THYROID FUNCTION TESTS

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How can Thyroid function be investigated?

- Tests for investigation of Thyroid dysfunction can be separated into Two categories:
- Tests to established Thyroid status:
  - Measurement of **[TSH]** in Plasma or Serum,
  - Measurements of **[Thyroid Hormones]** {T4 and T3} in Plasma or Serum;

- Tests to elucidate cause of Thyroid dysfunction:
  - Thyroid Auto-antibody,
  - Serum [Thyroglobulin],
  - Thyroid Peroxidase,
  - Biopsy of the Thyroid,
  - Ultrasound and Isotopic Thyroid Scanning;

- **IMPORTANT TO NOTE**:
- Thyroid status MUST be determined before using tests to elucidate cause of dysfunction;

What tests are used to determine Thyroid status?

- **Thyroid-Stimulating Hormone (TSH)**:
  - **Single most sensitive**, **specific** and **reliable test** of Thyroid status in both overt and subclinical thyroid dysfunction,
  - Can be used to diagnose Primary Hypothyroidism,
  - Can be used to differentiate Primary from Secondary Hypothyroidism,

- **Thyroid-Releasing Hormone (TRH)**:
  - Test to evaluate patients with Hyperthyroidism and Hypothyroidism;
  - Helpful in differential diagnosis of Hypothyroidism;

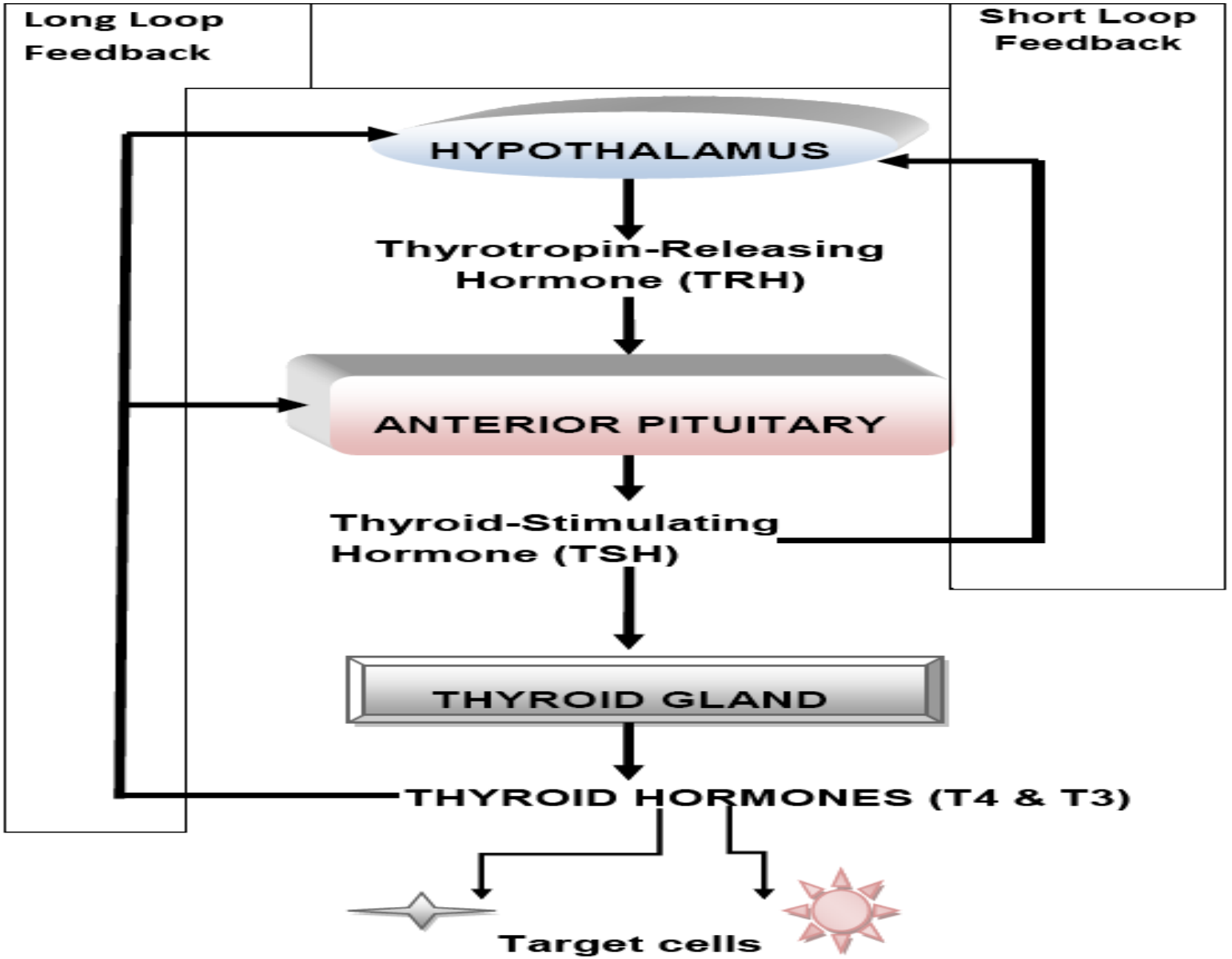
- **Free Thyroxine (FT4)**:
  - Used to evaluate Thyroid Function,
  - Used to diagnose Hyperthyroidism or Hypothyroidism,
- **Free Triiodothyronine (F T3)**:
  - Used to diagnose Thyroid Function,
  - Used to monitor replacement and suppressive thyroid therapy;

