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Practical Manual of

Thyroid in Pregnancy

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JAYPEE

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CHAPTER 2

Physiological Changes in Thyroid Function during Pregnancy

Shraddha Joshi Shastri, Vijaya Deepthi M

INTRODUCTION

The prevalence of thyroid disorders in pregnant women in the Indian Subcontinent is high with some studies showing 33.9%.[1] After Diabetes, they are the most common endocrine disorder found in pregnant women. A 2021 meta-analysis of observational studies in India found the pooled prevalence of hypothyroidism to be 11.07%, subclinical hypothyroidism being the most common accounting for 9.51%.[2] Prevalence is more in inland areas as opposed to coastal areas probably due to iodine deficiency. Also, a varied prevalence is noted in the different ethnic groups that are seen in India. Hyperthyroidism is rarer with some studies showing a prevalence of 2.3%. As the fetus is dependent completely on maternal thyroxin, free T4 in the 1st trimester, untreated hypothyroidism can lead to suboptimal IQ and learning difficulties in academics. Other complications of untreated hypothyroidism include miscarriage, premature birth, growth restricted fetus, stillbirths.[3] Thyroid disorders are usually preexisting but can develop after conception. It is important for clinicians to detect thyroid disorders preconceptionally or early on in pregnancy and treat adequately to prevent the said complications.

Thyroid disorders may be seen as an increase in size of the thyroid gland or a change in level of thyroid hormones or the presence of autoantibodies that are developed that affect the mother as well as the fetus and the neonate once born. Hence, it is important to understand the physiology of the thyroid gland in pregnancy for the correct interpretation of the thyroid function tests in the various trimesters of pregnancy.[4]

NORMAL PHYSIOLOGIC CHANGES IN PREGNANCY

The state of pregnancy witnesses significant changes in size and function of the thyroid gland. Nearing term, the thyroid gland increases by almost a third in size. The increase in the size of thyroid gland is mainly due to hyperplasia and increased vascularity. Within the thyroid follicle, iodide is organified onto tyrosine residues in thyroglobulin to generate mono- and di-iodotyrosine, which couple to form T4, and to a lesser extent, T3. Most circulating thyroid hormone is T4, and it is largely protein-bound, mainly to thyroxine-binding globulin (TBG), others being thyroxine binding prealbumin or transthyretin, and albumin. Positive feedback from the thyroid-stimulating hormone (TSH) from anterior pituitary as it stimulates the thyroid epithelial receptors, increases the production and release of thyroxine **(Fig. 1)**.

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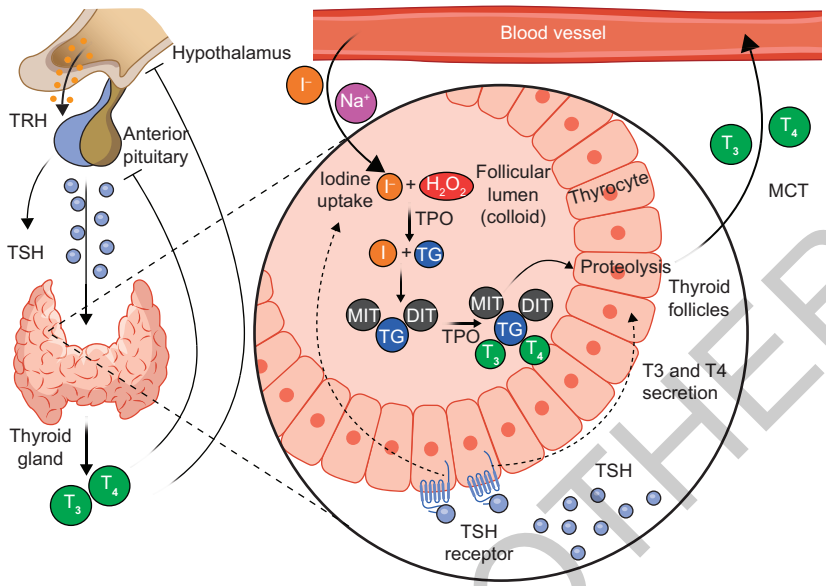


Fig. 1: Depicting normal production of thyroid hormones. (MCT: monocarboxylate transporter; TG: thyroglobulin; TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone)

Pregnancy is a state of increased metabolism, catering to a growing fetus which has its own metabolism. Hence, the size of thyroid gland increases and iodine uptake also increases. However, pregnancy is a euthyroid state. Hence, in spite of an increase in thyroid activity, the levels of TSH, free T4 and free T3 remain within the normal range.

