ENDOCRINOLOGY
SPECIAL INTEREST GROUP

THYROID DYSFUNCTION AND REPRODUCTION

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Dear Friends,

Greetings from ISAR,

ART is on the run and so are we running, but in this rut of number games, somewhere we forget the right ingredients of the recipe for a healthy future generation. ISAR this year has taken up the task of Moving towards, “Better practices, Better outcomes” and are touching upon many areas which will improve our understanding and help us manage our patients well. keeping this in mind a series of monographs are being prepared for easy reading on topics of academic interest which will impact outcomes in our practices and I am very happy to present to you our first of the series on a much talked about, yet lesser understood topic of “Thyroid Dysfunction and reproduction”

“There is no limit to how good you can get in pursuit of perfection.”
Sachin Kumar Puli

Let us keep our pursuit towards perfection on.

Thanks to the wonderful efforts of Dr Madhuri Patil and Special Interest Group team on Reproductive endocrinology for this very crisp document for easy reference and understanding.

Look forward to receiving many more similar ones.

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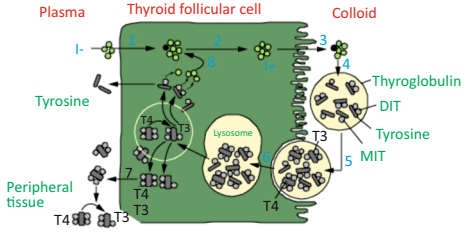
Role of thyroid in Female reproduction

Introduction

Thyroid dysfunction affects many organs including

- Male and female gonads
- Interferes with human reproductive physiology
- Reduces the likelihood of pregnancy
- Adversely affects pregnancy outcome

Thus thyroid function evaluation becoming relevant in the algorithm of reproductive dysfunction

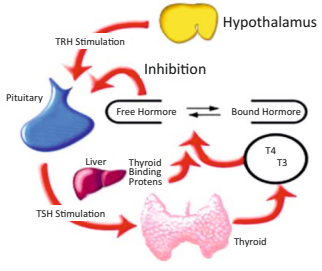


Thyroid Produces and Secretes two principal Metabolic Hormones Thyroxine (T_4) and triiodothyronine (T_3) which are

- Required for homeostasis of all cells
- Influence cell differentiation, growth, and metabolism
- Considered the major metabolic hormones because they target virtually every tissue

Functions of Thyroid-Stimulating Hormone (TSH)

- Regulates thyroid hormone production and secretion
- Is regulated by the negative feedback action of T_4 and T_3



Role of thyroid in Reproduction

Thyroid gland and gonadal axis interact continuously before and during pregnancy

- Adequate levels of circulating thyroid hormones (TH) are of primary importance for normal reproductive function
- T3 modulates FSH and LH action on steroid biosynthesis
- Multiple T3 binding sites have been identified in mammalian granulosa and stromal cells, and oocytes
- Any impairment of T3 concentrations is a cause of disruption of the normal female reproductive function

References

1. Bjoro T, Holmen J, Kru€ger O, Midthjell K, Hunstad K, Schreiner T, et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). Eur J Endocrinol 2000;143:639-47.
2. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev 2010;31:702-55.

Patients who are likely to be at increased risk of thyroid dysfunction

- Family history of thyroid disease
- Presence of goiter
- Patients with other autoimmune diseases (e.g. type 1 diabetes, coeliac disease)
- Patients with dyslipidemia (high cholesterol and/or high triglyceride)
- Those taking drugs like amiodarone, lithium, interferon

- Past history of neck surgery or irradiation
- Recent exposure to iodinated radiological contrast agents
- Suspicious thyroid symptoms postpartum or a previous episode of postpartum thyroiditis
- Chronic cardiac failure, coronary artery disease, arrhythmias, pulse >90/min and hypertension
- Menstrual disturbance or unexplained infertility
- Some genetic conditions (e.g. Down, Turner syndromes)
- Previous history of miscarriage or ore-term labour
- Obesity

There was high prevalence of hypothyroidism among women with family history, autoimmune disorder, dyslipidaemia, chronic heart disease, obesity, sub-fertility, certain genetic conditions like Down and Turners Syndrome and those on certain drugs like amiodarone, lithium and interferon

References

1. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 2000; 132(4):270–278.
2. Duntas LH, Orgiazzi J, Brabant G. The interface between thyroid and diabetes mellitus. Clinical endocrinology. 2011 Jul;75(1):1-9.
3. Jefferys A, Vanderpump M, Yasmin E. Thyroid dysfunction and reproductive health. The Obstetrician & Gynaecologist. 2015 Jan 1;17(1):39-45.
4. Molina MJ, Mayor AM, Franco AE, Morell CA, López MA, Vilá LM. Prevalence of systemic lupus erythematosus and associated comorbidities in Puerto Rico. J Clin Rheumatol. 2007; 13(4):202– 204.
5. Rotondi M, Magri F, Chiovato L. Thyroid and obesity: Not a one way-interaction. J Clin Endocrinol Metab. 2011; 96(2):344–346.
6. Tagami T, Kimura H, Ohtani S, et al. Multi-center study on the prevalence of hypothyroidism in patients with hypercholesterolemia. 2011; 58(6):449–457.
7. Wang C. The relationship between type 2 diabetes mellitus and related thyroid diseases. Journal of diabetes research. 2013;2013.

