., 2006; Rasmussen et al., 2007; Negro et al., 2010; Behrooz et al., 2011; Kim et al., 2011) and 5 on thyroid autoimmunity (Nohr et al., 2000; Negro et al., 2005, 2006, 2007; Revelli et al., 2009). All patients in the included studies were women with a thyroid disorder who received treatment during pregnancy. Treatment concerned PTU or MMI for hyperthyroidism, levothyroxine for (sub)clinical hypothyroidism and levothyroxine or selenium for thyroid autoimmunity. Controls were women with the same thyroid disorder who did not receive any treatment or euthyroid without any thyroid disorder and without treatment.

Quality of the studies

The characteristics of the included articles and quality assessment are reported in Table I. Six RCT’s were included, four of which were about treating thyroid autoimmunity and two RCTs studied treatment of (sub)clinical hypothyroidism (Negro et al., 2005, 2006, 2007; Kim et al., 2011). All other studies were evidence-level II studies, i.e. cohort and case–control studies. Eleven studies presented appropriate data, and could be included in meta-analyses on seven different pregnancy outcomes.

Treatment interventions for clinical hyperthyroidism

Eight studies on treatment of clinical hyperthyroidism in pregnancy were included (Momotani et al., 1984; Phuapradit et al., 1993; Millar et al., 1994; Wing et al., 1994; Momotani et al., 1997; Di et al., 2001; Rosenfeld et al., 2009; Chen et al., 2011). All these studies evaluated the effectiveness of PTU and/or MMI.
Table I Characteristics and quality features of the 22 studies included in systematic review of treatment of thyroid disorders before conception and in early pregnancy.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study type</th>
<th>Population</th>
<th>Reference values</th>
<th>Intervention group</th>
<th>Intervention</th>
<th>Controls</th>
<th>Outcome measure(s)</th>
<th>Level of evidence</th>
<th>Quality features</th>
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<tbody>
<tr>
<td>Hyperthyroidism</td>
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<tr>
<td>Momotani et al.</td>
<td>1984</td>
<td>Retrospective cohort</td>
<td>643 neonates from mothers with Graves' disease</td>
<td>Not described</td>
<td>126 infants whose mothers received treatment and were euthyroid</td>
<td>MMI individual dose</td>
<td>50 infants whose mothers did not receive MMI and were hyperthyroid</td>
<td>Congenital malformations</td>
<td>II</td>
<td>Matching: no</td>
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<tr>
<td>Phuapradit et al.</td>
<td>1993</td>
<td>Prospective cohort</td>
<td>112 hyperthyroid pregnant women</td>
<td>Not defined</td>
<td>90 women with hyperthyroidism, euthyroid with treatment</td>
<td>PTU 50 mg/d</td>
<td>22 women hyperthyroid women, hyperthyroid despite treatment</td>
<td>Pre-eclampsia, miscarriage, preterm delivery, neonatal hypothyroidism, congenital anomalies, neonatal hypothyroidism</td>
<td>II</td>
<td>Matching: no</td>
</tr>
<tr>
<td>Wing et al.</td>
<td>1993</td>
<td>Prospective cohort</td>
<td>132 hyperthyroid pregnant</td>
<td>TSH 0.4–5.0 mIU/ml fT4 4.5–13.2</td>
<td>99 hyperthyroid pregnant women treated with PTU</td>
<td>PTU 150–600 mg, median daily dose 450 mg MMI 10–60 mg, median daily dose 40 mg Started preconception-second trimester</td>
<td>33 hyperthyroid pregnant women treated with MMI</td>
<td>II</td>
<td>Matching: yes</td>
<td></td>
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<tr>
<td>Millar et al.</td>
<td>1994</td>
<td>Prospective cohort</td>
<td>147 hyperthyroid pregnant women</td>
<td>TSH 0.4–5.0 mIU/ml fT4 4.5–13.2 mIU/ml</td>
<td>90 hyperthyroid women, euthyroid with treatment</td>
<td>PTU 50–150 mg 3 dd1 or MMI 10–20 mg 2 dd1</td>
<td>57 hyperthyroid women, hyperthyroid despite treatment</td>
<td>PE, LBW (&lt;2500 g), prematurity delivery (&lt;37 weeks), SGA (&lt;10th percentile)</td>
<td>II</td>
<td>Matching: yes</td>
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<tr>
<td>Momotani et al.</td>
<td>1997</td>
<td>Prospective cohort</td>
<td>77 pregnant women treated for hyperthyroidism</td>
<td>TSH 0.3–3.5 mIU/l fT4 7.7–15.6 pmol/l</td>
<td>34 women treated with PTU</td>
<td>PTU individual dose MMI individual dose</td>
<td>43 women treated with MMI</td>
<td>Neonatal hypothyroidism</td>
<td>II</td>
<td>Matching: no</td>
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<tr>
<td>Di Giantonio et al.</td>
<td>2001</td>
<td>Prospective cohort</td>
<td>1330 pregnant women</td>
<td>Not defined</td>
<td>241 hyperthyroid pregnant women</td>
<td>MMI/Carbamazole individual dose</td>
<td>1089 euthyroid pregnant euthyroid women</td>
<td>Miscarriage rate, major congenital malformations</td>
<td>II</td>
<td>Matching: no</td>
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<tr>
