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Therapeutic Drug Monitoring During Pregnancy and Lactation: Thyroid Function Assessment in Pregnancy—Challenges and Solutions

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Abstract

The diagnosis and monitoring of thyroid disease necessitates the knowledge of thyroid pathophysiology and of the technical limitations of current thyroid-related biochemical tests. Thyroid disease diagnosis and monitoring are further complicated during pregnancy and lactation, due to pregnancy-related changes in thyroid hormone metabolism. Dramatic changes that occur in thyroxine and triiodothyronine ranges during pregnancy pose challenges for hypothyroid gravidas. Very early in pregnancy, levothyroxine replacement needs to be increased. Moreover, increases in thyroid hormone replacement need to be conducted individually and on a timely basis. For reasons that are still not entirely clear, although dependent in part on changes in thyroxine binding, free thyroxine (FT4) levels decrease as pregnancy progresses necessitating the use of trimester-specific reference intervals for appropriate replacement. Thyroxine binding protein levels vary by hormonal status, inheritance, and disease states and are higher in pregnancy; hence, FT4 assays became popular because they measure the unbound hormone. However, current FT4 immunoassays are estimate tests that do not reliably measure FT4 and are known to be sensitive to alterations in binding proteins and therefore are method-specific. The need to reliably identify hypothyroxinemic pregnant patients, especially in the first trimester, is of prime importance for early fetal brain development before the fetal thyroid functions. This article addresses 1) the current limitations of laboratory-free thyroxine immunoassay methodologies and especially during pregnancy; 2) trimester-specific reference intervals for thyroid function tests; and 3) the study of levothyroxine pharmacokinetics in pregnant and nonpregnant women.

Keywords

therapeutic drug monitoring; gestation; thyroxine; pharmacokinetics

INTRODUCTION

The diagnosis of hypothyroidism depends on accurate measurement of serum free (unbound) thyroxine (FT4) and of thyroid-stimulating hormone (thyrotropin [TSH]). In the case of primary hypothyroidism, patients present with elevated TSH levels and decreased FT4,

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whereas those with normal FT4 concentrations are considered to have mild or subclinical hypothyroidism.

Hypothyroidism during pregnancy poses a unique challenge to clinicians, because dosing regimens developed for nonpregnant women do not address the metabolic changes or all therapeutic targets that are important to pregnant women. Prepregnancy and during the early months, hypothyroidism has been associated with higher rates of spontaneous abortions, preeclampsia, stillbirth, intrauterine growth restriction, and prematurity.¹ Because thyroxine (T4) is critical for fetal brain development, low maternal T4 can result in subtle neurodevelopmental and neuropsychologic deficits² and, in extreme cases, in mental retardation.¹

Gestation-Specific Reference Intervals

The goal of levothyroxine replacement is to reach and remain within normal gestation-specific levels. Longitudinal studies of healthy, iodine-sufficient women were conducted to define pregnancy-specific reference intervals for FT4, T4, triiodothyronine (T3), and TSH.^{3–5} For comparison, these studies were also conducted on the same women when not pregnant.^{3–5} Serum total T4 and T3 concentrations were measured in the same profile using tandem mass spectrometry; T4 concentrations were approximately 45% higher during the first trimester and remained at a similar level until delivery, whereas T3 levels increased. Higher thyroxine concentrations are of clinical importance for the health of the pregnant mother and are of particular significance for fetal neurodevelopment during the early part of gestation.

The importance of trimester-specific reference intervals for pregnant women and the health of the developing fetus are now widely recognized and in the last few years, many studies have been conducted to define gestation-specific intervals for different ethnicities and populations in different geographic areas with varying levels of iodine sufficiency.⁶ Although TSH is generally considered the primary test for evaluating thyroid status during pregnancy, one cannot rely solely on TSH results during pregnancy and in some other situations when accurate measurements of FT4 are critical. In light of published reports suggesting that isolated hypothyroxinemia may be associated with impaired fetal psychomotor development and decreased intelligence quotient, ascertaining that FT4 concentrations are within the normal range is of prime importance during pregnancy.