Causes of thyroid Disease

Causes of hypothyroidism

Primary Hypothyroidism

1. Autoimmune disease
   - Atrophic thyroiditis
   - Hashimoto's thyroiditis
2. Iatrogenic
   - Radiotherapy
   - Thyroidectomy
   - Antithyroid drugs
3. Transient
   - Subacute thyroiditis
   - Postpartum thyroiditis
4. Iodine deficiency

Secondary Hypothyroidism

- Pituitary Failure
- Pituitary Tumour

Tertiary Hypothyroidism

- Hypothalamic failure

Causes of hyperthyroidism

1. Autoimmune
   - Grave's disease
2. Toxic nodular goiter
3. Toxic adenoma
4. Subacute thyroiditis
5. Iodine therapy
6. Drugs
   - Amiodarone
   - Lithium

References

Jefferys A, Vanderpump M, Yasmin E. Thyroid dysfunction and reproductive health. The Obstetrician & Gynaecologist. 2015 Jan 1;17(1):39-45.

Screening infertility patients for thyroid dysfunction

- Thyrotoxicosis, subclinical hypothyroidism and overt hypothyroidism, and autoimmune thyroid disease linked with reduced fertility
- Screening all symptomatic patients essential
- But today screening asymptomatic patients both female and male has become mandatory, though initially routine or opportunistic screening of asymptomatic patients was not recommended as there was no evidence supporting the benefits of treating asymptomatic patients
- Most situations use TSH as the sole test for thyroid function
- Addition of Free T4 and thyroid antibody helps in identifying subclinical hypo and hyper thyroidism and thyroid autoimmune disorders
- As 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 T4) should prompt a repeat serum TSH level and for thyroid autoantibodies to be checked. If the serum TSH persists above 2.5 mU/l
- Women who are euthyroid with AITD, close monitoring of thyroid function if pregnancy results and monitoring of fetal wellbeing and subsequently neonatal review is essential

References

1. Baskin HJ, Cobin RH, Duick DS, et al. American Association of Clinical Endocrinologists American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002; 8(6):457– 469.
2. Gillett M. Subclinical hypothyroidism: subclinical thyroid disease: scientific review and guidelines for diagnosis and management. Clin Biochem Rev 2004;25:191–4.
3. Jefferys A, Vanderpump M, Yasmin E. Thyroid dysfunction and reproductive health. The Obstetrician & Gynaecologist. 2015 Jan 1;17(1):39-45.
4. Poppe K, Velkeniers B. Female infertility and the thyroid. Best Pract Res Clin Endocrinol Metab 2004;18:153–65.
5. Prummel MF, Wiersinga WM. Thyroid peroxidase autoantibodies in euthyroid subjects. Best Pract Res Clin Endocrinol Metab 2005;19:1–15.
6. Unuane D, Velkeniers B, Anckaert E, Schiettecatte J, Tournaye H, Haentjens P, et al. Thyroglobulin autoantibodies: is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? Thyroid 2013;23:1022-8.
7. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43:55-68.

Interpreting Results of thyroid tests and possible explanations for various result combinations

	High T4	Normal T4	Low T4
High TSH	Irregular use of thyroxine Amiodarone Pituitary hyperthyroidism (TSH-producing pituitary tumour - rare) Thyroid hormone resistance (very rare)	Subclinical Hypothyroidism T4 under replacement	Primary hypothyroidism
Normal TSH	As above Some drugs (steroids, Beta-blockers, NSAIDS) Non-thyroidal illness T4 replacement (sometimes stablises With normal TSH and FT4)	Normal	Some drugs (anticonvulsants, anti-T3, anti-T4) Pituitary or hypothalamic hypothyroidism Severe non - thyroidal illness
Low TSH	Primary hyperthyroidism	Subclinical hyperthyroidism Subtle T4 over replacement Non-thyroidal illness	Pituitary or Hypothalamic hypothyroidism Severe non-thyroidal illness

The above table gives the diagnosis and probable cause of thyroid disease with TSH and T4 values

Hormonal changes in Thyrotoxicosis

Changes in SHBG	Normal T4	Low T4
• Increased SHBG • Estrogen level 2-to 3-fold higher compared to normal women during all phases of menstrual cycle • Metabolic clearance rate of E2 is decreased due to increased binding to SHBG • Progesterone levels decreased w	• Mean plasma levels of testosterone and ASD increase • Production rates of testosterone and ASD are significantly elevated • Conversion ratio of ASD to estrone, and testosterone to E2 is increased	• Mean LH levels in both the follicular and luteal phases of menstrual cycle are significantly higher • LH peaks may be absent in patients with amenorrhea • Baseline FSH levels may be increased • Augmented Gn response to GnRh

Hyperthyroidism results in

- Menstrual disturbances -
  - Amenorrhea
  - Oligomenorrhea
  - Hypomenorrhea
  - Anovulation
- Reduced Fertility in both subclinical and overt hyperthyroidism
- Suppressed serum TSH was more frequent in all infertile women when TPO-Antibodies were positive as compared to women who were not TPO-Antibodies positive (7 vs 1%; P <0.05)
- One study has shown doubling of miscarriage rate in a group of hyperthyroid women without AITD, compared with euthyroid controls. The proposed mechanism was a toxic effect of excess thyroid hormone on embryogenesis.

