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Review

Thyroid dysfunction and reproductive health

Amanda Jefferys BMBS BMedSci MRCOG,[a] **Mark Vanderpump** MBChB MD FRCP,[b] **Ephia Yasmin** MBBS MD MRCOG[c,*]

[a]Subspecialist Trainee in Reproductive Medicine, Bristol Centre for Reproductive Medicine, Southmead Hospital, Bristol BS10 5NB, UK
[b]Consultant Physician and Honorary Senior Lecturer in Diabetes and Endocrinology, Royal Free Hampstead NHS Trust, London NW3 2QG, UK
[c]Consultant in Reproductive Medicine and Surgery, Bristol Centre for Reproductive Medicine, Southmead Hospital, Bristol BS10 5NB, UK
Correspondence: Ephia Yasmin. Email: ephia.yasmin@gmail.com

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Key content

- Thyroid disease is a common condition in the reproductive medicine setting due to the complex interplay between the hypothalamo-pituitary axis and the thyoid gland.
- Abnormalities in thyroid function, including hyperthyroidism and hypothyroidism, can have an adverse effect on reproductive health and result in reduced rates of conception, increased early pregnancy loss, and adverse pregnancy and neonatal outcomes.
- There is increasing evidence for the role of autoantibodies in subfertility and early pregnancy loss, even in euthyroid women.
- Evidence suggests that treating thyroid disorders and keeping thyroid-stimulating hormone levels at the lower end of normal in euthyroid women may improve conception rates in subfertile women and reduce early pregnancy loss.

Learning objectives

- To gain an overview of the effect of thyroid disorders on reproductive health.
- To review the evidence on how to optimise thyroid function to improve reproductive outcomes.

Ethical issues

- Screening for thyroid disease should be considered in women presenting with subfertility and recurrent early pregnancy loss.

Keywords: reproductive health / screening / subfertility / thyroid disease / thyroid gland

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Introduction

Thyroid hormones act systemically to control metabolism. Because function of the thyroid gland is under the control of the hypothalamo-pituitary axis, changes in thyroid function can impact greatly on reproductive function before, during and after conception. Thyroid disease is the most common endocrine condition affecting women of reproductive age.

This review summarises the effect of thyroid disorders on reproductive health and the current evidence on how thyroid function should be optimised to improve reproductive outcomes.

The thyroid gland and abnormalities of function

The thyroid gland controls rate of metabolic processes throughout the body via the production of two hormones triiodothyronine and thyroxine (T_4). These hormones also have key roles in growth and development, particularly brain development.[1] Thyroid hormone release is under the control of the hypothalamus and anterior pituitary (Figure 1). Thyroid disease is classically divided into hyperthyroidism and hypothyroidism, and the causes of thyroid disease are numerous (Table 1). There is also a subset of patients who are euthyroid and have positive thyroid autoantibodies. The role of these antibodies in reproductive health has received increasing attention over recent years.

Subfertility

Subfertility affects between 1% and 5% of couples worldwide.[2] Thyroid disease has long been associated with subfertility, although national guidance does not currently recommend routine measurement of thyroid function in asymptomatic women presenting with subfertility.[3]

Hyperthyroidism

Hyperthyroidism (both clinical and subclinical) is thought to be found in approximately 2.3% of women presenting with subfertility,[4] compared with an incidence of 1.5% of women in the general population.[5] The link between hyperthyroidism and menstrual irregularity is well established and is most frequently associated with hypomenorrhoea and polymenorrhoea.[6] The likely mechanism for these menstrual disturbances is an increased sensitivity to gonadotrophin-releasing hormone,[7] resulting in a raised level of luteinising hormone and sex hormone-binding globulin,[8] causing a rise in total estrogens.[9] However, these thyroid-induced