Immunoassays in Pregnancy

In general, the currently available FT4 immunoassays are essentially FT4 estimate tests that do not measure FT4 directly and are known to be sensitive to alterations in binding proteins.⁷ As a result, pregnancy-induced elevations in thyroxine binding globulins as well as decreases in albumin can influence FT4 measurements in a method-specific manner.^{8–11} Such FT4 immunoassays may not be accurate enough to identify hypothyroxinemic pregnant patients, especially during the first trimester when adequate maternal FT4 levels are critical for early fetal brain development. Furthermore, the immunoassays currently available on the market for FT4 are inaccurate at extremes of binding protein/analyte concentrations and when heterophilic antibodies are present.^{12–15} Moreover, pregnancy is characterized by both these conditions, making accurate determination of FT4 by conventional direct analog immunoassay methods difficult and unreliable.⁹

The Measurement of Free Thyroxine During Pregnancy

A true FT4 measurement should not be influenced by plasma proteins. However, in actuality, FT4 immunoassays measure some derivative of total T4.¹⁶ In analysis studies conducted with a constant FT4 concentration and increasing concentrations of total T4, it

was illustrated that FT4 immunoassays responded to the changes in total T4 and did not reflect the constant FT4 concentration. The inaccuracy of FT4 immunoassays is further illustrated in a study of patients with severe nonthyroidal illness whose sera is typically characterized by low albumin and a low FT4 measured by two different immunoassay methods.¹⁷ After stepwise additions of human serum, albumin brought both FT4 immunoassay measurements into the reference range. It was clearly illustrated that both methods are binding protein-dependent and reflect unreliable FT4 assessments when albumin is low.

Several studies focused on the comparison of FT4 analysis by various immunoassays available on the market in sera with various thyroxine-binding capacities. A comparison conducted of serum FT4 concentrations in pregnant women without a history of thyroid abnormalities assessed by immunoassays from nine different manufacturers versus the gold standard equilibrium dialysis followed by immunoassay or by ultrafiltration and tandem mass spectrometry. Repeatedly, the mass spectrometry and immunoassay values did not correlate well with each other. However, mass spectrometry values correlated very well with equilibrium dialysis values and the agreement was maintained across gestation.³ Using tandem mass spectrometry, we demonstrated an increase in serum FT4 concentrations very early in gestation followed by a FT4 decrease throughout the rest of the pregnancy.³ These two parameters are of importance because they reflect the physiology of FT4 in pregnancy, which is not illustrated by immunoassays. Furthermore, FT4 and total T3 correlated better with the log-transformed TSH when measured by tandem mass spectrometry.

During pregnancy, the increase in number of binding sites for T4 results in a substantial decrease in serum FT4 concentrations, except for the compensatory increase in thyroidal secretion of T4. Because of their hypofunctioning thyroid, hypothyroid gravidas are unable to respond in this manner and require empiric levothyroxine dose adjustment to compensate for this increased binding.¹⁸ There is some controversy regarding the clinical significance of subclinical hypothyroidism and of isolated hypothyroxinemia during pregnancy,¹⁹ partly because of the limitations of assay methodology, even in large series,²⁰ and partly as a result of an experimental design that has focused on screening of clinically euthyroid women rather than on levothyroxine-treated hypothyroid gravidas.

Levothyroxine Replacement in Pregnancy

The progressive increase in serum thyroxine binding globulins is followed by an increase in thyroidal secretion of thyroid hormone and an increase in the extrathyroidal thyroxine pool level at midgestation.^{21–26} Furthermore, increasing plasma volume and T4 requirements (related to changes in the metabolism of bound and unbound T4) continue throughout pregnancy. Serum T4 levels normally increase by approximately 45% by 6 weeks of gestation,^{6,20,27,28} but little is known regarding the appropriate levothyroxine replacement in pregnancy and whether dosing should change throughout gestation to optimize efficacy.²⁹ The development of sensitive assays for measuring TSH has led to a secular reduction in levothyroxine replacement doses over time, although many physicians will empirically increase levothyroxine dose at the first antenatal visit to compensate for the known increases in thyroid hormone binding (discussed previously) and to mimic the changes in T4 biosynthesis that occur in euthyroid gravidas.

