# Management of thyroid disorders in pregnancy: an antenatal clinic audit

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**ABSTRACT**

**Background and purpose:** Optimization of maternal thyroid hormone levels is of paramount importance specifically during the first trimester of pregnancy, due to the relatively delayed maturation of fetal thyroid gland. This audit evaluated the referral process of pregnant women to the antenatal endocrinology clinic, as per local guidelines.

**Methods:** A total of 100 pregnant women referred to the antenatal endocrinology clinic were evaluated between April 2017 and April 2018. Demographic parameters, obstetric/endocrine history, timing of referral and thyroid status were documented by reviewing the handwritten and electronic records of each patient.

**Results:** Among the evaluated women, 90% were referred directly by general practitioners. One third of women were referred during the first trimester. The reasons for referral were: overt/subclinical hypothyroidism (74%), current/previous hyperthyroidism (17%), history of thyroidectomy (5% due to thyroid cancer; 4% for other reasons), thyroid nodule (1%). Only 34% of the women had TSH levels below 2.5mU/L before the first appointment, while subclinical hypothyroidism was evident in 41%. In 25% of cases, the TSH test was performed only at the time of the first appointment, while readjustment of levothyroxine dose was evident in approximately half of the hypothyroid cases.

**Conclusion:** These pregnant women were appropriately referred to the antenatal endocrinology clinic. However, failure to up-titrate the levothyroxine dose was relatively frequently observed, while many cases were seeking specialist care late in their pregnancy. The management of women with thyroid disorders could be improved through educational programs targeting those who wish to conceive or have recently conceived.

**KEYWORDS**

Thyroid disorders, treatment algorithm, pregnancy, gestational age.

## Introduction

Fetal growth and development are dependent on bioavailable levels of thyroxine and triiodothyronine [1]. Given the delayed maturation of the fetal thyroid gland, which is estimated to take place between the 14th and the 18th week of gestation, the bioavailability of thyroid hormones in the fetal circulation is directly linked to the optimal function of the maternal hypothalamus-pituitary-thyroid axis and the resulting levels of thyroid hormones [2,3]. In fact, the greatest demand in thyroid hormones occurs very soon after gestation starts, increases until mid-gestation and thereafter stabilizes up until delivery [4].

Thyroid hormones exert anabolic effects on fetal metabolism. Their primary role consists of stimulating fetal oxygen consumption and controlling the effectiveness of other hormones and growth factors that impact on fetal development, such as insulin-like growth factors1. From a physiological point of view, thyroid hormones induce fetal brain and somatic tissue development, and promote general accretion of fetal mass. Closer to term, thyroid hormones trigger terminal differentiation of fetal tissues and mediate the maturational effects of glucocorticoids that ensure neonatal viability [1].

Disorders of thyroid function complicating pregnancy are not uncommon. The prevalence of overt hypothyroidism during pregnancy ranges from 0.3 to 0.5%, whereas rates of subclinical hypothyroidism (SCH) with either positive or negative thyroid peroxidase antibodies are estimated to range from 4 to 6%. On the other hand, overt hyperthyroidism is evident in 0.1-0.4% of pregnancies, with Grave's disease accounting for up to 85% of cases. Finally, subclinical hyperthyroidism is observed in 2-5% of pregnant women [5].

A significant body of evidence has indicated that thyroid dysfunction may have an adverse impact on the maternal-fetal unit. Hypothyroidism is associated with a higher risk of gestational hypertension, pregnancy loss, premature birth, low birth weight and lower neonatal IQ. Moreover Instead, inadequate control of maternal hyperthyroidism might result in pregnancy loss, intrauterine growth restriction, stillbirth, maternal congestive heart failure, thyroid storm, as well as prematurity and low birth weight [6,7]. As described in a meta-analysis of 2,532,704 women, pregnant women with overt hypothyroidism or hyperthyroidism

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had up to 1.19 or 1.24 higher odds of preterm delivery compared with the reference group [8]. However, evidence regarding the implications of SCH in pregnancy outcomes remains conflicting, with meta-analyses reporting either a direct association [9] or no link with preterm birth [8]. In vivo studies exhibited impaired memory performance and spatial learning in the offspring of animals with maternal SCH during pregnancy. [10]

The joint endocrinology/obstetrics clinic at the Royal Free Hospital is very active, monitoring the health of future mothers throughout their pregnancy until the time of delivery, and forming individual healthcare plans according to the needs of every patient. In 2017, the Royal Free London NHS Foundation Trust published guidelines to help general practitioners and obstetricians with the management of pregnant women with thyroid disorders, which provide a clear stepwise approach [7].

The aim of the present audit was to evaluate the referral process of pregnant women to the hospital's antenatal endocrinology clinic, considering the standards set by the Trust guidelines [7]. Moreover, we screened the management of hypothyroid women by primary care physicians from the time of their first pregnancy test until their appointment at the clinic.