- **Thyroid-Binding Globulin (TBG):**
  - Plasma [TBG], major carrier protein of thyroid hormones,
  - Used to evaluate patients with abnormal Total [T4] or [T3],
  - Must be done with Total [T4] and [T3], for interpretation;
- **Total Thyroxine (Total T4)**:
  - Used in assessing Thyroid Function,
  - Used to monitor Replacement and Suppressive Therapy,
- **Total Triiodothyronine (Total T3)**:
  - Used to evaluate Thyroid Function,
  - Mainly used to diagnose Hyperthyroidism,
  - Used to monitor Replacement and Suppressive therapy,

How significant is plasma TSH test (TSH, Thyrotropin)?

- Reference range of [TSH]: 0.4 to 4.5mU/L,
- TSH release is very sensitive to alterations in plasma **[Thyroid Hormones],**
  - Decrease in Plasma [Thyroid Hormones] causes Increase secretion of TSH,
  - Increase in Plasma [Thyroid hormones] suppresses secretion of TSH,
- Feedback control mechanism in HPT axis (**Fig. 1**)

Fig. 1: HPT-axis



- Measurement of [TSH] in basal blood sample provides one of the single most sensitive, specific and reliable test of Thyroid status in both Overt & Subclinical Thyroid dysfunction;
  - In **Primary Hypothyroidism**: Plasma [TSH] is increased above Normal reference range (**Why?**),
  - In **Primary Hyperthyroidism** (e.g., Thyrotoxicosis) Plasma [TSH] is reduced below Normal reference range (**Why?**),

- In Thyrotoxicosis plasma [TSH] is low; **Why?**
  - Thyroid produces too much T4 and T3, which then suppresses release of TSH via Negative Feedback control of HPT-axis;

- **TAKE NOTE**:

1. When lab result shows raised plasma [TSH], then plasma FT4 should be measured;
2. When lab result shows low plasma [TSH], then both plasma FT4 and FT3 should be measured;

Why should FT4 & FT3 be measured in the second case?

- Because the Thyroid gland over secretes only T3, in patients with **T3 Toxicosis,** thus both FT4 & FT3 should be measured to diagnose this form of Thyrotoxicosis;
  - Such condition occurs in patients who previously had Thyroidectomy or had been treated with Radioactive Iodine for Thyrotoxicosis in the past,
- **Exceptions**: both raised and undetected plasma [TSH] may be seen in some Euthyroid patients;

How are results of plasma or serum [TSH] tests interpreted?