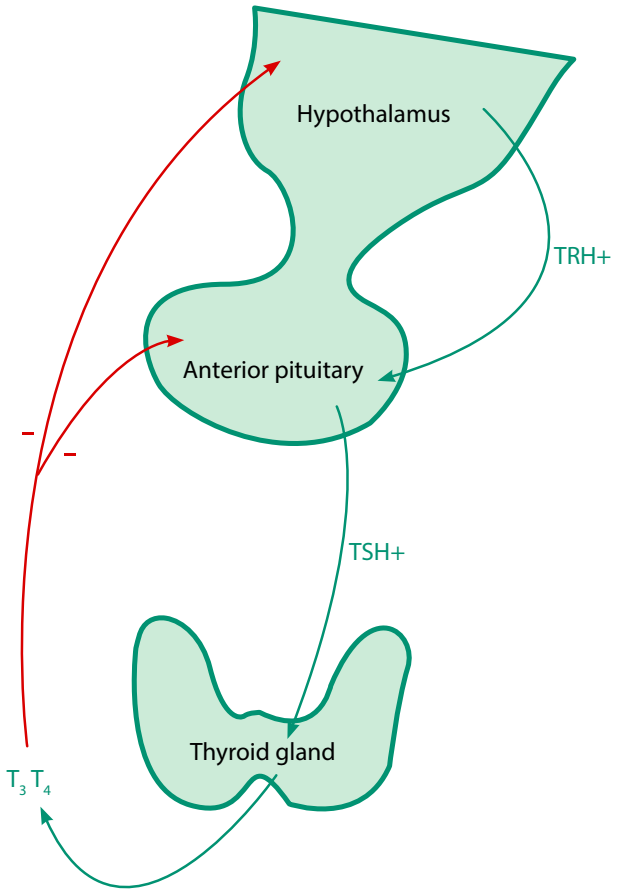

Figure 1. Regulation of thyroid hormone release. T3 = triiodothyronine; T4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

changes in the hypothalamo-pituitary-ovarian axis do not appear to be associated with anovulation and most women with hyperthyroidism remain ovulatory.[10]

Although treatment of hyperthyroidism in subfertile women is advisable for general health and to improve pregnancy outcomes, there is no evidence that treatment of either clinical or subclinical hyperthyroidism improves rates of ovulation.[11] The impact of treatment of hyperthyroidism on pregnancy rates in the subfertility setting is yet to be assessed. Importantly, as radioactive iodine is a commonly employed treatment for hyperthyroidism, particularly Graves' disease, radioactive iodine has not been associated with deterioration in gonadal function or adverse outcomes in offspring.[12] However, postponement of pregnancy for at least 6 months after treatment is recommended.[13]

Hypothyroidism

Hypothyroidism is common, with overt hypothyroidism affecting 0.5% of women of reproductive age. Mild thyroid failure or subclinical hypothyroidism has a prevalence of approximately 2–4%,[14] and is characterised by raised serum thyroid-stimulating hormone (TSH) of more than 4.5 mU/l in combination with a normal T_4 (9–25 pmol/l) and no clinical symptoms or signs of hypothyroidism.[15] Hypothyroidism is known to affect pulsatile release of gonadotrophin-releasing hormone, which is required for cyclical release of follicle-stimulating hormone and luteinising hormone and subsequent ovulation.[16] Hypothyroidism in childhood and adolescence is associated with a delay in reaching sexual maturity, and in adulthood is associated with menstrual disturbances (particularly oligomenorrhoea, menorrhagia and amenorrhoea) and in some cases anovulation.[10] Additionally, thyroid hormone receptors are known to be expressed by ovarian granulosa cells, cumulus cells and oocytes themselves,[17] and may have a role in enabling activation of luteinising hormone receptors and progesterone production.[18] Hypothyroidism may also alter feedback to the pituitary by changing estrogen metabolism and circulating levels of sex hormone-binding globulin.[19] There is evidence of a dose-dependent association, with women with higher serum TSH levels having greater menstrual disturbance and anovulatory cycles.[20] Women presenting with subfertility also appear to have raised mean serum TSH levels[4] and increased rates of subclinical[21] and overt[22] hypothyroidism compared with controls. This is compounded by an increase in T_4 binding to thyroxine-binding globulin in response to rising estrogen levels as a result of controlled ovarian hyperstimulation, potentially tipping normally euthyroid women into a temporarily hypothyroid state.[23] There is a suggestion that raised levels of serum TSH may be associated with reduced rates of fertilisation during assisted conception,[24] and reduced pregnancy rates overall in women with a serum TSH of more than 2.5 mU/l.[25] Improvements in implantation,