## Methods

In this audit, 100 women with thyroid disorders referred to the antenatal endocrinology clinic at the Royal Free Hospital, North London, between April 2017 and April 2018, were consecutively screened. During this screening process, reference was made to the Trust guidelines for the management of patients with thyroid disorders in pregnancy [7]. Table 1 lists the local criteria for referral to the antenatal endocrinology clinic. The audit was registered in the database of the Royal Free Hospital.

For each patient, we recorded: age, gestational age, and reason for referral. Details of previous endocrine disorders were retrieved by reviewing handwritten patients' notes as well as electronic medical records. Moreover, we recorded the current therapeutic dose of levothyroxine and any dose readjustments as per the guidelines. Hormonal status was recorded around the time of the first appointment, consulting the women's electronic records to retrieve serum levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3).

**Table 1** Criteria for referral to antenatal endocrinology clinic according to local guidelines.

| REFERRAL CRITERIA |
|---|
| Grave's disease with (or without) thyrotoxicosis. |
| Thyroid cancer. |
| Lump in thyroid first discovered in pregnancy. |
| Large multinodular goiter (may present problems if anesthetic is required). |
| Newly diagnosed primary hypothyroidism or subclinical hypothyroidism. |
| Newly diagnosed thyrotoxicosis. |
| Patients with known autoimmune thyroid disease (positive thyroid peroxidase antibodies) who are not currently on thyroxine treatment. |
| Patients on thyroxine replacement for secondary (central) hypothyroidism due to pituitary / hypothalamic disease. |

Thyroid status was classified as hypothyroid, euthyroid and hyperthyroid, on the basis of the TSH and FT4/FT3 levels indicated in the latest American Thyroid Association guidelines6. Considering that the pregnancy-specific reference ranges for thyroid hormone levels in pregnancy are only indicative, we considered TSH<2.5mU/L as the most rational cut-off level for optimal thyroid function [7]. Subclinical hypothyroidism was defined as TSH levels higher than the pregnancy-specific reference range, i.e. higher than 2.5mU/L, in the context of normal FT4 levels. Subclinical hyperthyroidism was defined as TSH levels lower than the laboratory reference range in the context of normal FT4 levels [6,11].

## Statistical analysis

Statistical analysis was performed using SPSS version 22.0. The descriptive analysis was performed presenting quantitative data as mean values ± SD, while qualitative data were presented as frequency (percentage, %) values. On the basis of the thyroid hormone levels recorded at the time of the first appointment in the antenatal endocrinology clinic, the cases were classified as euthyroid, hyperthyroid or hypothyroid. Moreover, the euthyroid women were further classified into those with TSH levels within or outside the accepted pregnancy-specific range (i.e. 2.5mU/L).

## Results

The mean age of the women referred to the endocrine antenatal clinic was 34.9 years. The average gestational age at the time of the first appointment was 14.2 weeks and 2.8 days. The pregnant women were mainly referred directly by primary care practitioners, while some were referred by other physicians, such as obstetricians (7%), general endocrine clinic staff (2%) or the respiratory team (1%). The first TSH test was done prior to referral in 75% of the cases, and after the first visit to the antenatal clinic in the other 25% of the cases. Moreover, we found a documented increase in levothyroxine dose only in half of women treated for thyroid hypofunction (prevalence, 52%).

Table 2 presents the reasons for the referrals to the antenatal endocrinology clinic. Rates of referral per trimester were as follows: 33%, first trimester; 59%, second trimester; and 8%, third trimester. The reasons for referral were compatible with the Trust guidelines in 99% of cases. Only one woman was referred due to detection of a thyroid nodule, for which the

**Table 2** Frequency of the different reasons for referral to the antenatal endocrinology clinic.

| REASONS FOR REFERRAL | FREQUENCY (%) |
|---|---|
| Hypothyroidism, current or previous | 74% |
| Hyperthyroidism, current or previous | 17% |
| Thyroidectomy due to cancer | 5% |
| Thyroidectomy for other reasons | 4% |
| Thyroid nodule | 1% |

primary care practitioner was seeking further advice on management.

As regards the thyroid status of these pregnant women at their first appointment at the antenatal endocrinology clinic, normal thyroid hormone levels were observed in 34% of cases, SCH was documented in 41% of cases, clinical hypothyroidism was evident in 2%, subclinical hyperthyroidism was identified in 13% and clinical hyperthyroidism was documented in 10%. Finally, among the hyperthyroid women, more than half of the cases showed only biochemical evidence of subclinical hyperthyroidism (57%) and the remaining cases (43% of hyperthyroid subgroup) exhibited clinical thyroid disease.

## Discussion

According to the results of this audit, all pregnant women referred to the antenatal endocrinology clinic were at high risk of thyroid disorders, requiring specialist input as per local guidelines. However, the referral was mainly delayed until the second or even third trimester of pregnancy. Moreover, a considerable proportion of the women had never had their thyroid function tested prior to the first appointment. Additionally, TSH levels were found to be outside the pregnancy-specific range in many cases. Finally, only half of the women previously under treatment with levothyroxine had had their dose increased by the time of their first positive pregnancy test.