<td>Rosenfeld et al.</td>
<td>2009</td>
<td>Prospective cohort</td>
<td>1256 pregnant women</td>
<td>Not defined</td>
<td>115 hyperthyroid women receiving treatment</td>
<td>PTU individual doses</td>
<td>1141 euthyroid pregnant women receiving no treatment</td>
<td>Congenital anomalies, preterm delivery (&lt;37 weeks), low birth rate, miscarriage, stillbirth</td>
<td>II</td>
<td>Matching: no</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>2011</td>
<td>Case–control</td>
<td>2830 women with hyperthyroidism</td>
<td>Not defined</td>
<td>516 hyperthyroid pregnant women receiving PTU</td>
<td>PTU individual dose MMI individual dose</td>
<td>65 hyperthyroid pregnant women receiving MMI</td>
<td>Low birthweight (&lt;2500 g)</td>
<td>II</td>
<td>Matching: no</td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Leung et al.</td>
<td>1993</td>
<td>Prospective cohort</td>
<td>23 women with primary hypothyroidism 45 women with subclinical hypothyroidism</td>
<td>TSH 0.5–5.0 mIU/ml fT4 4.5–13.2 mIU/ml</td>
<td>9 hypothyroid women, euthyroid with treatment</td>
<td>Levotyroxine individual dose</td>
<td>14 hypothyroid women, hypothyroid despite treatment</td>
<td>Gestational hypertension</td>
<td>II</td>
<td>Matching: no</td>
</tr>
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Continued
<table>
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<tr>
<th>First author et al.</th>
<th>Year</th>
<th>Study type</th>
<th>Population</th>
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<th>Intervention group</th>
<th>Intervention</th>
<th>Controls</th>
<th>Outcome measure(s)</th>
<th>Level of evidence</th>
<th>Quality features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abalovich, Blazer</td>
<td>2002</td>
<td>Case–control</td>
<td>150 hypothyroid pregnant women</td>
<td>TSH 0.5–4.0 mIU/l</td>
<td>99 hypothyroid pregnant women, euthyroid with treatment</td>
<td>Levothyroxine individual dose</td>
<td>16 hypothyroid women at first visit, no treatment</td>
<td>Pregnancy rate, miscarriage rate, preterm delivery</td>
<td>II</td>
<td>Matching: no</td>
</tr>
<tr>
<td>Idris, Matalon, Rasmussen</td>
<td>2003</td>
<td>Case–control</td>
<td>27.386 full-term newborns</td>
<td>Not defined</td>
<td>246 infants born to treated hypothyroid mothers</td>
<td>Levothyroxine individual dose</td>
<td>139 infants born to healthy euthyroid mothers</td>
<td>Gestational age, birthweight, Apgar scores, neonatal thyroid function</td>
<td>II</td>
<td>Matching: yes</td>
</tr>
<tr>
<td>Idris, Matalon, Rasmussen</td>
<td>2004</td>
<td>Retrospective cohort</td>
<td>167 women with subclinical or clinical hypothyroidism</td>
<td>TSH 0.1–5.5 mIU/l</td>
<td>127 hypothyroid women with treatment</td>
<td>Levothyroxine individual dose</td>
<td>40 hypothyroid women despite treatment</td>
<td>Caesarean section rate, NICU admission, LBW</td>
<td>II</td>
<td>Matching: no</td>
</tr>
<tr>
<td>Rasmussen, Negro, Behrooz, Thyroid autoimmunity</td>
<td>2010</td>
<td>Case–control</td>
<td>4500 pregnant women: 2259 universal screening group, 2257 women case finding group</td>
<td>TSH 0.27–2.5 mIU/l</td>
<td>431 infants with craniosynostosis</td>
<td>Levothyroxine individual dose</td>
<td>4094 infants without congenital malformations</td>
<td>Maternal levothyroxine use</td>
<td>II</td>
<td>Matching: no</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2011</td>
<td>Case–control</td>
<td>64 infertile women with subclinical hypothyroidism undergoing IVF/ICSI</td>
<td>TSH &lt; 4.5 mIU/l</td>
<td>32 women with treatmet</td>
<td>Levothyroxine 50–125 µg</td>
<td>32 women without treatment</td>
<td>Number high quality embryo's, embryo implantation rate, clinical pregnancy rate/cycle, miscarriage rate, live birth rate/cycle</td>
<td>I</td>
<td>Randomization: computer generated Concealed: yes Blinding: yes ITT: no</td>
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<td>Nohr et al.</td>
<td>2000</td>
<td>RCT</td>
<td>46 pregnant women euthyroid with TPO-Ab</td>
<td>TSH 0–4.0 mIU/l</td>
<td>19 hypothyroid women with treatment, euthyroid during pregnancy</td>
<td>Levothyroxine individual dose</td>
<td>19 hypothyroid women with treatment, subclinically hypothyroid during pregnancy</td>
<td>IQ level, cognitive performance, verbal performance</td>
<td>II</td>
<td>Matching: no</td>
</tr>
<tr>
<td>Vissenberg et al.</td>
<td>2011</td>
<td>RCT</td>
<td>139.168 women with singleton pregnancies</td>
<td>TSH 0.1–5.5 mIU/l</td>
<td>1102 women with treated hypothyroidism</td>
<td>Levothyroxine</td>
<td>138, 066 euthyroid controls without thyroid disease</td>
<td>Caesarean section rate, perinatal mortality, congenital malformations</td>
<td>II</td>
<td>Matching: no</td>
</tr>
</tbody>
</table>
Negro et al. 2005 RCT 490 euthyroid women undergoing IVF/ICSI