Table 1. Causes of thyroid disease

Hypothyroidism	Hyperthyroidism
Primary hypothyroidism	Autoimmune
Autoimmune disease	• Grave's disease
• Atrophic thyroiditis	Toxic nodular
• Hashimoto's thyroiditis	Goitre
Iatrogenic	Toxic adenoma
• Radioiodine therapy	Subacute thyroiditis
• Thyroidectomy	Iodine therapy
• Antithyroid drugs	Drugs (amiodarone, lithium)
Transient	
• Subacute (de Quervain's) thyroiditis	
• Postpartum thyroiditis	
Iodine deficiency	
Secondary hypothyroidism	
• Pituitary failure	
• Pituitary tumour	
Tertiary hypothyroidism	
• Hypothalamic failure	

pregnancy and live birth rates have been reported following treatment with levothyroxine (L-T_4) in those with overt,[26] and subclinical hypothyroidism.[27,28] However, even following thyroid replacement therapy, egg numbers and fertilisation rates,[29] and implantation, pregnancy and live birth rates[30] appear to be reduced compared with euthyroid controls. On the basis of this evidence there has been a recent shift in practice to maintain serum TSH levels below 2.5 mU/l pre-conceptually in the subfertility setting, in line with the American Thyroid Association guidelines for first trimester serum TSH.[31]

Thyroid autoantibodies

Autoimmune conditions implicated in subfertility and reproductive health include antiphospholipid antibodies, diabetes mellitus and systemic lupus erythematosus.[32] There has been longstanding speculation over the importance of thyroid autoantibodies in the subfertility setting. Autoimmune thyroid disease (AITD) is the most common cause of hypothyroidism in women of reproductive age. Thyroid autoantibodies are present in almost all patients with Hashimoto's thyroiditis, two-thirds of those with postpartum thyroiditis and three-quarters of those with Graves' disease.[33] Thyroid autoimmunity is thought to be present in up to 25% of the general population.[34] The prevalence of thyroid autoimmunity has been found to be consistently increased in the subfertile population compared with fertile controls,[35] and is found to be high in those with endometriosis[4] and polycystic ovary syndrome.[36] It is well established that a proportion of people with AITD have normal serum TSH.[33] It has been suggested that thyroid autoantibodies are an early sign of lymphocytic infiltration and therefore a predictor of thyroid disease.[37] Increased rates of subfertility are also seen in euthyroid women with AITD[35] and it is the management of this group that has created the greatest debate among clinicians.

AITD has been consistently associated with poorer outcomes in the fertility setting in euthyroid women and specifically in those undergoing assisted conception, including lower fertilisation rates, poorer embryo quality and lower pregnancy rates.[25,38] Although it appears that AITD is a precursor to overt thyroid disease, there is no significant fluctuation in serum TSH during the course of assisted conception treatment in either AITD-positive women or controls,[38] therefore it seems unlikely that these differences in outcomes can be explained by women being pushed into a temporarily hypothyroid state during treatment. Antithyroid antibodies have been found in the ovarian follicular fluid of women with AITD at levels that correlate with serum antibody levels.[38] Possible mechanisms proposed[39] for this apparent reduction in fertility include an increased T-cell population within the endometrium, polyclonal B cells cross-reacting with trophoblast placental tissue, vitamin D deficiency (which has been associated with both lower success rates following assisted conception and thyroid autoimmunity), natural killer cell hyperactivity and migration into the uterus, and cross-reactivity with placental and zona pellucida antibodies. Alternatively, AITD may merely be occurring concurrently with other autoimmune conditions that are known to affect fertility or may coexist with other conditions associated with subfertility, such as endometriosis or polycystic ovary syndrome.[38]

There is little evidence to suggest whether treating euthyroid women with AITD with thyroxine replacement therapy (L-T_4) in the assisted reproduction setting improves outcome. In a retrospective analysis of 348 women, some improvement in ovarian response to stimulation was seen in treated women.[40] However, in this and another retrospective analysis of 418 women[41] no improvements in implantation or pregnancy rates were demonstrated with treatment with L-T4.