Almost all indications for referral were compatible with the criteria set by Trust guidelines, and the main problem was current or previous hypothyroidism. Only one case was referred for specialist advice on management of a newly identified thyroid nodule. Moreover, 90% of cases were referred directly to the antenatal endocrinology clinic, while up to 2% of women (2/100) were initially referred to the general endocrinology clinic. These results are generally reassuring as regards the level of awareness within the primary sector of the need for specialist management of women with more complicated thyroid disorders [7], and they showed up to 99% compliance with criteria set by local guidelines.

However, it should be noted that only 33% of the cases screened were referred within the first trimester. This implies either delayed presentation of pregnant women to primary care practitioners or difficulties, for primary healthcare providers, in optimizing the management of thyroid hypofunction in early pregnancy, which might result into hypothyroidism later on in pregnancy. Currently available guidelines [6,7] do not specify the optimal timing of referral to an antenatal endocrinology clinic, however, considering that such clinics deal with complicated thyroid disorders, a prompt referral might be considered to be warranted. NICE guidelines support access to the general antenatal care ideally by 10 weeks of gestation [12]. Previous audits and studies described results similar to our findings, namely appointments within the first trimester were confirmed in only half of evaluated cases, [13] or the majority of women were referred during the second trimester [14].

This audit showed that in 75% of the women thyroid function was tested following confirmation of pregnancy. Given that 90% of the cases were referred directly by their general practitioners, on the basis of a known history of thyroid disorder, the proportion of women who had already had thyroid tests performed by the time of conception was surprisingly low. In fact, our results are comparable with those of other studies and audits that indicate suboptimal screening of thyroid function early in pregnancy in women at high risk of thyroid disorder, given that thyroid hormones were evaluated in 17.8-27% of cases [13-15]. Unfortunately, this issue is longstanding and underlines the need for further education in the context of pre-partum management.

Conflicting advice is provided by different authorities regarding the ideal timing of thyroid function testing in a pregnant woman [16]. Many of the available guidelines recommend increased surveillance of thyroid function in women considered to be at high risk of developing thyroid disease during pregnancy [6,11,17,18]. An elevated risk of thyroid dysfunction should be expected in women with a known history of thyroid disorders, women residing in areas with moderate to severe iodine insufficiency, women with type 1 diabetes, a history of head or neck radiation, severe obesity, fertility issues or clinical symptoms or signs suggestive of either thyrotoxicosis or hypothyroidism, women treated with lithium or amiodarone, as well as women recently exposed to iodinated radiological contrast agents [6,11,17,18]. Since evidence supporting universal screening remains limited [16,18], a case-finding approach is currently implemented. As reported by international authorities, the optimal timing for testing thyroid function should be by the time of confirming the pregnancy, at least in high-risk cases [11,19].

Almost one quarter of the women included in this study had TSH levels higher than the pregnancy-specific reference range at the time of the first appointment. The Trust guidelines recommend a 25% increase in the thyroxine dose immediately after confirmation of pregnancy [7]. However, the proportion of women who actually increased their levothyroxine dose prior to their first appointment in the specialist clinic was surprisingly low, estimated to be 53% of previously treated patients with hypothyroidism. Comparable results were described in the TEARS study (Thyroid, Epidemiology, Audit and Research Study) from Scotland, where an increase in levothyroxine dose was observed in approximately 60% of cases, 34% of whom were within the first trimester [20]. Significantly lower rates were reported in a similar Australian study, where 21% of women had their levothyroxine dose increased prior to their first appointment in the specialist clinic [14]. The THERAPY trial confirmed that increasing the levothyroxine dose by two tablets weekly in women with previously treated hypothyroidism is sufficient to cover the physiologically increased levothyroxine requirements during pregnancy [21]. Interestingly, the additional levothyroxine requirements of a hypothyroid pregnant woman seem to differ according to the actual cause of the hypothyroidism [22].

With regard to its clinical implications, this audit highlights some important issues that could be readdressed, aiming to enhance the management of thyroid disorders during pregnancy. Improved counseling of women with hypothyroidism wishing to conceive would ensure a more prompt adjustment of medication and likely reduce the risk of a maternal thyroid hormone imbalance developing within the first crucial weeks

of gestation. On a secondary level, educational sessions could involve repeated presentation of the Trust guidelines and place emphasis on algorithms for managing those pregnant hypothyroid women who may not require specialist intervention. Primary care physicians should become aware of the importance of targeted testing, at least in cases that might warrant referral to a specialist antenatal clinic.

In conclusion, the results of this audit indicate that primary care practitioners are correctly referring pregnant women to the antenatal endocrinology clinic; however, referrals are often delayed until the second trimester. Further education is required to ensure optimal management of women with hypothyroidism prior to gestation, with simple measures that could be implemented by the individual as well as by the GP. Finally, further studies are required to establish firm guidelines regarding the management of women with SCH especially in early pregnancy.

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