References

1. Akande EO, Hockaday TD. Plasma oestrogen and luteinizing hormone concentrations in thyrotoxic menstrual disturbance. Proc R Soc Med 1972;65:789–90.
2. Kakuno Y, Amino N, Kanoh M, Kawai M, Fujiwara M, Kimura M, et al. Menstrual disturbances in various thyroid diseases. Endocr J 2010;57:1017–22.
3. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Batrinos M. Menstrual disturbances in thyrotoxicosis. Clin Endocrinol 1994;40:641–4.
4. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev 2010;31:702–55.
5. Ohara N, Tsujino T, Maruo T. The role of thyroid hormone in trophoblast function, early pregnancy maintenance, and fetal neurodevelopment. J Obstet Gynaecol Can 2004;26:982–90.
6. Pontikides N, Kaltsas Th, Krassas GE. The LH, FSH, PRL and progesterone levels in thyrotoxic female patients before and after treatment. J Endocrinol Invest 1990;13(Suppl 2):164.
7. Tanaka T, Tamai H, Kuma K, Matsuzuka F, Hidaka H. Gonadotropin response to luteinizing hormone releasing hormone in hyperthyroid patients with menstrual disturbances. Metabolism 1981;30:323–6.

Hormonal changes in Hypothyroidism

Changes in SHBG and E2	Changes in androgens	Changes in FSH and LH
• Plasma blinding activity of SHBG decreased which result in decreased plasma concentrations of E2, but increase in unbound fractions • Decreased rates of metabolic clearance of estrone • Increase in excretion of 2 oxygenated estrogen	• Decreased rates of metabolic clearance of ASD • Plasma blinding activity of SHBG is decreased which result decreased plasma concentration o testosterone, but increase in unbound fractions • Increase in peripheral aromatization • 5 alpha/beta ratio of androgen metabolites decreased	• Blunted or delayed LH response to GnRH • In presence of delayed LH response, serum PRL concentration may be increased due to hypothalamic TRH increasing both TSH and PRL secretion

- Mean duration of infertility was significantly longer in women with hypothyroidism 3.8 vs. 2.6 years (P< 0.005). Higher serum TSH levels have greater menstrual disturbance and anovulatory cycles.
- In women with PCOS, a significant association was seen between thyroid dysfunction as reflected by TSH > 2 mIU/l, and insulin resistance, which was independent of age and BMI
- Greater than threefold increased risk of abnormal CCCT in infertility patients with hyperprolactinemia and abnormal thyroid function as compared with age-matched controls (18.6% vs 6.98 %). Therefore, patients with hyperprolactinemia and thyroid dysfunction with elevated FSH levels should have CCCT repeated after their endocrinopathy is corrected
- With COS, SCH may occur, which may alter treatment outcome
- Marked rise in E2 levels associated with controlled ovarian stimulation (COS) (Rapid 10-fold E2 increase after COS - 3492 vs. 359 pmol/L (P < 0.0001)) induces an additional strain on the hypothalamic-pituitary-thyroid axis and impairs TH distribution and kinetics.
- Elevated E2 levels induce a marked increase in serum T4- binding globulin (TBG)concentrations (34 vs. 25 mg/liter; P < 0.0001)
- Serum TSH increased significantly after COS and are higher as compared with pre-COH values, (3.0 verses 2.3 mIU/liter P < 0.0001)
- Severely impair thyroid function following COS without thyroid autoimmunity is transient, while in the presence of thyroid autoimmunity might lead to abnormal thyroid function throughout pregnancy if pregnancy occurs
- Hypothyroidism does not increase the risk of miscarriage in the absence of AITD being and subsequently neonatal review is essential