Management of thyroid disease in the subfertility setting

Given the above evidence, it seems reasonable to measure thyroid function routinely in women presenting with subfertility. Initially this should include a serum TSH measurement only. Given that improvements in reproductive outcomes are seen in those in whom the serum TSH is less than 2.5 mU/l, serum TSH levels should be maintained below 2.5 mU/l for those with both clinical and subclinical hypothyroidism. A first finding of subclinical hypothyroidism (serum TSH of more than 2.5 mU/l with normal free T_4) should prompt a repeat serum TSH level and for thyroid autoantibodies to be checked. If the serum TSH persists above 2.5 mU/l, treatment with L-T_4 is warranted to bring the TSH below 2.5 mU/l. The dose of L-T_4 should be titrated until the serum TSH is brought to 2.5 mU/l or less, and during this period monitoring of LT4-4 and TSH every six weeks is warranted. The evidence is lacking over the benefit of commencing L-T_4 in those who are euthyroid with AITD. It should, however, prompt close monitoring of thyroid function if pregnancy results and monitoring of fetal wellbeing and subsequently neonatal review. A flow chart summarising management of thyroid disease in the fertility setting can be found in Figure 2.

Miscarriage

Miscarriage is common, affecting approximately one in five pregnancies.[42] Recurrent miscarriage, defined as three consecutive miscarriages, affects 1% of couples.[43] Given that thyroid hormone plays an important part in embryonic development,[44] particularly neurodevelopment, and that until approximately 10 weeks of gestation the fetus is dependent on placental transfer of T_4 from the mother, it is unsurprising perhaps that thyroid disease has long been

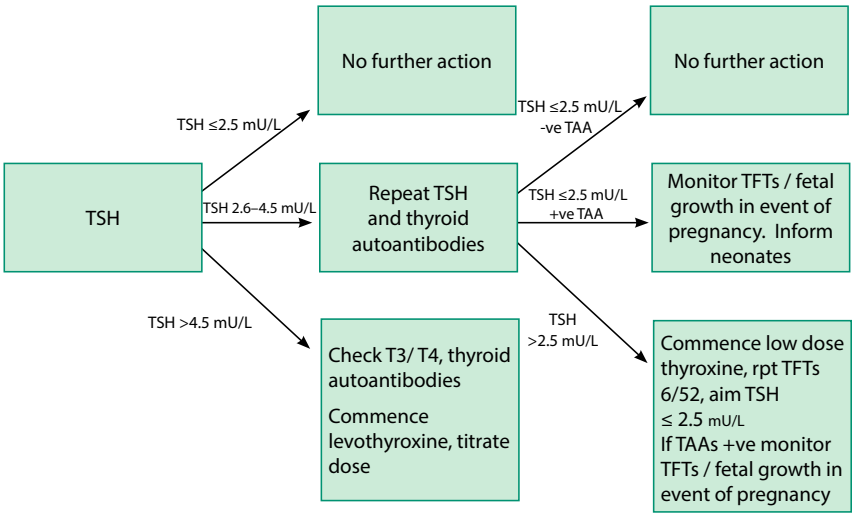

Figure 2. Management of hypothyroidism in the fertility setting. T_3 = triiodothyronine; T_4 = thyroxine; TAA= thyroid antithyroglobulin antibody; TFT = thyroid function test; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

associated with miscarriage.[45] Thyroid hormone receptors are also known to be present on the placenta, suggesting that it may have a role in placental development.[46] However, there has previously been insufficient evidence of an association to warrant routine screening of thyroid function in asymptomatic women presenting with recurrent miscarriage.[47]

Hyperthyroidism

Evidence for a direct association between hyperthyroidism (in the absence of AITD) and miscarriage is limited. However, one study[48] has suggested a doubling of miscarriage rate in a group of hyperthyroid women without AITD, compared with euthyroid controls. The proposed mechanism for this was a toxic effect of excess thyroid hormone on embryogenesis.