TSH is generally considered a more sensitive test than FT4 for detecting both hypo- and hyperthyroidism.³⁰ TSH serves as a surrogate measure of the adequacy of levothyroxine replacement based on the assumption that this integrated measure of pituitary–thyroid axis response to T4 parallels all the other desired clinical effects of T4 replacement. Importantly, during the first trimester, because TSH is linearly suppressed by human chorionic gonadotropin, it is not a reliable measure of levothyroxine adequacy in early pregnancy. As

human chorionic gonadotropin levels decrease, this suppression is lost and TSH can reflect maternal thyroid status. Furthermore, the TSH–FT4 relationship cannot be relied on to detect unusual conditions characterized by discordance in the ratio of TSH/FT4, patients with central hypothyroidism, or TSH-secreting pituitary tumors. In any case, the key issue for levothyroxine replacement adequacy during early pregnancy is not any maternal response, but rather the adequacy of transplacentally delivered thyroid hormone for the fetus. It remains unclear if one can assume that fetal levels adequate for neurodevelopment will exactly parallel those required to limit TSH secretion in the mother.

What New Approaches Are Being Implemented?

Levothyroxine Pharmacokinetics in Pregnancy—Levothyroxine is one of the most prescribed drugs for women of reproductive age, yet several major gaps still exist in our understanding of levothyroxine homeostasis and replacement in pregnancy. Although clearance of many commonly prescribed drugs varies throughout pregnancy as a result of multiple changes in the expression and activities of multiple cytochrome P450s (CYPs), uridine 5′-diphosphoglucuronosyltransferases, glomerular filtration rate, renal organic ion transporters, volume of distribution, and drug transporters in the liver, intestine, and placenta, including p-glycoprotein and BCRP, it remains unlikely that these previously described changes are of key importance to optimizing levothyroxine replacement. Levothyroxine is metabolized primarily by the deiodinases, some hepatic, and other tissue-specific enzymes.³¹ Several novel techniques are incorporated into this study design, including the use of a stable isotope to assess levothyroxine clearance in pregnancy and the measurements of FT4 and C13-levothyroxine using tandem mass spectrometry.

Our preliminary data in pregnant women suggest that none of the changes in, for example, CYP2D6, CYP3A, or in Phase II enzymes is likely to account, in a temporally meaningful fashion, to gestational changes in levothyroxine pharmacokinetics.³² We determined altered pharmacokinetic clearance of thyroid hormones during pregnancy. The data obtained from these studies will give insight into the mechanism of these changes during pregnancy and can be applied directly to clinical practice to allow a more quantitative understanding of the frequency, magnitude, and duration of changes in thyroid hormone requirement during pregnancy.

As a rule, levothyroxine replacement therapy should bring serum TSH levels into the normal range. Nonpregnant women who are replaced with levothyroxine are usually adjusted to maintain TSH at 0.2 mIU/L or greater to avoid symptomatic hyperthyroidism. By contrast, in pregnancy, treatment is often targeted to FT4 values (by IA) in the mid- to upper normal range as a result of known independent effects of human chorionic gonadotropin on TSH. Usually, a levothyroxine dose adequate to normalize TSH levels also results in FT4 concentrations that are slightly elevated or in the upper half of the normal reference interval. The higher FT4 values likely reflect the need to generate from (exogenous) levothyroxine, the 20% of the daily T3 production rate otherwise derived from the thyroid gland.

Levothyroxine dose adjustments are often necessary in pregnancy. Based on preliminary data obtained in our laboratory, nonpregnant pharmacokinetic parameters are not consistent with levothyroxine pharmacokinetic estimates projected in the published literature.³² Levothyroxine was absorbed slowly with a median time of maximum drug concentration of 8 hours. The mean oral clearance is slower and mean serum half-life was longer in pregnant women ($P < 0.039$). The area under the curve was significantly higher in pregnant women ($P < 0.03$). Future work will focus on a larger sample size, the mechanism responsible for the changes in pharmacokinetics, and whether these changes should necessitate dose schedule changes in pregnancy.

In conclusion, pregnancy-associated changes in thyroid hormone economy are of significant clinical relevance to women with established hypothyroidism because they usually result in increased levothyroxine dose requirements by the pregnant women. The vast majority of hypothyroid women require an increase in their prepregnancy dose of levothyroxine to prevent gestational hypothyroidism and its associated morbidity. The amount of this increase varies widely with the median estimated to be 40% to 50% above the preconception replacement dose and is related, at least in part, to the degree of residual thyroid function. Abnormal maternal gestational thyroid function tests are associated with a variety of maternal and fetal issues, including spontaneous miscarriages and preterm delivery. Pregnancy-specific reference intervals are term-specific, analytical method-specific, geographically specific, and vary with ethnicity.

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