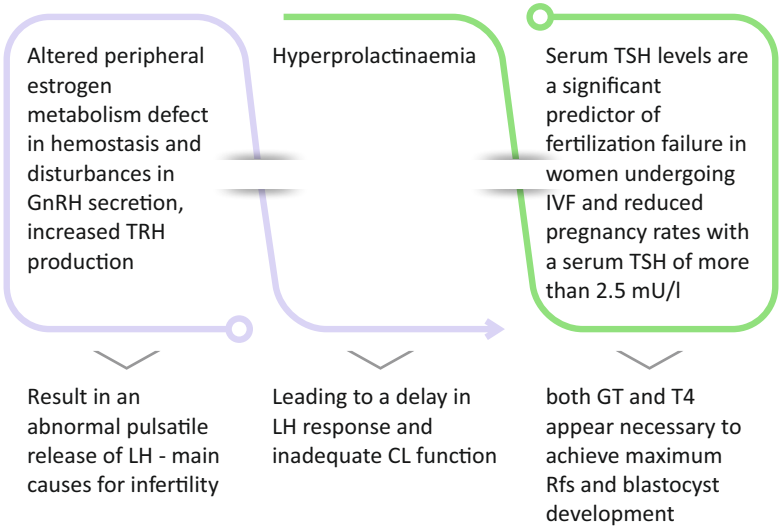
Hypothyroidism results in

- Ovulatory dysfunction results by decreasing levels of sex-hormone-binding globulin and increasing the secretion of prolactin
- Menstrual disturbances due to estrogen breakthrough bleeding and defects in hemostasis factors
- Corpus luteum insufficiency
- Lower PRs and adverse pregnancy outcome

References

1. Foster KF, Robinson RD, Nalesnik SW. Hyperprolactinemia and Thyroid Abnormalities Are Associated with Abnormal Clomiphene Citrate Challenge Tests (CCCT). Fertility and Sterility. 2000 Sep 1;74(3):S63.
2. Gillett M. Subclinical hypothyroidism: subclinical thyroid disease: scientific review and guidelines for diagnosis and management. Clin Biochem Rev 2004;25:191–4.
3. Mueller A, Schöfl C, Dittrich R, Cupisti S, Oppelt PG, Schild RL, Beckmann MW, Häberle L. Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome. Human reproduction. 2009 Aug 3;24(11):2924-30
4. Poppe K, Velkeniers B. Female infertility and the thyroid. Best Pract Res Clin Endocrinol Metab 2004;18:153–65.
5. Wakim AN, Polizotto SL, Buffo MJ, Marrero MA, Burholt DR. Thyroid hormones in human follicular fluid and thyroid hormone receptors in human granulosa cells. Fertil Steril 1993;59:1187–90.
6. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2011;95:1650–54.
7. Krassas GE. Thyroid disease and female reproduction. Fertil Steril 2000;74:1063–70.
8. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Paunkovic J, Paunkovic N, et al. Disturbances of menstruation in hypothyroidism. Clin Endocrinol 1999;50:655–9.
9. Rahman AHA, Abbassy HA, Abbassy AA. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocr Pract 2010;16:792–7.

Mechanism of Ovulatary dysfunction in Hypothyroidism Due to numerous interactions of thyroid hormones with the female reproductive system



Thyroid hormones also synergize with the FSH-mediated LH/hCG receptor to exert direct stimulatory effects on granulosa cell function and P4 production. There is also direct effect of thyroid hormones on the gonads that occurs by modulation of T3 actions on FSH,LH and steroid biosynthesis.

References

1. Cramer DW, Sluss PM, Powers RD, McShane P, Ginsburg ES, Hornstein MD, Vitonis AF, Barbieri RL. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function?. Journal of assisted reproduction and genetics. 2003 Jun 1;20(6):210-5.
2. Fumarola A, Grani G, Romanzi D, Del Sordo M, Bianchini M, Aragona A, et al. Thyroid function in infertile patients undergoing assisted reproduction. Am J Reprod Immunol 2013;70:336–41.
3. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Paunkovic J, Paunkovic N, et al. Disturbances of menstruation in hypothyroidism. Clin Endocrinol 1999;50:655–9.
4. Poppe K, Velkeniers B. Female infertility and the thyroid. Best practice & research Clinical endocrinology & metabolism. 2004 Jun 1;18(2):153-65
5. Unuane D, Tournaye H, Velkeniers B, Poppe K. Endocrine disorders & female infertility. Best Practice & Research Clinical Endocrinology & Metabolism. 2011 Dec 1;25(6):861-73.

Overt and Subclinical hypothyroidism

Prevalence of Overt hypothyroidism

14% of infertile women vs 4% of controls ($P < 0.002$)

It results in

- Ovulatory dysfunction - 15 %
- Premature ovarian failure - 40%
- Idiopathic group - 4.8 %
- Tubal infertility group - 18 %
- Endometriosis group - 0 %

Subclinical hypothyroidism

Results in

Ovulatory dysfunction and idiopathic infertility in 0.5 to 0.88 %

SCH of greater clinical importance in infertile women with unexplained infertility, especially when the luteal phase is inadequate, and such patients should be investigated in depth for thyroid dysfunction

Women presenting with subfertility also appear to have raised mean serum TSH levels and increased rates of subclinical and overt hypothyroidism compared with controls. This is compounded by an increase in T4 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.

In view of the recent evidence it is best to maintain serum TSH levels below 2.5 mU/l pre-conceptually in sub-fertile women.

References

1. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002;12:63–8.
2. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404–33.
3. Joshi JV, Bhandarkar SD, Chadha M, Balaiah D, Shah R. Menstrual irregularities and lactation failure may precede thyroid dysfunction or goitre. J Postgrad Med 1993;39:137–41.
4. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21:1081–125.