Hypothyroidism

Physiological changes of pregnancy including increased levels of thyroxine-binding globulin in response to estrogen stimulation, coupled with reduced clearance of thyroxine-binding globulin and increased glomerular filtration rate increasing clearance of free thyroid hormones, result in a reduction in circulating levels of free thyroid hormones.[49] The requirement for thyroid hormone production is therefore greater. This can be compounded by relative iodine deficiency resulting from increased renal clearance and placental transfer to the fetus.[49] A normal thyroid gland will be able to compensate, however, a thyroid gland which is already underactive or where there is subclinical hypothyroidism may not be able to adequately compensate.[49] However, there is no evidence that overt or subclinical hypothyroidism are increased in those with pregnancy or recurrent pregnancy loss. Studies[27,28] have attempted to establish whether treatment of women with subclinical hypothyroidism with thyroxine reduces miscarriage rates. Although these studies have consistently found significantly lower miscarriage rates in those women with subclinical hypothyroidism who are treated with L-T_4, none have evaluated thyroid autoantibody-negative women separately from thyroid autoantibody-positive ones. It is therefore difficult to draw conclusions on the effect of treatment in women with autoantibody-negative subclinical hypothyroidism.

Thyroid autoantibodies

A 2011 systematic review and meta-analysis[50] has confirmed the association between AITD in euthyroid women and miscarriage, with an apparent three-fold increase in the odds ratio of miscarriage in women positive for thyroid autoantibodies. The exact mechanism for this apparent increase in miscarriage rates is not clear, however, it has been suggested that because AITD is thought to be an early sign of thyroid disease, these women may have reduced thyroid reserves in pregnancy when demand for thyroid hormones increases.[23]

A few studies have assessed the impact of interventions including administration of intravenous immunoglobulin and L-T_4 replacement[41] on miscarriage rates in women with AITD. There is a suggestion that low dose L-T_4 in these women may be beneficial in reducing miscarriage rates in women with and without a history of recurrent miscarriage. However, studies to date are small and no firm conclusions can be drawn from this. A large multicentre double-blinded placebo controlled trial (TABLET trial, University of Birmingham;

http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/womens/tablet/index.aspx) is now under way to investigate the effects of low-dose thyroxine replacement in euthyroid women with AITD, which may provide more concrete answers.

Management of thyroid disease in those with recurrent miscarriage

On the basis of current evidence, screening of women with a history of recurrent miscarriage is warranted. Overt thyroid disease should be managed with L-T_4 replacement therapy and the serum TSH brought within the target range for pregnancy (that is, at or below 2.5 mU/l).[51] At present there is insufficient evidence to support thyroid replacement in those with subclinical hypothyroidism and AITD, however, continuing research may more definitively prove a benefit in the future, especially in those with AITD.

Pregnancy

Pregnancy has a profound effect on thyroid gland function.[52] Serum β human chorionic gonadotrophin (β-hCG), which rises sharply in early pregnancy, is closely related structurally to serum TSH, hence cross-reactivity at the receptor stimulates thyroid hormone release and supresses serum TSH levels. Beyond the first trimester, serum β-hCG levels fall accompanied by a rise in serum TSH. As discussed previously, the physiological changes of pregnancy are such that the demand for thyroid hormones is increased as pregnancy progresses,[52] making pregnant women with overt or subclinical thyroid disease more susceptible to a derangement in thyroid function.

