ClinicalEvidence

Hyperthyroidism in pregnancy

Search date June 2014

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ABSTRACT

INTRODUCTION: Hyperthyroidism is characterised by high levels of serum thyroxine and triiodothyronine, and low levels of thyroid-stimulating hormone. The main causes of hyperthyroidism in pregnancy are Graves' disease and chorionic gonadotrophin (hCG)-mediated hyperthyroidism. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of antithyroid drug treatments for hyperthyroidism in pregnancy? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2014 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found no studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antithyroid drugs (carbimazole/thiamazole and propylthiouracil).

Key points

- Hyperthyroidism is characterised by high levels of serum thyroxine and triiodothyronine, and low levels of thyroid-stimulating hormone (TSH).

  Thyrotoxicosis is the clinical effect of high levels of thyroid hormones, whether or not the thyroid gland is the primary source.

  The main causes of hyperthyroidism in pregnancy are Graves' disease and chorionic gonadotrophin (hCG)-mediated hyperthyroidism.
- Untreated severe hyperthyroidism in pregnancy is associated with obstetric and maternal complications.
- We found no RCTs on the effects of antithyroid drugs (carbimazole/thiamazole and propylthiouracil) in hyperthyroidism in pregnancy. However, there is consensus that they are effective.

  Observational studies have shown an increase risk of congenital malformation in children born to mothers taking antithyroid drugs.
- There have been alerts on the risk of hepatotoxicity with propylthiouracil.

Clinical context

DEFINITION

Hyperthyroidism is characterised by high levels of serum thyroxine (T4), high levels of serum triiodothyronine (T3), or both, and low levels of thyroid-stimulating hormone (TSH, also known as thyrotrophin <0.05 mU/L). [1] Subclinical hyperthyroidism is characterised by decreased levels of TSH (<0.1 mU/L) but with levels of T4 and T3 within the normal range. Healthy pregnancy can be characterised by a low or suppressed TSH (even <0.1 mU/l) in the first trimester. The terms hyperthyroidism and thyrotoxicosis are often used synonymously; however, they refer to slightly different conditions. Hyperthyroidism refers to overactivity of the thyroid gland leading to excessive production of thyroid hormones. Thyrotoxicosis refers to the clinical effects of unbound thyroid hormones, whether or not the thyroid gland is the primary source. Hyperthyroidism in pregnancy is most commonly caused by Graves' disease (diffusely enlarged thyroid gland on palpation, ophthalmopathy, and dermopathy), toxic multinodular goitre (thyrotoxicosis and increased radioiodine uptake with multinodular goitre on palpation), but can also be due to toxic adenoma (benign hyperfunctioning thyroid neoplasm presenting as a solitary thyroid nodule), or chorionic gonadotrophin (hCG)-mediated hyperthyroidism. [1] **Diagnosis** Most pregnant women with hyperthyroidism are diagnosed prior to conception. The diagnosis of hyperthyroidism is established by a raised serum total or free T4 or T3 hormone levels, reduced TSH level, and high radioiodine uptake in the thyroid gland along with features of thyrotoxicosis. During pregnancy, radioactive iodine testing is contraindicated. Diagnosis is, therefore, usually by other laboratory tests (elevated T4 and the presence of thyrotrophin receptor stimulating antibodies). [1] The usual symptoms are irritability, heat intolerance and excessive sweating, palpitations, weight loss with increased appetite, increased bowel frequency, and

oligomenorrhoea. As many of these may be part of normal pregnancy, diagnosing new Graves' disease in pregnancy may be difficult. [1]

INCIDENCE/ PREVALENCE

In pregnancy, the most common causes of hyperthyroidism are Graves' disease and human chorionic gonadotrophin (hCG)-mediated hyperthyroidism. Graves' disease is seen in 0.1% to 1.0% (0.4% clinical and 0.6% subclinical) of pregnant women. [2] [3] HCG-mediated hyperthyroidism is transient and mild and usually does not require treatment; it is seen in 1% to 3% of pregnant women. [4] [5]

AETIOLOGY/ RISK FACTORS

Smoking is a risk factor, with an increased risk of both Graves' disease (OR 2.5, 95% CI 1.8 to 3.5) and toxic nodular goitre (OR 1.7, 95% CI 1.1 to 2.5). [6] In areas with high iodine intake, Graves' disease is the major cause; whereas in areas of low iodine intake, the major cause is nodular goitre. [7] A correlation between diabetes mellitus and thyroid dysfunction has been described. In a Scottish population with diabetes, the overall prevalence of thyroid disease was found to be 13%, highest in women with type 1 diabetes (31%). As a result of screening, new thyroid disease was diagnosed in 7% of people with diabetes (hyperthyroidism in 1%). [8] Around 50% of women who experience hyperemesis gravidarum have elevated T4 levels. [1]