Autoimmune thyroid disease (AITD) and Infertility

- Most common autoimmune disorder affecting 5 – 20 % of women in the childbearing period
- Thyroid autoantibodies are an early sign of lymphocytic infiltration and therefore a predictor of thyroid disease
- Increased rates of subfertility are also seen in euthyroid women with AITD
- Prevalence 5 - 10-fold higher among women than men, probably because of a combination of genetic factors estrogen-related effects and chromosome X abnormalities
- Prevalence - 65 % vs 7 % in controls ($P < 0.0001$)
- Increased prevalence of AITD among infertile women, especially those with endometriosis and ovarian dysfunction, polycystic ovarian syndrome (PCOS) and constitutes a risk factor for the development of hypothyroidism
- Significant 4-fold increase in incidence in women with unexplained infertility as compared to mechanical infertility
- Infertile PCOS women with TPO values exceeding the upper level of normal were found significantly more in CC resistant patients, thus, elevated anti TPO levels are associated with poor treatment response in PCOS
- Associated with lower fertilisation rates, poorer embryo quality, lower implantation rate and lower pregnancy rates with risk of early miscarriage
- LT4 therapy has been shown to have a beneficial effect on surrogate infertility endpoints such as menstrual cycle, LH pulsatality and hyperprolactinemia in women with AITD
- Often undiagnosed because it may be present without overt thyroid dysfunction for several years. There is sstrong association between AITD and
  - Endometriosis - 25 - 44 % verses 9 - 14 % in control ($P < 0.001$)
  - Unexplained infertility 41 % as compared to 15 % of controls
  - Premature ovarian failure due to shared autoimmune etiology
  - PCOS - 27 vs 8 % in control ($P < 0.001$)

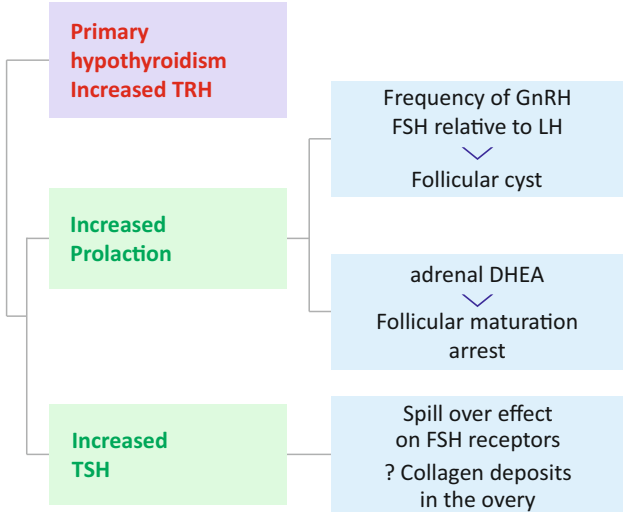
References

1. Bellver J, Soares SR, Alvarez C, Munoz E, Ramírez A, Rubio C, Serra V, Remohí J, Pellicer A. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Human reproduction. 2007 Dec 10;23(2):278-84.
2. Janssen OE, Mehlmauer N, Hahn S, Offner AH, G€artner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol 2004;150:363–9.
3. Mida M, Verhoest P, Boulanger JC, Vitse M. Role of the thyroid in first-trimester miscarriage [Article in French]. Rev Fr Gynecol Obstet 1989;84:901–4.
4. Ott J, Aust S, Kurz C, Nouri K, Wirth S, Huber JC, Mayerhofer K. Elevated antithyroid peroxidase antibodies indicating Hashimoto's thyroiditis are associated with the treatment response in infertile women with polycystic ovary syndrome. Fertility and sterility. 2010 Dec 1;94(7):2895-7.
5. Revelli A, Casano S, Piane LD, Grassi G, Gennarelli G, Guidetti D, et al. A retrospective study on IVF outcome in euthyroid patients with anti-thyroid antibodies: effects of levothyroxine, acetyl-salicylic acid and prednisolone adjuvant treatments. Reprod Biol Endocrinol 2009;7:137.
6. Scofield RH. Autoantibodies as predictors of disease. Lancet 2004;363:1544–6.
7. Stagnaro-Green A, Glinoer D. Thyroid autoimmunity and the risk of miscarriage. Best Practice & Research Clinical Endocrinology & Metabolism. 2004 Jun 1;18(2):167-81.
8. Twig G, Shina A, Amital H, Shoenfeld Y. Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. J Autoimmun 2012;38: J275–81.
9. Unuane D, Velkeniers B, Anckaert E, Schiettecatte J, Tournaye H, Haentjens P, et al. Thyroglobulin autoantibodies: is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? Thyroid 2013;23:1022–8.
10. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH. Significance of (sub) clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Human reproduction update. 2011 May 28;17(5):605-19.
11. Zhong YP, Ying Y, Wu HT, Zhou CQ, Xu YW, Wang Q, et al. Relationship between antithyroid antibody and pregnancy outcome following in vitro fertilization and embryo transfer. Int J Med Sci 2012;9:121–5. s in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43:55-68.