- Use High Sensitivity TSH Assay to determine [TSH];
  - Normal Range: Plasma [TSH] is 0.4 to 4.5mIU/L,
- **TSH is under**:
  - Negative Feedback Control of plasma FT4 & FT3,
  - Positive Control of TRH from Hypothalamus;
- Deficiency of FT4 or FT3: Plasma [TSH] increases;
- **Plasma [TSH] greater than 20mIU/L** is good indicator of **Primary Thyroid Failure**;
- Plasma [TSH] between 4.5 and 15mIU/L is borderline thyroid dysfunction, it requires careful evaluation;

- In **Secondary Hypothyroid** status, plasma [TSH] may be low, normal or borderline range;
- Plasma [TSH] above 15mIU/L is good evidence for Primary Hypothyroidism;
- Plasma [TSH] below 5 is very good evidence against Primary Hypothyroidism;
- Presence of Low [FT4] with [TSH] less than 10mUI/L strongly suggests Secondary Hypothyroidism;
- High plasma [FT4] and [FT3] suppresses plasma [TSH] level, in almost all case of Hyperthyroidism, thus, [TSH] is falls below 0.3mUI/L or less than 0.1mIU/L,

Interpreting the use of plasma [TSH] for monitoring

- Plasma [TSH] can be used to follow patients being treated with Thyroid Hormones;
  - High plasma [TSH] indicates under-treatment,
  - Low plasma [TSH] usually indicates over-treatment,
- Abnormal [TSH] should be interpreted with [FT4] or [FT3] before modifying therapy, because plasma [Thyroid Hormones] changes faster than [TSH],
- Patients recently started using Thyroid Hormone, or who are non-compliant until shortly before a visit to the doctor may have normal [FT4] and [FT3], though their [TSH] may still be elevated;

- Plasma [TSH] may be affected by acute illness and several medications, including Dopamine and Glucocorticoids (Non-Thyroidal Illness, NTI);
- **TAKE NOTE**:
- Plasma [TSH] & [FT4] are used to differentiate Secondary and Primary Thyroid dysfunctions;
  - Decrease [FT4] and Normal or Elevated [TSH] may indicate Primary Thyroid disorder; **Why?**
  - Decrease [FT4] with decreased [TSH] indicates Secondary Thyroid disorder; **Why?**
    - **Always refer to HPT-axis for answers!!**