Human chorionic gonadotropin (hCG) and chorionic thyrotropin are secreted by the placenta and they act on the thyroid and stimulate it.[5] This is due to similar molecular structure of α-hCG and TSH, and their respective receptors being similar. Toward the end of the 3rd month of pregnancy in humans, when hCG levels are highest, it causes significant thyroid-stimulation along with TSH.[6] During this time, blood levels of TSH often are suppressed. In conditions like molar pregnancy, hCG-secreting tumors, multiple pregnancies where hCG levels are very elevated, the thyrotropic activity is so much that it could cause clinical hyperthyroidism.

EFFECT OF HUMAN CHORIONIC GONADOTROPIN

As described by Glinoer D et al.,[7] TSH and α-component of hCG are similar. Their receptors are similar. Hence, hCG can bind to the TSH receptor on thyroid epithelial cells. As a result, it causes:

- Increased thyroxine production, free T4 levels in the 1st trimester
- Slight reduction in serum TSH levels in the 1st trimester **(Fig. 2)**

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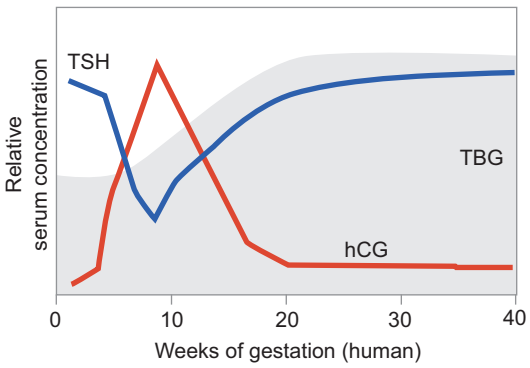


Fig. 2: Levels of human chorionic gonadotropin (hCG) against the gestational age of the fetus. (TBG: thyroxine-binding globulin; TSH: thyroid-stimulating hormone)

- Slight increase in the TSH levels in the 2nd trimester. TSH levels increase further in the 3rd trimester.

Hence, we require trimester cut-offs while interpreting TSH levels. Also, TSH values vary greatly with respect to the geographic location and ethnicity of the population.

Pregnancy, therefore, is a hypermetabolic state with increased demand on the thyroid gland. This, however, does not appear to affect normal individuals but in women with subclinical hypothyroidism, this extra demand in pregnancy can setup clinical disease.

EFFECT OF ESTROGEN ON THYROID-BINDING GLOBULIN

The main serum protein that transports thyroid hormones in blood is the TBG. It is the protein with the highest affinity for T4 (thyroxine). Estrogen stimulates increased production of binding proteins in the liver. The normal rise of estrogen levels during pregnancy is such that there is roughly a doubling in serum TBG concentrations. Rise in levels of TBG binds with free T4 and leads to lowered free T4 concentrations. Consequently, enhanced production of TSH by the anterior pituitary induces a rise in secretion of thyroid hormones. A new physiological equilibrium is noted between free and bound thyroid hormones and, thus, a significant increase in total T4 and T3 levels. The demand remains stable till term. Hence, there is a rise in total T3 and T4 levels. Free T3 and T4 levels are either normal or in the upper limits of normal. It is, therefore, recommended to check both serum TSH and unbound hormone levels. In usual practice, free T3 levels are not used. So, serum TSH and free T4 levels are used to evaluate thyroid function **(Fig. 3)**.

IODINE METABOLISM

The requirement of iodine increases from 150 to 250 μg/day during pregnancy. This is due to:

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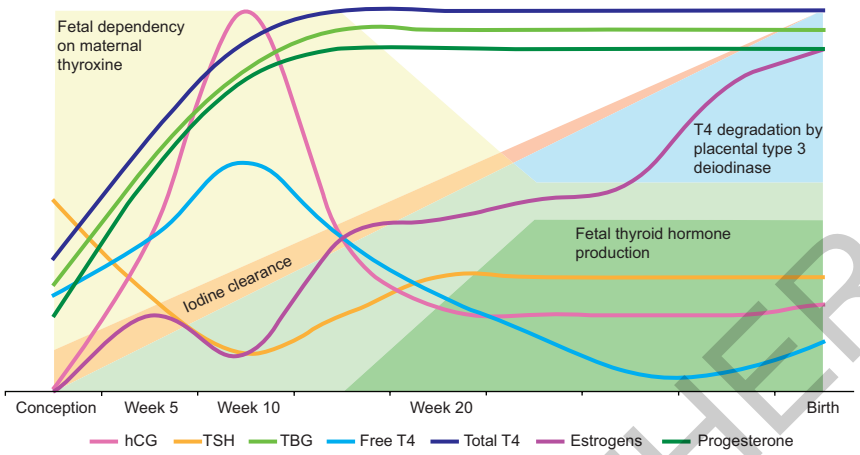


Fig. 3: Levels of various hormones against the gestational age of the fetus.