Thyroid disorders and PCOS

Hypothyroidism as differential diagnosis of PCOS

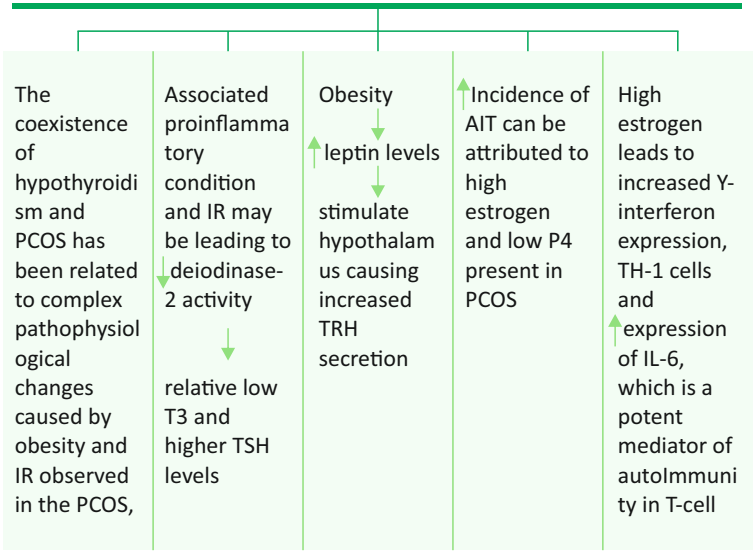
Why hypothyroidism can mimic PCOS



- Severity of abnormal ovarian morphology and increased ovarian volume also depends on duration and severity of underlying primary hypothyroidism
- 14% of SCH patients may present dyslipidaemia, dysglycemia, insulin resistance, ovulatory dysfunction, infertility, obesity, and abnormal menstrual cycle, mimicking PCOS
- High levels of total and free testosterone, LH, PRL, fasting and postprandial insulin, HbA1C, HOMA-IR, serum lipoprotein, triglyceride, total cholesterol, unfavourable LDL and HDL and low levels of SHBG are independent risk factors for metabolic syndrome or myocardial infarction in SCH

- Normalization of ovarian volume in all patients, with or without polycystic appearing ovaries after treatment for hypothyroidism
- TSH correlated with total cholesterol, insulin, and prolactin
- Moreover thyroid disorders are also common in women with PCOS (Figure below). The only difference is that C-peptide was higher in PCOS group
- High TSH level in the presence of normal thyroxin concentration (subclinical hypothyroidism) should be an exclusion criterion from precise diagnosis of PCOS
- According to the current recommendation, definitive PCOS diagnosis should be made after exclusion of thyroid dysfunction

Thyroid disorders are more common in PCOS as compared to normal population because



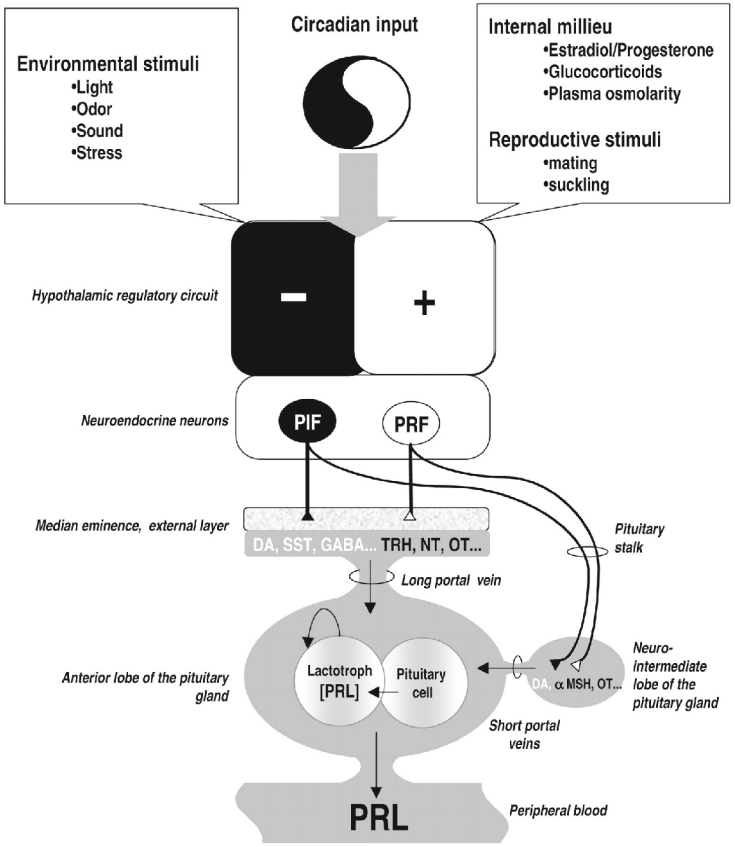
Pathophysiological pathway connecting these hypothyroidism and PCOS has not been clearly delineated as of now. But the most obvious connection, perhaps, is the increased BMI and insulin resistance, which is common to both conditions.