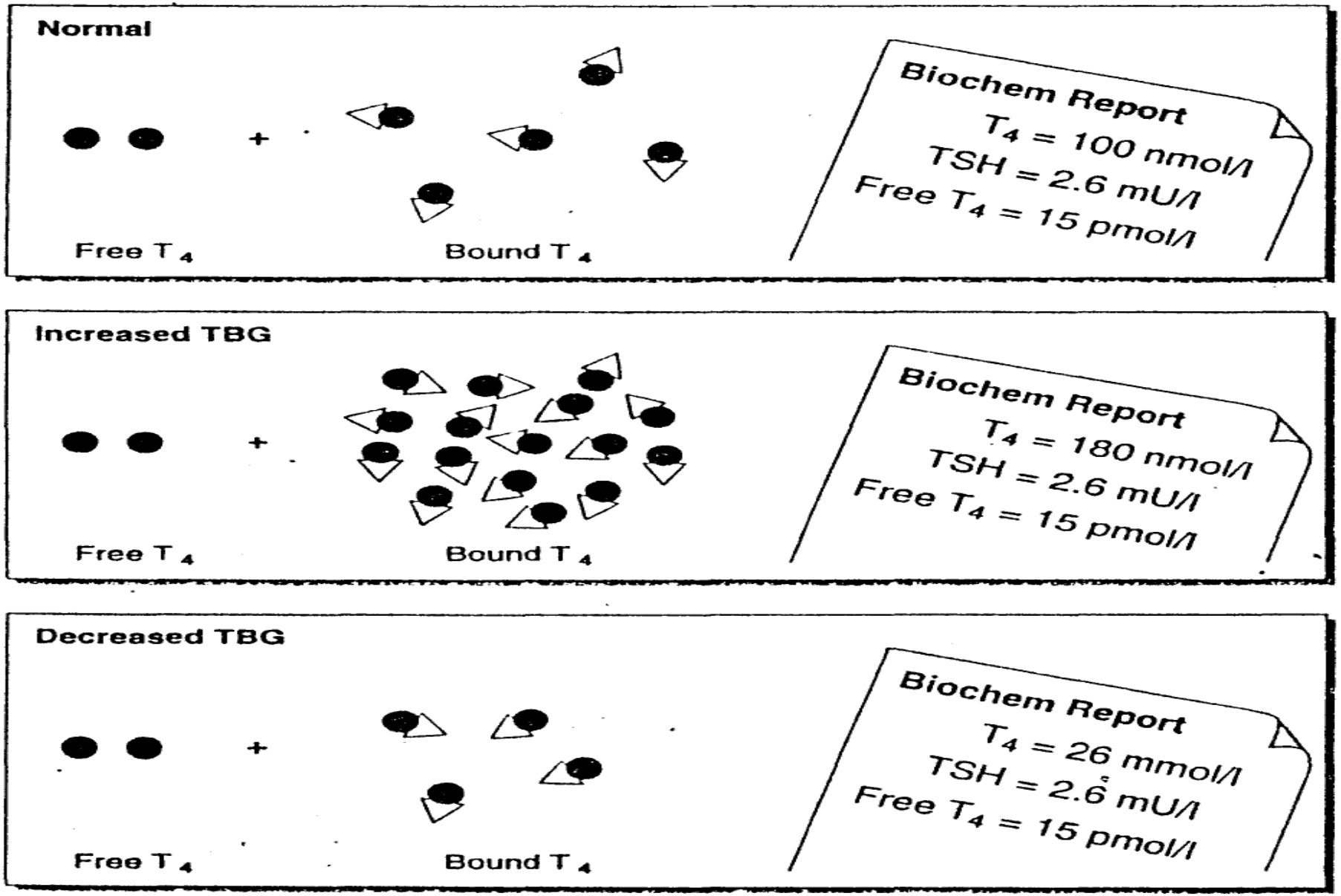
Significance of FT4 & FT3 tests for Thyroid Function

- Plasma [FT3] (Reference range: 3 to 9pmol/L);
- Plasma [FT4] (Reference range: 10 to 27pmol/L);
- Plasma [FT3] and [FT4] can be determined by:
  - Radioimmunoassay (RIA),
  - Enzyme-Linked Immunosorbent Assay (ELISA),
  - Enzyme Immunoassay (EIA),
  - Microplate Enzyme Immunoassay (MEIA);
- Plasma FT4 is reliable test in combination with [TSH],
- Plasma FT3 in combination with [TSH] are the recommended tests in most cases;
- Final choice of test should be made by the Physician;

What is the Thyroxine Binding Globulin (TBG) test?

- TBG Test include the following:
  - Determination of Plasma [TBG],
  - Determination of Plasma [Total T4],
  - Determination of Plasma [FT4],
- INTERPRETATION OF Results of TBG Test:
- See **Fig. 2**

Fig. 2: TBG Test and Interpretation of results (Gaw et al 1999)



The interpretation of thyroid hormone results when TBG concentration changes.

IMPORTANT TO NOTE

- Conditions that causes increase in Plasma [TBG]:
  - Pregnancy,
  - Hormone Replacement Therapy,
  - Oral Contraceptives,
  - Infections,
  - Hepatitis,
- Conditions that causes decrease in Plasma [TBG]:
  - Hypoproteinemia,
  - Nephrotic syndrome,
  - Malnutrition
- **Plasma [FT4] & [FT3] are not affected by changes in plasma [TBG],**

How significant is plasma Total Thyroxine (T4) test?