Hyperthyroidism

Graves' disease is the most common cause for hyperthyroidism in pregnancy, affecting up to 1% of pregnancies.[9] Often the diagnosis will have already been made, but for those in whom the diagnosis of hyperthyroidism is made in pregnancy, it can be difficult to differentiate from gestational hyperthyroidism, which affects between 1% and 3% of all pregnancies and occurs because of stimulation of TSH receptors by β-hCG.[52] Free T_4 levels are generally raised in both conditions but TSH receptor antibodies are usually positive and diagnostic of Graves' disease. As free T_4 levels tend to return to normal in the second trimester, supportive management is generally all that is needed in cases of gestational hyperthyroidism and thyroid replacement is not indicated. As Graves' hyperthyroidism is associated with adverse pregnancy outcome, including preterm delivery, pre-eclampsia, growth restriction, heart failure and stillbirth,[52] women should be advised to achieve euthyroidism before planning a pregnancy. Conception should be delayed for 6 months after radioactive iodine therapy.[31] For those on medical therapy propylthiouracil is the preferred agent, because of lower levels of teratogenicity, however, guidelines[31] now suggest changing to carbimazole in the second trimester because of concerns over propylthiouracil-associated hepatotoxicity in offspring. Whichever agent is used, doses should be kept at the lowest possible level to achieve euthyroidism.

Hypothyroidism

Hypothyroidism in pregnancy is a relatively common condition with overt disease affecting approximately 0.5% of women, and subclinical disease approximately 2.5%.[4] Although more frequent in overt hypothyroidism, both overt and subclinical hypothyroidism are associated with an increased risk of adverse obstetric and neonatal outcomes (Table 2).[53] Because of the fetal requirement for maternal T_4 until approximately 12 weeks of gestation, neurodevelopmental delay is a particular risk in these infants.[53] Very rarely in cases of autoimmune thyroiditis there is a risk of transplacental transfer of TSH receptor-blocking antibodies resulting in neonatal hypothyroidism. Evidence suggests that adequate L-T_4 replacement from early pregnancy in those with clinical and subclinical hypothyroidism reduces risks of adverse outcomes to the background risk of the general population.[54]

Thyroid autoimmunity

It is likely that euthyroid women with AITD have lymphocytic infiltration of the thyroid gland.[37] It has been suggested that these women have a 5–10% risk of developing hypothyroidism in pregnancy,[9] as a result of the increased requirement for T_4 in pregnancy.[52] Studies have suggested that euthyroid women with AITD have a two-fold to four-fold increased risk of preterm labour.[47] At present, however, as this is the only prospective randomised trial comparing treatment with thyroxine with non-treatment control, routine treatment of euthyroid women with AITD with L-T_4 in pregnancy is not recommended.[31]

Management of thyroid disease in pregnancy

Although not currently recommended,[31] there is evidence to suggest that routine screening of the general population for

Table 2. Complications of hypothyroidism in pregnancy

Maternal	Neonatal
Anaemia	Fetal distress in labour
Postpartum haemorrhage	Prematurity/low birthweight
Cardiac dysfunction	Congenital malformations
Pre-eclampsia	Perinatal death
Placental abruption	Stillbirth
	Neurodevelopmental delay
	Congenital hypothyroidism (if autoimmune)

Box 1. Risk factors for thyroid dysfunction

- History of thyroid dysfunction/thyroid surgery
- Family history of thyroid disease
- Goitre
- Positive thyroid autoantibodies
- Clinical symptoms/signs of hypothyroidism
- Diabetes type I
- History of miscarriage/preterm delivery
- Other autoimmune disorders
- History of subfertility
- History of therapeutic head or neck irradiation
- Age ≥30 years
- Previous treatment with amiodarone
- Previous treatment with lithium
- Recent exposure to iodinated radiological contrast agents

Table 3. Trimester-specific TSH reference ranges

Trimester	TSH reference range (mU/l)
1st	0.1–2.5
2nd	0.2–3.0
3rd	0.3–3.0

TSH = thyroid-stimulating hormone.

thyroid dysfunction, at the start of pregnancy, may be beneficial, as targeted screening of high-risk cases has been found to miss approximately one-third of cases of overt and subclinical hypothyroidism. At present a high-risk screening approach is currently adopted, therefore women at high risk (Box 1) should be screened.