References

1. De-Medeiros SF, Yamamoto MM, de-Medeiros MA, Barbosa JS, Norman RJ. Should subclinical hypothyroidism be an exclusion criterion for the diagnosis of polycystic ovary syndrome?. Journal of reproduction & infertility. 2017 Apr;18(2):242.
2. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Human reproduction update. 2012 Jul 4;18(6):618-37
3. Muscogiuri G, Sorice GP, Mezza T, Prioletta A, Lassandro AP, Pirronti T, Della Casa S, Pontecorvi A, Giaccari A. High-normal tsh values in obesity: Is it insulin resistance or adipose tissue's guilt?. Obesity. 2013 Jan 1;21(1):101-6.

Thyroid disorders and hyperprolactinemia

Hypothyroidism increased TRH production which acts as a PRF by its stimulatory effect on the lactotrophs with mild to moderate increase in prolactin levels. Hypothyroidism can result in hypertrophy of the pituitary gland. Therefore primary hypothyroidism should be considered as a differential diagnosis of diffuse pituitary enlargement with high TSH levels. MRI should be done for diagnosis and then follow- up for monitoring the changes in pituitary size with treatment for hypothyroidism.

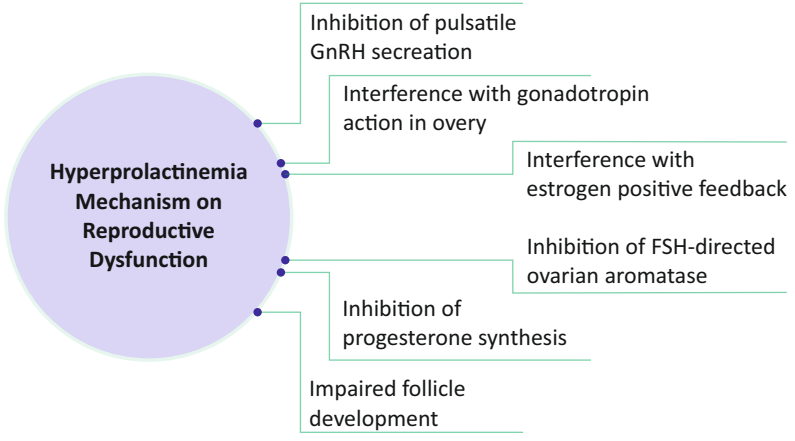


Hyperprolactinemia can have effects on Endocrine-Metabolic Functions. It results in

- Increase lactogenesis
- Androgenic effects
- Reduced SHBG
- Hyperinsulinemia and insulin resistance
- Decrease bone density
- Hypothalamic-pituitary dysfunction
- Impaired Ovarian Steroidogenesis

Hyperprolactinemia is usually associated with menstrual and ovulatory disorders like amenorrhea, oligomenorrhea, anovulation, ovulatory cycle with short or inadequate luteal phase and galactorrhoea. Hypothyroidism also results in anovulatory cycles in the reproductive age group.

Hyperprolactinemia as result of hypothyroidism can result in reproductive dysfunction as depicted in the below figure.



Correction of hypothyroidism by replacement thyroid hormone will correct hyperprolactinemia. Thus, making the correct diagnosis and initiating thyroid hormone therapy can prevent unnecessary treatment with dopamine agonists.

References

1. Honbo KS, Van Herle AJ, Kellett KA. Serum prolactin levels in untreated primary hypothyroldism. The American journal of medicine. 1978 May 1;64(5):782-7.
2. Jokic D, Wang X. Primary hypothyroidism associated with hyperprolactin- emia and pituitary adenoma. Thyroid Sci (2011) 6:CR1–4
3. Koller KJ, Wolff RS, Warden MK, Zoeller RT. Thyroid hormones regulate levels of thyrotropin-releasing-hormone mRNA in the paraventricular nucleus. Proceedings of the National Academy of Sciences. 1987 Oct 1;84(20):7329-33.
4. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiological reviews. 2001 Jul 1;81(3):1097-142.

Treatment

Treatment with Lt4
In overt hypothyroidism

- Normalize prolactin level Normal LH responses to LHRH
- Reduce menstrual disturbances
- Increase the chances of spontaneous fertility

In Sub-clinical Hypothyroidism
Treatment is required in presence of irregular menses, preceding ART and after COH

R-I131 for treatment of hyperthyroidism

- Average dose 10 mCi (370 MBq)
- Conception avoided for 12 months after the administration of R-I131
- Genetic risk is negligible, and reproductive health of treated women and progeny normal
- Treatment with R-I131 bears no significant detrimental effect on gonads

- In women with previously diagnosed overt or subclinical hypothyroidism taking L-T4 before pregnancy, the dose should be increased initially by 25 g daily once pregnancy is confirmed to compensate for the increased T4 demand of pregnancy.
- 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.

References

1. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21:1081–125.
2. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ 2011;342:d2616.