- TSH 0.27–4.2 mIU/l
- FT4 9.3–18.0 ng/ml or 12–33.5 pmol/l
- TPO-Ab 0–100 kIU/l

36 euthyroid women, TPO Ab positive receiving treatment

Levithroxine 1 mg/kg/d

36 euthyroid women, TPO Ab positive receiving placebo

412 euthyroid women, TPO-Ab negative undergoing IVF/ICSI

Pregnancy rate, miscarriage rate

I Randomization: computer generated
Concealed: yes
Blinding: yes
ITT: yes

Negro et al. 2006 RCT 984 euthyroid pregnant women

- TSH 0.27–4.2 mIU/l
- FT4 9.3–18.0 ng/ml or 12–33.5 pmol/l
- TPO-Ab 0–100 kIU/l

57 euthyroid women, TPO Ab positive receiving treatment

Levithroxine 0.5, 0.75 or 1.0 μg/kg

58 euthyroid women, TPO Ab positive receiving no treatment

869 pregnant women, TPO Ab negative

Miscarriage, gestational hypertension (>140/90), pre eclampsia, preterm birth (<37 weeks), placental abruption

I Randomization: computer generated
Concealed: yes
Blinding: yes
ITT: yes

Negro et al. 2007 RCT 232 pregnant women

- TSH 0.27–4.2 mIU/l
- FT4 9.3–18.0 ng/ml or 12–33.5 pmol/l
- TPO-Ab 0–100 kIU/l

77 euthyroid women, TPO Ab positive receiving treatment

Selenomethionine 200 μg/day started in the first trimester till 12 months post-partum

74 euthyroid women, TPO Ab positive receiving placebo

81 Caucasian pregnant women, euthyroid TPO-Ab negative

PPTD, permanent hypothyroidism 12 months after delivery

I Randomization: computer generated
Concealed: yes
Blinding: yes
ITT: yes

Revelli et al. 2009 Retrospective cohort 93 euthyroid women undergoing IVF

- TPO-Ab 0–35 UI/ml
- Tg-Ab 0–40 UI/ml

55 euthyroid women, TPO Ab and/or Tg Ab positive, receiving treatment

Levithroxine 50 μg/day First day of stimulation at least 10 weeks of pregnancy

35 euthyroid women, TPO Ab and/or Tg Ab positive, receiving no treatment

200 infertile women, TPO-Ab or Tg-Ab receiving no treatment

Miscarriage rate, Pregnancy rate/IVF cycle

II Matching: yes

Note: Microsomal antibodies is the previous nomenclature for TPO antibodies.

All studies have an adequate sample size n > 10.

Ab, antibody; CS, Caesarean section; ET, embryo transfer; GDM, gestational diabetes mellitus; IF, infertility; LGA, large for gestational age; LT4, levothyroxine; MC, miscarriage; MMI, methimazole; NICU, Neonatal Intensive Care Unit; PA, placental abruption; PE, pre-eclampsia; PIH, pregnancy induced hypertension; PND, perinatal death; PPTD, post-partum thyroid disease; PTED, preterm delivery; PU, propylthiouracil; RDS, respiratory distress syndrome; RM, recurrent miscarriage; SGA, small for gestational age; Tg, thyroglobulin; TPO, thyroid peroxidase.
Patients treated with PTU
One cohort study reported on pregnancy outcomes in 115 hyperthyroid women treated with PTU compared with 1141 euthyroid controls without treatment (Rosenfeld et al., 2009). No significant differences were seen for the prevalence of miscarriage (RR: 1.24, CI: 0.64–2.41; P = 0.53), preterm delivery (RR: 1.71, CI: 0.9–3.25; P = 0.10), congenital malformations (RR: 0.39, CI: 0.05–2.83; P = 0.35) or live birth rate (RR: 0.99, CI: 0.94–1.05; P = 0.86) for PTU-treated hyperthyroid women versus euthyroid women without treatment.

