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Benign thyroid disease in pregnancy: A state of the art review

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ABSTRACT

Thyroid dysfunction is the commonest endocrine disorder in pregnancy apart from diabetes. Thyroid hormones are essential for fetal brain development in the embryonic phase. Maternal thyroid dysfunction during pregnancy may have significant adverse maternal and fetal outcomes such as preterm delivery, preeclampsia, miscarriage and low birth weight. In this review we discuss the effect of thyroid disease on pregnancy and the current evidence on the management of different thyroid conditions in pregnancy and postpartum to improve fetal and neonatal outcomes, with special reference to existing guidelines on the topic which we dissect, critique and compare with each other.

Overt hypothyroidism and hyperthyroidism should be treated appropriately in pregnancy, aiming to maintain euthyroidism. Subclinical hypothyroidism is often pragmatically treated with levothyroxine, although it has not been definitively proven whether this alters maternal or fetal outcomes. Subclinical hyperthyroidism does not usually require treatment and the possibility of non-thyroidal illness or gestational thyrotoxicosis should be considered.

Autoimmune thyroid diseases tend to improve during pregnancy but commonly flare-up or emerge in the post-partum period. Accordingly, thyroid auto-antibodies tend to decrease with pregnancy progression.

Postpartum thyroiditis should be managed based on the clinical symptoms rather than abnormal biochemical results.

Contents

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Introduction

Thyroid disease, after diabetes, is the commonest endocrine disorder during pregnancy. The background prevalence of spontaneous hypothyroidism is between 1% and 2% in iodine-replete communities; it is 10 times more common in women than in men [1]; subclinical hypothyroidism, defined as a raised serum thyroid stimulating hormone (TSH) levels in presence of normal thyroid hormone levels, affects about 8% of women. Similarly, the prevalence of hyperthyroidism in women is between 0.5% and 2%, and is 10 times more common than in men in iodine-replete communities [1]; subclinical hyperthyroidism, defined as low serum TSH in the presence of normal thyroid hormone levels and in the absence of hypothalamic and pituitary disease or non-thyroidal illness or medications that inhibit TSH secretion, affects about 3% of the population. This review will explore the interplay between thyroid disease and pregnancy and the evolving evidence on the management of the different thyroid conditions in pregnancy and the postpartum period, with special emphasis on existing guidelines on this field.

Methods

We undertook a focused review of the literature and discussions with colleagues. We carried out a search of the published literature in Medline, PubMed (www.pubmed.gov) and Google Scholar (www.scholar.google.com) with a broad range of combinations of the medical subject headings (MeSH) terms, 'pregnancy', 'miscarriage', 'breastfeeding', 'thyroid diseases', 'hypothyroidism', 'thyrotoxicosis', 'hyperthyroidism', 'anti-thyroid drugs', 'carbimazole', 'methimazole', 'propylthiouracil', 'thyroiditis', 'post-partum thyroiditis', 'autoimmune thyroid disease', 'non-thyroidal illness', 'thyroid function tests', 'congenital malformations' and 'neurodevelopmental defects'. Inclusion criteria were 'English language' and articles retrieved from 1960 to December 2015. References of articles included were read to identify any further articles that were missed from the above database searches and personal archived references were also sought. Whenever available, we gave preference to *meta*-analyses, systematic reviews, randomised controlled trials (RCTs) and prospective epidemiological studies. As appropriate, we included retrospective and non-randomised studies, and case reports.

Thyroid physiology in pregnancy

Approximately 94% of thyroid hormones are secreted by the thyroid gland as thyroxine or tetraiodothyronine (T4) and 6% as triiodothyronine (T3) (Fig. 1). T4 is catalytically converted to the more metabolically active T3 in peripheral tissues by deiodinases and a portion of peripherally-produced T3 returns to the circulation and it is because of this peripheral conversion that the plasma T4 to T3 ratio is approximately 4:1 [2,3]. Both T4 and T3 are mostly bound to carrier proteins in the serum, chiefly thyroxine-binding globulin (TBG). However, it is the free hormones (free T4 (fT4) and free T3 (fT3)) that are available to be actively transported into cells and exert their effects.

Changes in maternal thyroid function during pregnancy result from a combination of increased metabolic demands, increased serum TBG concentrations, stimulation of the TSH receptor by human chorionic gonadotropin (hCG) [4], an increased mother-to-foetus transfer of thyroxine and an increased intraplacental breakdown of T4 and T3 (resulting from the placental expression of deiodinase 3). Total T4 and T3 concentrations increase by 50% as a result of a 50% increase in circulating TBG levels by 6–8 weeks of gestation; their levels plateau at around 16 weeks of gestation [5]. Maternal TSH is usually within normal limits during pregnancy but it can be decreased in the first trimester due to the increased hCG levels and the cross-reactivity of this hormone on TSH receptors [6]; both are glycoprotein hormones with a common α subunit and a considerable homology between their β subunits. Therefore hCG has a weak thyroid stimulating activity [6]. hCG levels increase following fertilisation and peak at 10–12 weeks of gestation, leading to a rise in the total serum T4 and T3 concentrations and subsequently reduction of thyrotropin-releasing hormone (TRH) and TSH levels as a result of negative feedback. This hormonal interplay results in a biochemical picture of subclinical hyperthyroidism, which can be considered as a physiological finding. The decrease in hCG secretion later in pregnancy leads to reduction of serum fT4 and fT3 concentrations and finally the normalisation of TSH levels [4]. Thyroid hyperfunction and symptoms, if present, subside as hCG production falls, typically at 14–18 weeks of gestation. Ideally, the assay-specific TSH reference ranges for each trimester should be calculated based on the local population in iodine sufficient areas and pregnant women recruited for such calculations should be euthyroid and thyroid antibody negative. When this is not feasible, a reasonable alternative is to use the consensus ranges as per the various guidelines (Table 1) [7–9]. However, it is worth emphasizing that these guideline reference ranges are mainly drawn from Western populations; for example, the TSH in Chinese populations has been shown to be higher than these reference values [7].

Iodine and pregnancy

Iodine is an essential component of thyroid hormones and requirements increase during pregnancy. Iodine deficiency is associated with thyroid dysfunction and subsequently with impaired fetal development [10]. It is nowadays accepted that severe maternal iodine deficiency can have adverse implications for the mother, including hypothyroidism and goitre; for the foetus, including miscarriage and stillbirth; for the neonate, including neonatal mortality; and for the child, including impaired neurological development, faltering growth and cretinism [10–12]. Iodine supplementation is recommended as a treatment of maternal hypothyroidism in severely iodine deficient populations and there is good evidence that