- Plasma [Total T4] (Reference range: 70 to 150 nmol/L);
- Plasma [Total T4] can be determined by:
  - Radioimmunoassay (RIA),
  - Enzyme-Linked Immunosorbent Assay (ELISA),
  - Enzyme Immunoassay (EIA),
  - Microplate Enzyme Immunoassay (MEIA);
- All labs should **STOP** measuring Plasma [Total T4], because it is affected by many factors;

What factors affect Interpretation of [Total T4] results?

- Plasma [Total T4] depends on Plasma [TBG], thus results should be interpreted with care;
- Plasma [TBG] may be Low in some patients with Inherited but harmless deficiency,
  - Plasma [Total T4] is Low in these patients, but plasma [FT4] may be Normal;
- Plasma [TBG] may be elevated in Pregnant women and in Women using Oestrogen-containing Oral Contraceptive Pill,
  - Plasma [Total T4] may be elevated well above Reference range, but plasma [FT4] may be normal;
- Plasma [FT4] is recommended in conditions where [TBG] may be altered, e.g., Pregnancy, users of Oral Contraceptive Pill, patients with Nephrotic Syndrome

How significant is plasma Total Tri-Iodothyronine (T3) test?

- Plasma [Total T3] (Reference range: 1.2 to 2.8nmol/L);
- Plasma [Total T3] can be determined by:
  - Radioimmunoassay (RIA),
  - Enzyme-Linked Immunosorbent Assay (ELISA),
  - Enzyme Immunoassay (EIA),
  - Microplate Enzyme Immunoassay (MEIA);
- Gradually laboratories are moving over to FT3 measurements as more FT3 assays become available;