PROGNOSIS

Obstetric and medical complications are directly related to control of hyperthyroidism in pregnancy. Poor control is associated with miscarriages, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm, and maternal congestive heart failure. [9] Pregnant women with Graves' disease usually show remission in the third trimester, allowing them to stop taking antithyroid drugs. In cases where remission does not occur, there is an increased risk of neonatal thyrotoxicosis. [1]

AIMS OF INTERVENTION

To eliminate the symptoms of hyperthyroidism and hyperthyroidism-related complications in pregnancy, with minimum adverse effects of treatment.

OUTCOMES

Thyroid function (levels of T4, T3, TSH, change of state from hyperthyroid to euthyroid/hypothyroid); **congenital abnormalities**; and **hepatotoxicity**. **Adverse effects**.

METHODS

Clinical Evidence search and appraisal June 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2014, Embase 1980 to June 2014, and The Cochrane Database of Systematic Reviews 2014, issue 6 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs).

QUESTION What are the effects of antithyroid drug treatments for hyperthyroidism in pregnancy?

OPTION CARBIMAZOLE OR THIAMAZOLE New

- We found no direct information from RCTs about carbimazole or thiamazole in the treatment of hyperthyroidism in pregnancy.
- Observational studies have shown that carbimazole and thiamazole may increase congenital malformations including urinary system malformations, choanal and oesophageal atresia, omphalocele, and other adverse effects.

Benefits and harms

Carbimazole or thiamazole versus placebo/no treatment:

We found one systematic review (search date 2013), [1] which found no RCTs.

Carbimazole or thiamazole versus propylthiouracil:

We found one systematic review (search date 2013), [1] which found no RCTs.

Carbimazole versus thiamazole:

We found one systematic review (search date 2013), [1] which found no RCTs.

Further information on studies

[1] The systematic review reported that congenital anomalies such as aplasia cutis (scalp lesions) and, very rarely, choanal atresia (blocked nasal passage) or oesophageal atresia have been reported with methimazole (also known as thiamazole). The systematic review went on to note that the FDA has classed both PTU and methimazole as being of risk to the fetus because of the potential for fetal hypothyroidism. The review, therefore, suggested doses of antithyroid drug should be kept as low as possible and, once normal thyroid function has been achieved and symptoms stabilised, doses should be tapered down.

Comment:

We have included data on adverse effects from recently published observational studies below. These do not, however, represent a systematic review of all such reports, and readers should consult appropriate sources for such data.

A large Danish nationwide register-based cohort study, including 817,093 children live-born from 1996 to 2008, described an increased prevalence of congenital malformations in children exposed to antithyroid drug therapy (ATD) in early pregnancy. [10]

The prevalence of birth defects was: propylthiouracil (PTU) 8.0%; methimazole (MMI, also known as thiamazole)/carbimazole (CMZ) 9.1%; no ATD (no ATD use in pregnancy) 5.4%; compared to non-exposed (never used ATDs) 5.7% (among-group P value <0.001, head-to-head comparisons not reported). [10] Note: in this study the results for MMI and CMZ were not reported separately. [10]

The prevalence of birth defects in children born to mothers who shifted in early pregnancy from MMI/CMZ to PTU was 10.1% (shifted *v* non-exposed: adjusted OR = 1.82 (95% CI 1.08 to 3.07). [10]

The study reported that MMI/CMZ and PTU were associated with urinary system malformation. Choanal atresia, oesophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis were common in MMI/CMZ-exposed children (adjusted OR = 21.8 [95% CI 13.4 to 35.4]). [10]

A further report of this same Danish cohort looked in more detail at congenital heart defects in children exposed to MMI/CMZ (n = 1097) compared to children with no ATD exposure (n = 811,730). They reported an overall increase in congenital heart defects in children exposed to MMI/CMZ (adjusted HR 1.84, 95% CI 1.26 to 2.68). However, in a subgroup analysis of different congenital heart defects only those of the cardiac septa (ventricular or atrial septal defects) were significantly associated with MMI/CMZ exposure (adjusted HR 1.87, 95% CI 1.14 to 3.08). [11]

In a cohort study from Japan, pregnancy outcomes of mothers with Graves' disease were reviewed (5967 live births). [12] The overall rate of major anomalies in the thiamazole (also known as methimazole) group was 4.1% (50 of 1231), and it was significantly higher than the 2.1% (40 of 1906)

in the control group (P = 0.002), but there was no increase in the overall rate of major anomalies in the propylthiouracil group in comparison with the control group (21/1399 [1.9%]; P = 0.709). [12]

OPTION PROPYLTHIOURACIL New

- We found no direct information from RCTs about propylthiouracil in the treatment of hyperthyroidism in pregnancy.
- Observational studies have shown that propylthiouracil may increase congenital malformations, including urinary system malformations and other adverse effects.
- There have been alerts on the risk of hepatotoxicity with propylthiouracil.