- Increased secretion of thyroid hormone by thyroid gland to maintain euthyroid status
- Increased renal iodine clearance
- Fetal iodine requirements

In inland areas with even mild or moderate iodine deficiency, gradual decrease in iodine stores is noted from the 1st to 3rd trimesters. Hence, pregnant women are advised to consume only iodized salt as India is one of the countries with areas of iodine deficiency. *Increasing iodine intake from the standard 100–150 µg/day to at least 200 µg/day during pregnancy is recommended by the World Health Organization.*

PLACENTAL TRANSFER OF THYROID HORMONES

As described by Calvo RM et al. (2002),[8] free T4 from the maternal circulation crosses the placenta and is the main source of thyroxine for the fetal brain development till 12 weeks of gestation until the fetal thyroid secretes hormones of its own. Maternal serum TSH does not cross the placenta; however, the TSH receptor stimulating and inhibiting hormones do cross the placenta and cause fetal hyper- or hypothyroidism, respectively. Maternal serum freely crosses the placenta and are taken up by the fetus. Hence, maternal iodine levels are critical for optimal fetal thyroid function. Radioactive iodine treatments are, hence, contraindicated in pregnancy as they enter fetal circulation and cause fetal thyroid ablation. Antithyroid drugs cross the placenta and suppress fetal thyroid function.

Thyroid Function Tests during Pregnancy

Serum TBG concentrations rise rapidly in early gestation and reach a plateau of roughly twice the nonpregnant level by around 15 weeks, remaining

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elevated for the rest of pregnancy. Total T4 shows a modest rise in the 1st trimester, whereas total T3 tends to increase more prominently.

As TBG increases, the free fractions of T4 and T3 transiently fall, but typically stay within the normal reference range. Maternal hCG and TSH show an inverse pattern: when hCG peaks at about 10 weeks' gestation, TSH reaches its nadir. Thereafter, as hCG concentrations decline, TSH gradually increases and then stabilizes for the remainder of pregnancy.

The *American Thyroid Association* has recommended that population based, trimester specific ranges for serum TSH values need to be ascertained after assessment of the local population. If population-specific data is unavailable, *4 μIU/mL to be considered as the upper limit of normal for TSH in pregnancy.*

Ministry of Health and Family Welfare, Govt. of India (2014), recommends *2.5 μIU/mL in the 1st trimester, 3 μIU/mL as the cutoff for TSH levels in the second and the third trimester.* These levels are based off of American Thyroid Association guidelines.[9]

As described by Tsuruta E et al.,[10] many of the pregnant women with hyperemesis gravidarum have thyroid profile laboratory values depicting hyperthyroidism. Higher levels of hCG are noted in these women and the severity of hyperemesis is directly related to the degree of hyperthyroidism, due to thyrotropic activity of the hCG. These clinical manifestations may be linked to a specific subpopulation of hCG molecules, specifically, hCG with reduced sialic acid content, having greater thyrotropic bioactivity. Treatment with antithyroid medication is recommended, if the symptoms of hyperthyroidism are supported by appropriate laboratory values.

PHYSIOLOGY OF THYROID IN THE FETUS AND THE NEONATE

Between 8 and 10 weeks of gestation, the human fetal thyroid gland develops the capacity to concentrate iodine and synthesize hormone at the same time that the pituitary begins to synthesize TSH. Fetus concentrates iodine and fetal thyroid starts producing thyroid hormones from 12 weeks onward. Until then maternal thyroxine is the main source for the fetal neurological development. Terminal stages of brain differentiation, including synaptogenesis, growth of dendrites and axons, myelination and neuronal migration seem to be profoundly affected by the presence of optimal levels of maternal thyroxin.[11]

In the absence of the pituitary gland, some thyroid development and hormone synthesis is possible but optimal function requires TSH. Development of the pituitary-thyroid axis is completed by 12–14 weeks. Significant increase in fetal TSH is paramount until 20 weeks for proper functioning of the axis independent of maternal thyroxin. As with