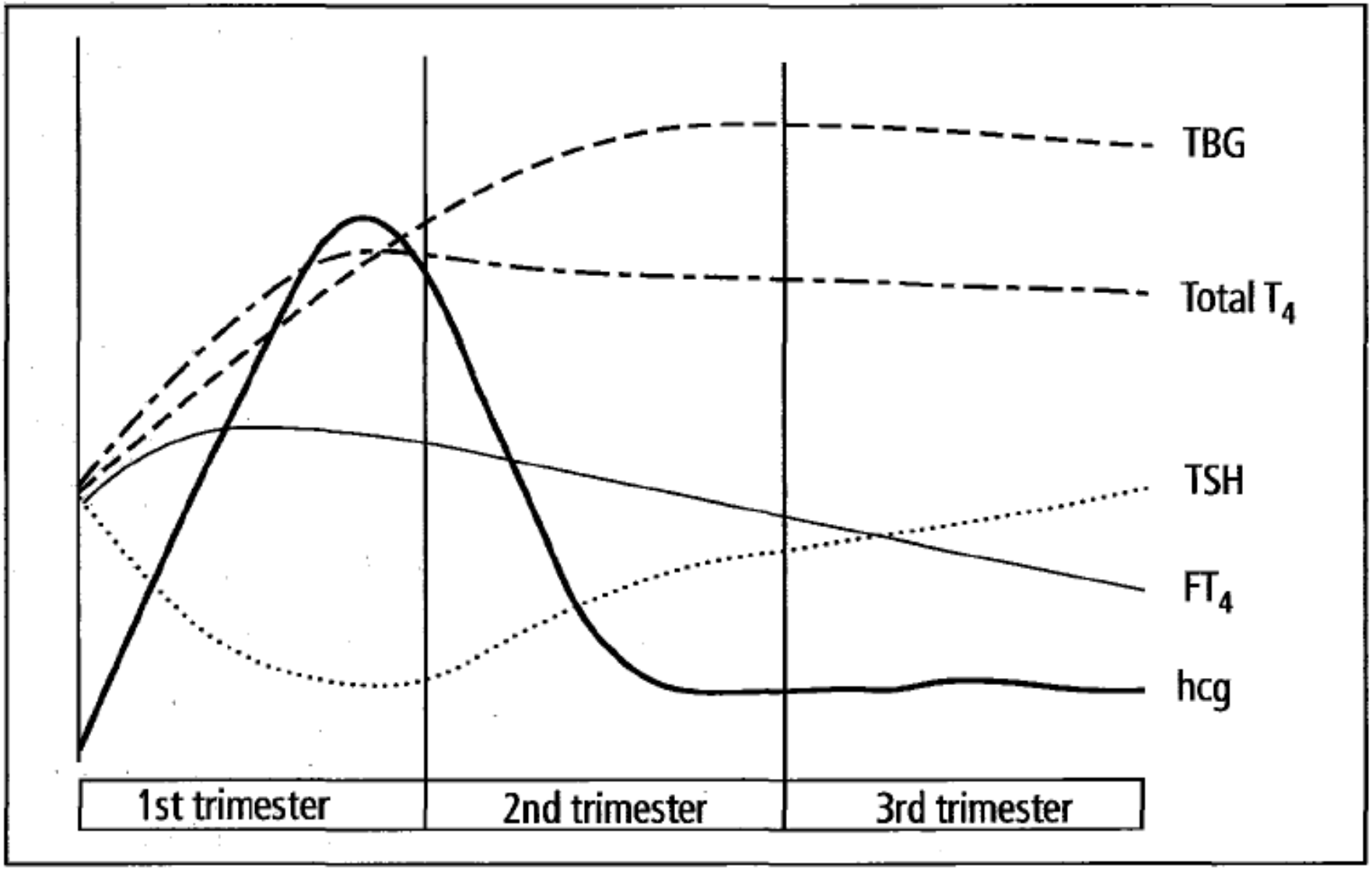
IMPORTANT TO NOTE

- Conversion of T4 to T3 depends on a number of situations such as, Chronic illness or Surgical stress, which cause a fall in T4 to T3 conversion (called low T3 syndrome);
- Starvation can alter T4 to T3 conversion with a fall in T3 as the body tries to reduce its metabolism to conserve energy;
- Plasma [Total T3] is useful test for Hyperthyroidism, because values are often raised proportionately more than Plasma [Total T4];
- Plasma [Total T3] assay is of no value in investigating patients with suspected Hypothyroidism, because plasma [Total T4] is usually low;

How reliable is Thyroid function test for assessing Thyroid status during Pregnancy?

- Plasma [TSH] is reliable indicator of Thyroid status during the **2nd and 3rd** Trimesters of pregnancy;
- Plasma [TSH] is not a reliable indicator during the 1st Trimester (**Why?**)
  - Because Plasma [TSH] is usually low,
  - May be due to weak Thyrotrophic effect of Placental hCG (Human Chorionic Gonadotrophin), which is high during 1st Trimester;
- Plasma [FT4] increases during 1st Trimester, then decline later; (**Fig. 3**)
- Plasma [TBG] increases during pregnancy, causing elevation in Plasma [Total T4] and [Total T3];

Fig. 3: Changes in plasma [TSH], [FT4], [TBG] & [h CG] during pregnancy (Beckett et al 2008)



SUMMARY

- Plasma [TSH] assay is the single best test for assessing Thyroid Status;
- Plasma [TSH] is elevated in Primary Hypothyroidism;
- Plasma [TSH] is low in Primary Hyperthyroidism;
- Normal Plasma [TSH] usually excludes Primary Thyroid Disorder;
- Plasma [FT4] and [TSH] can be used to assess severity of Thyroid disease and distinguish Subclinical from Overt disease;
- Plasma [FT3] and [TSH] can be used to determine severity of Hyperthyroidism and to identify patients with T3 Hyperthyroidism;

- Plasma [Free Thyroid Hormones] correlates more closely with Thyroid Status than Plasma [Total Thyroid hormones], which are heavily influenced by changes in Plasma [TBG];
- Thyroid Function Tests (TFT) are often abnormal in patients with Non-Thyroidal Illness (NTI), and should not be requested in hospitalised patients unless the presenting complaint is due to Thyroid Disease;

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