Patients treated with MMI
One cohort study reported on pregnancy outcomes in 241 hyperthyroid women treated with MMI compared with 1089 euthyroid controls without hyperthyroidism. The prevalence of miscarriage was not significantly different for MMI-treated hyperthyroid women compared with euthyroid women without treatment (RR: 0.94, CI: 0.55–1.61; P = 0.83; Di et al., 2001). Congenital malformations occurred in 8 (4%) of the treated cases versus 23 (2%) of the euthyroid controls (RR: 0.88, CI: 0.86–4.15; P = 0.12).

Another cohort study compared 126 infants whose mothers had been treated with MMI for hyperthyroidism with 50 infants whose mothers were hyperthyroid and did not receive any treatment (Momotani et al., 1984). The prevalence of malformed children was 6% in the non-treated group versus 0% in the treated group. This difference was not significant (RR: 0.06, CI: 0.00–1.09; P = 0.06).

PTU versus MMI
Two cohort studies reported on the prevalence of neonatal hypothyroidism in 133 hyperthyroid women treated with PTU compared with 79 hyperthyroid women treated with MMI. Meta-analysis showed no difference between the two groups (two studies, RR: 1.50, CI: 0.58–3.88; P = 0.40) (Wing et al., 1994; Momotani et al., 1997; Fig. 2). One of these two studies also reported on congenital malformations but did not find any significant difference between PTU and MMI (RR: 1.09, 0.12–10.15; P = 0.94; Wing et al., 1994).

One case–control study compared low birthweight in babies of 581 mothers with hyperthyroidism treated with PTU or MMI (Chen et al., 2011). No significant difference was found (RR: 0.55, 0.28–1.07; P = 0.08).

Adequate versus not adequately treated women
Two cohort studies reported on differences in pregnancy complications between women with hyperthyroidism who were adequately, and women who were not adequately, treated (Phuapradit et al., 1993; Millar et al., 1994). Not adequately treated hyperthyroidism was defined as a TSH lower and a thyroxine higher than the reference interval, despite treatment.

The first study found no significant differences in miscarriage rate, number of preterm deliveries and neonatal hypothyroidism between 90 women who had been adequately treated for hyperthyroidism with PTU compared with 22 women who were still hyperthyroid despite treatment with PTU (RR: 0.24, CI: 0.02–3.76; P = 0.31; RR: 1.34, CI: 0.32–5.63; P = 0.69, RR: 0.90, CI: 0.27–2.94: P = 0.86; Phuapradit et al., 1993).

The other study found evidence of a significantly lower risk for low birthweight (RR: 0.38, CI: 0.22–0.66: P = 0.0005), preterm delivery (RR: 0.23, 0.1–0.52: P = 0.0004) and severe pre-eclampsia (RR: 0.23, 0.06–0.89: P = 0.03) in 90 women who had been adequately treated with MMI or PTU for hyperthyroidism compared with 57 inadequately treated women. No significant differences were seen in neonates being small for gestational age (RR: 0.81, CI: 0.32–2.06: P = 0.67) between the two groups (Millar et al., 1994).

Treatment interventions for (sub)clinical hypothyroidism
Nine studies on treatment of (sub)clinical hypothyroidism in pregnancy were included. All these studies used levothyroxine as treatment.

Five studies reported on the effect of treatment interventions for clinical and/or subclinical hypothyroidism (Abalovich et al., 2002; Blazer et al., 2003; Matalon et al., 2006; Rasmussen et al., 2007; Negro et al., 2010).

One randomised study reported a significantly lower miscarriage rate in 82 women receiving levothyroxine treatment for hypothyroidism compared with 34 women with hypothyroidism without any treatment (RR: 0.24, CI: 0.07–0.76: P = 0.02; Negro et al., 2010). These were patients randomized for universal screening or selective screening in potentially high-risk patients for thyroid disorders in early pregnancy. No differences were found in the prevalence of gestational hypertension, pre-eclampsia, gestational diabetes, placental abruption, Caesarean delivery, respiratory distress syndrome, birthweight, preterm birth, Apgar scores or perinatal death. The treated group was also compared with 4384 euthyroid controls without any known thyroid disorder. For all pregnancy complications, including miscarriage, no significant differences were found. A meta-analysis could be performed for the outcome Caesarean section rate, for which no significant differences could be detected between hypothyroid-treated women compared with healthy euthyroid controls (two studies, RR: 1.21, CI: 0.54–2.7: P = 0.65; Matalon et al., 2006; Negro et al., 2010; Fig. 3a). There was significant statistical heterogeneity (I² of 90%) between the studies; therefore, these finding should be considered with care.

The second cohort study reported no differences in perinatal mortality (RR: 1.02, CI: 0.6–1.68: P = 0.79) or congenital malformations (RR: 0.83, 0.21–3.32: P = 0.075; Matalon et al., 2006).

A meta-analysis could be performed, including the third study, for the outcome miscarriage and preterm birth: a significant decrease was seen in women treated with levothyroxine compared with women without treatment (two studies, RR: 0.18, CI: 0.08–0.39, P < 0.01; Abalovich et al., 2002; Negro et al., 2010; Fig. 3b). A significant decrease was also shown for preterm delivery (two studies, RR: 0.41, CI: 0.24–0.68, P < 0.01; Abalovich et al., 2002; Negro et al., 2010; Fig. 3c).