Benefits and harms

Propylthiouracil versus placebo/no treatment:

We found one systematic review (search date 2013), [1] which found no RCTs.

Propylthiouracil versus carbimazole:

We found one systematic review (search date 2013), [1] which found no RCTs.

Propylthiouracil versus thiamazole:

We found one systematic review (search date 2013), [1] which found no RCTs.

Further information on studies

[1] The systematic review noted that the FDA has classed both PTU and methimazole as being of risk to the fetus because of the potential for fetal hypothyroidism. The review, therefore, suggested doses of antithyroid drug should be kept as low as possible and, once normal thyroid function has been achieved and symptoms stabilised, doses should be tapered down.

Comment:

We have included data on adverse effects from recently published observational studies below. These do not, however, represent a systematic review of all such reports, and readers should consult appropriate sources for such data.

A large Danish nationwide register-based cohort study, including 817,093 children live-born from 1996 to 2008, described an increased prevalence of congenital malformations in children exposed to antithyroid drug therapy (ATD) in early pregnancy. [10]

The prevalence of birth defects was: propylthiouracil (PTU) 8.0%; methimazole (MMI, also known as thiamazole)/carbimazole (CMZ) 9.1%; no ATD (no ATD use in pregnancy) 5.4%; compared to non-exposed (never used ATDs) 5.7% (among-group P value <0.001, head-to-head comparisons not reported). [10] Note: in this study the results for MMI and CMZ were not reported separately. [10]

The prevalence of birth defects in children born to mothers who shifted in early pregnancy from MMI/CMZ to PTU was 10.1% (shifted versus non-exposed: adjusted OR = 1.82 (95% CI 1.08 to 3.07). [10]

The study reported that MMI/CMZ and PTU were associated with urinary system malformation, and PTU with malformations in the face and neck region. The overall prevalence of birth defects was not significantly different for PTU versus MMI/CMZ exposure (P = 0.437); however, the number of exposed cases was smaller in the PTU group, and the CIs consequently wider (results presented graphically). [10]

A further report of this same Danish cohort focused on hospital-registered cases of birth defects in the face and neck region and in the urinary system after PTU exposure (n = 723) versus no PTU exposure in early pregnancy (n = 811,730). Fourteen cases of birth defects were identified in the face and neck region and/or in the genitourinary system after PTU exposure in early pregnancy; 11 children were exposed to PTU only (n = 564), whereas three children were born to mothers who switched from MMI/CMZ to PTU in early pregnancy (n = 159). Among children exposed to PTU only, compared with those with no PTU exposure, there was an increase in birth defects in the face and neck region was (adjusted HR 4.92, 95% CI 2.04 to11.86) and in the urinary system (adjusted HR 2.73, 95% CI 1.22 to 6.07). Seven children were diagnosed with a birth defect in the face and neck region (pre-auricular and branchial sinus/fistula/cyst) and seven children had a birth defect in the urinary system (single kidney cyst and hydronephrosis). Nine children underwent surgical treatment (6 with a birth defect in the face and neck region and 3 with a birth defect in the urinary system). [13]

In a cohort study from Japan, pregnancy outcomes of mothers with Graves' disease were reviewed (5967 live births). [12] The overall rate of major anomalies in the thiamazole (also known as methimazole) group was 4.1% (50 of 1231), and it was significantly higher than the 2.1% (40 of 1906) in the control group (P = 0.002), but there was no increase in the overall rate of major anomalies in the propylthiouracil group in comparison with the control group (21/1399 [1.9%]; P = 0.709). [12]

Hepatotoxicity is very rare but serious complication. Recently, a report from the Adverse Event Reporting System of the FDA called attention to the risk of hepatotoxicity in people exposed to PTU. [14] [15]

Clinical guide:
While severe liver injury with propylthiouracil is rare, it is very serious and may result in liver transplant or death. Healthcare professionals must be vigilant for the signs and symptoms of hepatotoxicity in people taking propylthiouracil. [16]

SUBSTANTIVE CHANGES

Carbimazole or thiamazole New option. One systematic review added. [1] Categorised as 'unknown effectiveness'.

Propylthiouracil New option. One systematic review added. [1] Categorised as 'unknown effectiveness'.

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Competing interests: BN declares that she has no competing interests.

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