The effect of the physiological changes in pregnancy on the thyroid gland has led to the development of specific reference ranges for thyroid function tests in pregnancy (Table 3).[31]

In women with previously diagnosed overt or subclinical hypothyroidism taking L-T_4 before pregnancy, the dose should be increased initially by 25 μg daily once pregnancy is confirmed to compensate for the increased T_4 demand of pregnancy.[50] Thyroid function should be monitored every four to six weeks and further increases in L-T_4 dose may be required to maintain an optimal serum TSH (0.5–2.5 mU/l).[31]

Women with pre-existing hyperthyroidism should continue on anti-thyroid medication and should have thyroid function closely monitored and kept within trimester-specific pregnancy ranges.[31] Fetal growth and heart rate should be monitored, particularly in those with anti-thyroid antibodies, because of the rare risk of fetal hyperthyroidism. Babies of all anti-thyroid antibody-positive women, whether hyperthyroid or euthyroid, should have a neonatal review after delivery because of the small risk of neonatal hyperthyroidism.[31]

As euthyroid women with AITD are at increased risk of developing hypothyroidism during pregnancy, current guidance suggests they should have thyroid function checked every four weeks in early pregnancy and at least once between 26 and 32 weeks.[31] This will ensure prompt detection and treatment to reduce risks.

Following delivery, thyroid function quickly returns to prepregnancy levels so L-T_4 therapy can therefore be changed to prepregnancy doses but thyroid function should be rechecked at six to eight weeks postpartum.[31] Those women with Graves' disease often enter into relative remission towards the end of pregnancy and will need to be assessed within two months of delivery as they are at increased risk of recurrence or exacerbation of Graves' disease.

Conclusion

Thyroid disease can have significant effects on reproduction from conception to birth, however, with appropriate screening, a high index of suspicion and prompt management, risks can be significantly reduced if not ameliorated. The benefits of L-T_4 replacement in euthyroid women with AITD both pre-conceptually and during pregnancy remain a grey area and further research is needed to confirm benefit.

Contribution to authorship

AJ performed literature search, co-designed the format of the article and wrote the review. MV performed critical appraisal of content and carried out revision of the article providing intellectual input. EY designed format with AJ and carried out draft revisions and approval of the final version.

Disclosure of interests

The authors have no conflicts of interest to declare.

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Thyroid dysfunction is extremely common in women and has unique consequences related to menstrual cyclicity and reproduction. Even minimal hypothyroidism can increase rates of miscarriage and fetal death and may also have adverse effects on later cognitive development of the offspring. Hyperthyroidi â€¦Â 1 Hormone Center of New York, Center for Health Research, Inc., 133 East 73rd Street, New York, NY 10021, USA. GPRedmond@aol.com. PMID: 15142372. DOI: 10.1089/105072504323024543. Abstract. Thyroid dysfunction is extremely common in women and has unique consequences related to menstrual cyclicity and reproduction. THYROID Volume 27, Number 3, 2017 Âª American Thyroid Association Âª Mary Ann Liebert, Inc. DOI: 10.1089/thy.2016.0457. SPECIAL ARTICLE.Â The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid disease in women during pregnancy, preconception, and the postpartum period. Methods: The specic clinical questions addressed in these guidelines were based on prior versions of the guidelines, stakeholder input, and input of task force members.Â Thyroid antibody positivity separately in-creases the risk of thyroid dysfunction following delivery and during the postpartum period. Thyroid disease can have significant effects on a woman's reproductive health and screening for women presenting with fertility problems and recurrent early pregnancy loss should be considered, suggests a new review.Â Thyroid dysfunction and reproductive health. The Obstetrician & Gynaecologist, January 2015 DOI: 10.1111/tog.12161. Cite This Page Thyroid function and human reproductive health, 2018. Unuane D, et al. Endocrine disorders and female fertility, 2011.Â Womenâ€™s Health Committee; The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Testing for hypothyroidism during pregnancy with serum TSH, 2015. Brent GA.Â Analyzing Thyroid Dysfunction in the Climacteric, 2018. Zhu BT, et al. Functional role of estrogen metabolism in target cells: review and perspectives, 1998.