One case–control study found a significantly lower birthweight in 246 neonates born to treated hypothyroid mothers compared with 139 neonates born to healthy euthyroid mothers. No difference was found in Apgar scores at 1 and 5 min. Overall, both TSH and free thyroxine serum levels were significantly higher in the study group compared with TSH and free thyroxine levels of the control group (Blazer et al., 2003).

The fifth study, a case–control study, described a higher risk for an infant with craniosynostosis if the mother was on levothyroxine substitution (RR: 3.05, CI: 1.8–5.14, P < 0.001; Rasmussen et al., 2007). Meta-analysis could be performed on congenital malformations. No
significant differences were found in treated hypothyroid women compared with healthy euthyroid controls (two studies, RR: 1.86, 0.52–6.64; P = 0.34; Matalon et al., 2006; Rasmussen et al., 2007; Fig. 3d). There was large heterogeneity between the studies (I² of 68%), although no statistical significance.

The sixth study was a randomized, not placebo controlled, trial that studied the effect of treatment with levothyroxine on IVF/ICSI in women with subclinical hypothyroidism (Kim et al., 2011).

In 32 women receiving treatment, a significantly higher number of Grade I or II embryos (data presented as mean ± SD; P = 0.007), embryo implantation rate (RR: 1.8, 1.00–3.25; P = 0.05) and live birth rate (RR: 2.13, 1.07–4.21; P = 0.03) were found compared with 32 untreated women. No significant differences were found for clinical pregnancy rate (RR: 1.42, 0.81–2.45; P = 0.22) or miscarriage rate (RR: 0.8, 0.00–1.36; P = 0.08).

Adequate versus not adequately treated women

Two cohort studies reported on pregnancy complications for women with clinical or subclinical hypothyroidism who were adequately, and women who were not adequately treated (Leung et al., 1993; Idris et al., 2005). Not adequately treated hypothyroidism was defined as a TSH higher and a thyroxine lower than the reference interval, despite treatment. In the case of subclinical hypothyroidism, a TSH higher than the reference interval despite treatment was defined as not adequately treated.

The first study showed no significant difference in the prevalence of gestational hypertension in 68 women not adequately treated for subclinical or clinical hypothyroidism compared with 38 women who were still hypothyroid despite treatment (RR: 0.14, CI: 0.01–2.20; P = 0.16 for clinical hypothyroidism; RR: 0.41, CI: 0.11–1.62; P = 0.21 for subclinical hypothyroidism; Leung et al., 1993). The second study reported no significant difference in NICU admissions (RR: 0.31, CI: 0.08–1.2; P = 0.09). A significant difference was found in low birth weight (RR: 0.31, CI: 0.11–0.92; P = 0.04) for 127 women with (sub)clinical hypothyroidism with normal TSH level with levothyroxine treatment compared with 40 women with abnormal TSH levels in the first trimester despite levothyroxine treatment, while Caesarean section rates were equal in the two groups, respectively 27.5 and 29.1% (Idris et al., 2005).

One case–control study reported on 38 women with hypothyroidism treated with levothyroxine during pregnancy (Behrooz et al., 2011). From the 19 children of mothers who were subclinically hypothyroid despite treatment, no significant difference was found in the IQ level, verbal performance or cognitive performance compared with 19 children of mothers who were euthyroid with treatment (data were continuous variables and presented as mean and SD).

### Treatment interventions for thyroid autoimmunity

Five studies reported on the effect of treatment interventions for thyroid autoimmunity. Treatment with levothyroxine was reported in three studies (Negro et al., 2005, 2006; Revelli et al., 2009) and treatment with selenomethionine in two studies (Nohr et al., 2000; Negro et al., 2007).

#### Levothyroxine in thyroid autoimmunity

The effect of levothyroxine treatment on pregnancy outcomes was evaluated in three studies, of which two were RCTs. One randomized study was in unselected pregnant women (Negro et al., 2006) and the other two studies (one cohort and one randomized) were in women scheduled to have IVF (Negro et al., 2005; Revelli et al., 2009). Levothyroxine was used at a dose of 1 μg/kg/day (Negro et al., 2005), a fixed dose of 50 μg/day (Revelli et al., 2009) or a titrated dose (Negro et al., 2006). Controls were euthyroid women with thyroid autoimmunity receiving placebo or no treatment. When the results on miscarriage rates were pooled, a near-significant relative risk reduction of 52% in miscarriages was found (total 175 women, three studies, RR: 0.58, CI: 0.32–0.11; P = 0.07: Fig. 4a). One randomized study reported on preterm birth, gestational hypertension, pre-eclampsia and placental abruption. One hundred and fifteen women were studied; a significant reduction in preterm births with levothyroxine was shown (RR: 0.31, CI: 0.11–0.90; P = 0.03). No significant differences were shown for hypertension (RR: 0.73, CI: 0.24–2.16; P = 0.57), pre-eclampsia (RR: 2.04, CI: 0.19–21.82; P = 0.56) or placental abruption (RR: 0.34, CI: 0.01–8.15; P = 0.51) (Negro et al., 2006).