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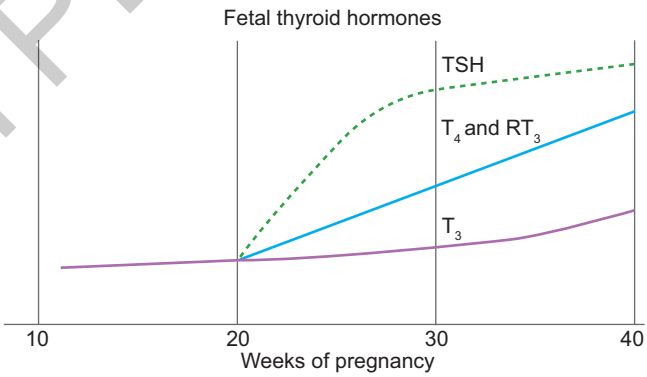
gonadotropins and other pituitary hormones, the rise in fetal thyroid activity parallels maturation of the hypothalamus and the establishment of the hypothalamic–pituitary portal circulation, which allows hypothalamic releasing hormones to reach the fetal pituitary. Fetal TSH concentrations increase and then level off around 28 weeks' gestation, remaining relatively high until delivery. Free T4 values climb steadily throughout this period, and by term, fetal T4 concentrations are higher than those of the mother **(Fig. 4)**. This pattern indicates a relative state of thyroidal hyperactivity in the fetus near term.[12]

During fetal life, T4 is the principal thyroid hormone produced, whereas both total and free T3 remain relatively low across gestation. In contrast, concentrations of reverse T3 (rT3) are high and tend to rise in parallel with T4. Most rT3 is generated by peripheral conversion of T4.[13] This pattern means that much of the fetal T4 pool is rapidly inactivated to rT3, which helps to limit energy expenditure and conserve substrates. At the cellular level, fetal thyroid hormones exert their effects by binding to nuclear thyroid hormone receptors and regulating the transcription of target genes.

Thyroid hormone receptors are widely distributed in the fetal brain, and present prior to the time the fetus is able to synthesize thyroid hormones.

Before the fetal thyroid gland becomes active, that is in the early weeks of pregnancy, the fetal brain is dependent on the placental transport of maternal T4. Hence, both overt and subclinical maternal hypothyroidism are associated with increased risks of miscarriage, preeclampsia, low birth weight, preterm delivery, and a decrease in IQ in the children.

Soon after birth, serum TSH concentrations increase rapidly to a peak at 30 minutes of age. They fall to baseline values by 48–72 hours. In response to this increase in TSH, total T4 and free T4 increase to peak values



Relationship of weeks of pregnancy with fetal thyroid hormone levels

Fig. 4: Fetal thyroid-stimulating hormone (TSH) rises and reaches a plateau around 28 weeks of pregnancy. Free T4 concentration increases progressively, reaching adult levels near term. T4 is the major thyroid hormone secreted by the fetus.

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by 24–48 hours of age. T3 levels increase even more, peaking by 24 hours of life. By 3–4 weeks of life, the thyroidal hyperactivity disappears. The postnatal rise in TSH is associated with a prolactin rise, suggesting that both are increased in response to TRH. The TRH surge is thought to be a response to rapid neonatal cooling.

CONCLUSION

Thyroid physiology undergoes profound and predictable adaptations during pregnancy to meet the metabolic demands of the mother and the developing fetus. These changes, driven primarily by rising levels of hCG, estrogen-induced increases in TBG, and enhanced iodine requirements, result in altered thyroid function tests that necessitate trimester- and population-specific reference ranges for accurate interpretation. Pregnancy itself remains a euthyroid state; however, women with limited thyroid reserve or pre-existing thyroid dysfunction may decompensate, leading to clinically significant disease.

Maternal thyroxine plays a critical role in early fetal neurodevelopment, particularly in the 1st trimester before the fetal thyroid becomes functional. Both overt and subclinical maternal hypothyroidism are, therefore, associated with adverse obstetric outcomes and long-term neurocognitive effects in the offspring. Adequate iodine intake, early identification of thyroid dysfunction, and appropriate monitoring are essential to ensure optimal maternal and fetal outcomes.

A clear understanding of the dynamic interplay between maternal, placental, and fetal thyroid physiology is fundamental for clinicians caring for pregnant women. Accurate interpretation of thyroid function tests, awareness of regional and ethnic variations, and timely intervention can significantly reduce preventable complications, underscoring the importance of thyroid health as an integral component of comprehensive antenatal care.

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Kiran Kurtkoti MBBS DGO DFP DNB FICOG FMCOG is a distinguished leader in the field of obstetrics and gynecology, currently serving as the President of the Association of Maharashtra Obstetric and Gynaecological Societies (AMOGS). He is the Director of Shashwat Multi-Speciality Hospitals India Pvt. Ltd, Pune, Maharashtra, India, and the Founder President of both the Maharashtra College of Obstetricians and Gynaecologists and the AMOGS Teachers Forum, organizations dedicated to advancing education and practice in women's health. He has been recognized for his outstanding contributions with prestigious awards, including the Dr Siuli Rudra Sinha Prize and the Dr CS Dawn Prize. He is also an accomplished author, having contributed numerous chapters to books on critical topics such as recurrent pregnancy loss (RPL) and medical termination of pregnancy (MTP).



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