One study also reported the effect of treatment with levothyroxine combined with acetylsalicylic acid and prednisolone in 36 women with thyroid autoimmunity who underwent an IVF treatment, and found significantly higher pregnancy rates compared with 38 controls receiving no treatment (RR: 4.14, CI: 1.47–11.66; P = 0.007). No difference was found in miscarriage rates (RR: 2.27, CI: 0.27–19.23; P = 0.45; Revelli et al., 2009).

If only the two randomized studies were included for meta-analyses using a random effect model, no significant risk reduction could be demonstrated (total 160 women, two studies, RR: 0.51, CI: 0.22–1.15; P = 0.10: Fig. 4b; Negro et al., 2005, 2006).
Selenomethionine in thyroid autoimmunity

In one randomized study, 111 euthyroid women with thyroid autoimmunity were given selenomethionine 200 μg/day or placebo started in the first trimester until 12 months post-partum (Negro et al., 2007). The prevalence of post-partum thyroiditis in the 77 treated patients was compared with those of 74 controls. A significant decrease in post-partum thyroiditis was shown in the treatment group (RR: 0.59, CI: 0.38–0.9; P = 0.01). At the end of the post-partum period, 11.7% of the women treated with selenomethionine had become permanently hypothyroid and 20.3% of the women who received placebo. This was not a significant difference (RR: 0.58, CI: 0.27–1.24; P = 0.16). One other randomized study evaluated post-partum thyroiditis in 46 women with thyroid autoimmunity (Nohr et al., 2000). Pooling the post-partum thyroiditis data of these two studies did not result in evidence of a difference in post-partum thyroiditis for selenium versus no treatment (RR: 0.85, 0.39–1.85; P = 0.69; Nohr et al., 2000; Negro et al., 2007: Fig. 4c). As there was significant heterogeneity between the two studies (I² of 80%), this finding should be considered with care.

Discussion

This review presents all available evidence on the effectiveness of treatment interventions for thyroid disorders in early pregnancy. Overall, we found that both MMI and PTU were effective in preventing pregnancy complications in hyperthyroid women. Furthermore,
treatment with levothyroxine prevented miscarriage and preterm birth in women with clinical hypothyroidism. In thyroid autoimmunity, however, there was insufficient evidence for the effectiveness of levothyroxine. The quantity and quality of the evidence on the effectiveness of any treatment intervention for thyroid disorders on pregnancy complications were low. For none of the thyroid disorders was an RCT with enough statistical power available.

**Hyperthyroidism**

The ESCPG and the ATA guidelines advise to treat hyperthyroidism (Abalovich et al., 2007; Stagnaro-Green et al., 2011). The European Society of Human Reproduction and Embryology (ESHRE) and the Royal College of Obstetricians and Gynaecologists (RCOG) do not have any guidelines on hyperthyroidism in pregnancy. The evidence of the ESCPG on treatment is classified as good according to the GRADE system (Grade 1: ⊕⊕⊕⊕). The US Preventive Services Task Force (USPSTF) recommendation level is A (U.S. Preventing Task Force Ratings: Strengths of Recommendations and Quality of Evidence, 2003). Treatment of choice is PTU because MMI is associated with typical malformations, such as aplasia cutis and choanal atresia.

Our review shows that the PTU and MMI treatment options have the same risks for developing neonatal hypothyroidism and congenital malformations and that the risk is the same compared with the normal euthyroid population. Because the prevalence of congenital malformations is very low, very large cohort studies are necessary to detect a possible teratogenic effect. The available studies did not have enough statistical power to reach a final conclusion. Case reports or case series point at a possible association of MMI use with aplasia cutis and choanal atresia but the low prevalence hampers to establish a causal teratogenic relation (Clementi et al., 1999; Baid and Merke, 2007). We did not include case reports in our systematic review. However, ~35 case reports on MMI treatment and congenital scalp defects were found in our literature search (Dutertre et al., 1991; Bolz and Nagel, 1994; Diez-Delgado et al., 1999). One study found that two of the eight observed cases were malformations, typically associated with MMI use i.e. choanal atresia and oesophageal atresia (Di et al., 2001). It cannot be excluded that hyperthyroidism is teratogenic by itself. The findings from Momotomi suggest that maternal uncontrolled hyperthyroidism may cause congenital malformations.
and the beneficial role of MMI treatment outweighs its eventual teratogenic effect (Momotani et al., 1984). There are no data to support an association between congenital abnormalities and PTU.

Only small cohort studies show a reduction in pregnancy complications by PTU treatment in hyperthyroidism. Low birthweight, preterm delivery and pre-eclampsia were reduced by treatment with both PTU and MMI. The risk for miscarriage and preterm delivery in women with treated hyperthyroidism was equal to a healthy population.

With the available evidence this review supports the ESCPG and ATA guidelines to use PTU as the treatment of first choice.

A preconception surgical intervention, such as subtotal thyroidectomy, or treatment with radioactive iodine should also be considered for hyperthyroidism. This might prevent any necessary treatment with antithyroid drugs during pregnancy. Women should be well informed before pregnancy on these possible treatment interventions and on the fact that it is only safe to become pregnant 6 months after treatment with radioactive iodine (Abalovich et al., 2007).

Clinical hypothyroidism

The ESCPG and the ATA guidelines advise to treat clinical hypothyroidism with levothyroxine. The evidence is classified as good according to the Grade system (Grade 1: ⊕⊕⊕⊕). The USPSTF recommendation level is A. The ESHRE and the RCOG do not have any guidelines on clinical hypothyroidism in pregnancy.

Only two small cohort studies compared untreated women with treated women and hence evidence of a direct treatment effect is poor. Withholding treatment from these women is not considered to be ethical, therefore large comparative studies or RCTs will not be performed. The other studies compared treated women with euthyroid controls or with women who were not adequately treated. Treatment of (sub)clinical hypothyroidism seems to lower the risk for miscarriage and preterm delivery. No studies were available on the effect of treatment on neonatal intelligence scores.

But even with treatment there is a higher risk for pregnancy complications, such as low birthweight and neonatal thyroid disorder. One study showed that neonates from treated hypothyroid mothers had a higher incidence of thyroid dysgenesis compared with the normal population (Blazer et al., 2003). This might reflect an insufficient level of hormone replacement therapy, despite an assumed adequate management. Or, this might reflect that hypothyroidism itself, or levothyroxine use, is a risk factor for pregnancy complications. This needs further attention.

Based on the seven studies, our review supports the guidelines in their advice to treat clinical hypothyroidism with levothyroxine.

Subclinical hypothyroidism

The ESCPG guideline recommends levothyroxine replacement in women with subclinical hypothyroidism, given the fact that the potential benefits outweigh the potential risks. For obstetrical outcome, USPSTF recommendation level is B; evidence is fair (Grade 1: ⊕⊕⊕). For neurological outcome, USPSTF recommendation level is I; evidence is poor (Grade: 0000). The ESHRE and the RCOG do not employ guidelines on subclinical hypothyroidism in pregnancy.

From the seven studies on (sub)clinical hypothyroidism, only one study reported separate data on subclinical hypothyroidism. This study showed that gestational hypertension was more often found in not adequately treated women than in adequately treated women, though the difference was not significant.

The recommendation in the current guidelines to treat subclinical hypothyroidism is based on minimal evidence and thought that the potential benefits outweigh the potential risks. For subclinical hypothyroidism, our review shows that there is currently insufficient evidence to recommend for or against universal treatment with levothyroxine.

Thyroid autoimmunity

The ESCPG and the ATA guidelines advise to monitor women with thyroid autoimmunity during pregnancy because these women are at risk for developing hypothyroidism. The ESCPG evidence is classified as good according to the Grade system (Grade 1: ⊕⊕⊕⊕) and here the USPSTF recommendation level is A. In the ATA guidelines, USPSTF recommendation level is B. The ESHRE and the RCOG do not have any guidelines on thyroid autoimmunity in pregnancy.

Following our review, only three studies were available on the effect of levothyroxine on miscarriage rate in euthyroid women with thyroid autoimmunity. One of these studies was a retrospective study that showed a non-significant risk reduction of 49% (Revelli et al., 2009).

The other two studies were prospective randomized trials and were included for meta-analysis. One study showed a significant reduction in preterm birth (Negro et al., 2006). The findings from a recently published systematic review on thyroid autoimmunity showed a significant difference at the meta-analysis of the two randomized studies using a fixed effect model (Thangaratinam et al., 2011). In view of the large clinical heterogeneity between included studies, pooling using the random effect model is preferable to the fixed method. The random-effect model provides identical results to fixed effects when there is no heterogeneity among the studies but more conservative claims of statistical significance in the presence of heterogeneity (Higgins, 2012).

Using a random model effect we were unable to demonstrate a significant difference.

These results confirm that thyroid function tests during pregnancy in women with thyroid autoimmunity are necessary but there is insufficient evidence to support treatment with levothyroxine in a euthyroid state.

Intelligence scores in the offspring

Associations have been reported between (sub)clinical hypothyroidism and lower intelligence scores in the offspring (Haddow et al., 1999; Klein et al., 2001). Also thyroid autoimmunity has been associated with lower scores on intellectual and motor development (Li et al., 2010; van den Boogaard et al., 2011). For many clinicians this is reason to treat subclinical hypothyroidism, especially in the presence of TPO-Ab, despite the current lack of evidence on the effectiveness of treatment (Vaidya et al., 2012). In this systematic review, only one case–control study of limited sample size (n = 38) could be included for this outcome (Behrooz et al., 2011). This study showed that IQ level and cognitive performance in children born of mothers treated with levothyroxine who had subclinical hypothyroidism during their pregnancy were similar to those who remained euthyroid (Behrooz
et al., 2011). The definite results of the ‘Controlled Antenatal Thyroid Screening’ study (ISRCTN 46178175) should reveal whether screening for and treatment of subclinical hypothyroidism and/or hypothyroxinaemia in pregnancy is of benefit for the intellectual development: preliminary results presented at the International Thyroid Conference in 2010 did not show a significant difference in the intent to treat analysis (Stagnaro-Green et al., 2011). The ‘TSH trial’ (NCT 00388297) is a study on the effect of levothyroxine treatment on intellectual scores in the offspring at age 5 years. The study population consists of pregnant women with first trimester subclinical hypothyroidism or hypothyroxinaemia diagnosed during pregnancy. The recruitment has been completed. The follow-up is until 2014 and final analyses are planned in 2015.

Heterogeneity and quality of the included studies

Cut-off levels

Different cut-off levels and assays have been used for the diagnosis of thyroid disorders. For now, standardized or trimester-specific reference intervals are unavailable. These intervals are needed to improve treatment of thyroid disorders in pregnancy and to compare study results. Geographical differences in iodine intake or ethnicities can complicate standardization of reference intervals (Benhadi et al., 2007). Aiming for national reference intervals seems therefore better.

Sample size

Many studies used small sample size and did not use any power analysis. This makes the results less solid for the studies that were not appropriate for meta-analysis.

Treatment

Two treatment interventions, PTU or MMI, were used in the studies, with varying dosages. Some studies included both PTU and MMI treatment in the same study group. This makes it hard to interpret study results and conclude on treatment effect comparing PTU and MMI.

Control groups

It is difficult to draw final conclusions from the studies that employ a euthyroid population without any thyroid disease as a control group. The same holds for studies where treated women with or without normalisation of their thyroid function are compared.

Matching of the study subjects

In only nine of the 22 included studies, study subjects and controls were matched. This can also have distorted the results. Because of the heterogeneity the outcome of meta-analysis comparing hypothyroid patients with euthyroid controls for the outcome Caesarean section rate and congenital malformations should be considered with care. The same holds for the meta-analysis comparing treatment with selenium in women with thyroid autoimmunity for the outcome post-partum thyroid disease.

The little evidence makes it difficult to make a clear statement about screening for thyroid disease in early pregnancy. The ESCPG recommend selective screening at the first prenatal visit or at diagnosis of pregnancy for women who are at risk for thyroid disease. USPSTF recommendation level is B; evidence is fair (Grade 2: ⊕⊕OO). ATA guidelines state that there is insufficient evidence to recommend for or against screening. Level I USPSTF.

Only one RCT was available on universal screening versus case finding (Negro et al., 2010). This study showed that in both groups the total number of adverse pregnancy outcomes was the same but that treatment of hypothyroidism or hyperthyroidism in a low-risk group was associated with a lower rate of adverse outcomes. This study did not include screening for thyroid autoimmunity and also a power analysis was not performed to determine sample size. Cost-effectiveness analysis was not performed. Also the results will be influenced, because in both groups the patients classified as being at high risk received the same intervention.

There are conflicting data on whether case finding is sufficient to identify women with thyroid disorder. One study describes that about one-third of thyroid disorders will be missed with case finding (Vaidya et al., 2007).

It should be realized that universal screening will be difficult to introduce as most women have their first visit at 8–10 weeks of pregnancy. This is late to start treatment, especially for preventing early miscarriages. Preconception screening seems therefore better, but thyroid function often starts changing in the first trimester because of an increased need for thyroid hormone (Panesar et al., 2001).

Conclusion

For the treatment of hyperthyroidism, we conclude that both MMI and PTU are effective in preventing pregnancy complications. Since PTU is equally effective and has not been associated with typical malformations, such as aplasia cutis or choanal atresia, reported for MMI, it is the preferred thioamide during pregnancy. Treatment with levothyroxine is recommended for women with clinical hypothyroidism because it lowers the risk for miscarriage and preterm delivery. For subclinical hypothyroidism, there is insufficient evidence to recommend for or against universal treatment with levothyroxine. Levothyroxine seems to lower the risk for miscarriage and preterm birth in women with thyroid autoimmunity but this is based on only three small studies. Randomized, placebo controlled trials are highly warranted to study the effects of treatment with levothyroxine, especially for thyroid autoimmunity, on pregnancy outcomes in view of its high prevalence.

This overall lack of evidence precludes a recommendation for universal screening.

Screening of thyroid dysfunction in pregnancy can only be justified within a setting of an RCT. Cost-effective analysis is required to resolve the debate of universal screening.

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Authors’ roles

J.A.M.P., E.F., P.H.B. and M.G. all contributed substantially to the design of this review. R.V. and E.V.D.B. screened all titles, abstracts,
articles and extracted data for meta-analyses. M.G. and P.H.B. were third reviewer in case consensus could not be reached directly. M.W. supervised the analysis and interpretation of data. R.V. drafted the article, all other authors critically revised multiple versions of the manuscript. All authors gave their final approval of the version to be published.

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