Monitoring patients on treatment

- Thyroid function should be monitored every four to six weeks and increases in dose of L-T4 may be required to maintain an optimal serum TSH levels below 2.5 mU/L
- TSH - most appropriate test when monitoring patients receiving thyroxine
- Where thyroid function needs to be assessed before 6 weeks, Free T4 should be used, as the TSH will not have plateaued at this stage

Once pregnancy is established

- Fetal growth and heart rate should be monitored, particularly in those with anti-thyroid antibodies, as the risk of miscarriage is higher
- Thyroid function should be checked every 4 weekly during the first trimester in those women who are euthyroid but are AITD positive as they are an increased risk of developing hypothyroidism during pregnancy
- If thyroid function remains normal in the first trimester it should be rechecked once between 26-32 weeks.
- Following delivery, the dose of L-T4 needs to be reduced to pre-pregnancy levels as TSH and Free T4 levels quickly return to pre-pregnancy levels
- Thyroid function should be rechecked at six to eight weeks postpartum.
- Usually women with Graves' disease have remission in their third trimester . These women should be reassessed postpartum as they are at increased risk of recurrence or exacerbation

References

1. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21:1081–125.

Thyroid Function and Male Infertility

Both hyper and hypothyroidism can affect male fertility

Thyrotoxicosis in the Male

- Increased SHBG levels results in increased circulating levels of total Testosterone and decreased testosterone metabolic clearance rate and Bioavailable testosterone
- Total and free estradiol (E2) concentrations were often elevated, and consequently, free testosterone/free E2 ratio was lower
- Relative free E2 elevation may contribute to the higher incidence of gynecomastia and decreased libido
- LH and FSH responses to GnRH administration were exaggerated
- Abnormalities of the hypothalamic-pituitary-gonadal axis significantly correlated with increased serum T4 levels and entirely reversible with restoration of a euthyroid status

Thyrotoxicosis, Spermatogenesis and fertility

- Mean semen volume was within normal range
- Mean sperm density was lower when compared with controls though did not reach statistically significance
- Sperm morphology - Normal sperms lower
- Mean sperm motility was lower
- Also associated with Erectile dysfunction (70%), hypoactive sexual desire, premature ejaculation and delayed ejaculation

R-I131 treatment for hyperthyroidism and reproduction

Because of potential mutagenic effects of radiation on gonads, there is a legitimate concern regarding the possible side effects.

Post therapy

- Mean basal FSH concentration was within the normal limits and did not change after therapy
- LH was normal and did not change aftert herapy,
- Testosterone levels were reduced 45 days after R-I131 therapy and returned to basal values 1 year later
- Count and motility improved
- Sperm morphology did not show any significant modification

Hypothyroidism in males

Hormonal Changes

- Decreased SHBG and total and free testosterone concentrations in approximately 60%
- TH administration induces rise in both SHBG and total serum testosterone
- Normal LH and FSH levels, suggesting that the primary defect is not in Leydig cells
- Impaired hypothalamic-pituitary-gonadal axis results in subnormal free testosterone levels
- Blunted GT responses to GnRH
- Primary hypothyroidism impairs the ability of the pituitary gland to respond to GnRH
- DHEA, DHEA sulfate, estrogenic metabolites of DHEA (androstenediol and its sulfate), and pregnenolone sulfate are decreased
- Results in pituitary tumors with hyperprolactinemia and hypogonadotropic hypogonadism
- Hyposecretion of ACTH and cortisol - attributed to diminished cortisol clearance
- Associated with growth retardation and alterations in GH secretion and action
- Produces delayed or precocious puberty in pre-pubertal boys and hypogonadism in post-pubertal

Hypothyroidism, Spermatogenesis and fertility

- Decreased libido or impotence
- 64% prevalence of Erectile dysfunction (70%), hypoactive sexual desire, delayed ejaculation and 7% prevalence for, premature ejaculation
- After euthyroidism was reached, half of the patients with DE had no complaints, ED almost disappeared, and patients with HSD found a significant improvement of symptoms while on therapy
- All patients demonstrated features of hypogonadotropic hypogonadism, with testicular biopsies revealing histological abnormalities
- Decrease in seminal volume, progressive spermatozoa forward motility was observed
- Cause abnormalities in SHBG, GTs and Total Testosterone that are essential to maintain normal spermatogenesis
- No abnormality in sperm density
- Sperm morphology was the only parameter that was significantly affected
- When correlated with semen analysis, the prevalence of positive thyroid peroxidase (TPO) antibodies was significantly higher in patients with teratozoospermia (6.7 vs. 1.6%; $P < 0.04$) & asthenozoospermia (7.2 vs. 1.6%; $P < 0.5$), compared with normozoospermia

Treatment of thyroid disorders and Male infertility

- Thyrotoxicosis has a significant but reversible effect on sperm motility
- Although radioactive Iodine (I) in ablation doses may transiently affect the gonads, it does not decrease fertility or increase genetic malformation rate in the offspring
- After treatment with L-T4, the sperm parameters tended to normalize

References

1. Carani C, Isidori AM, Granata A, Carosa E, Maggi M, Lenzi A, Jannini EA. Multicenter study on the prevalence of sexual symptoms in male hypo-and hyperthyroid patients. The Journal of Clinical Endocrinology & Metabolism. 2005 Dec 1;90(12):6472-9.
2. Corona G, Wu FC, Forti G, Lee DM, O'Connor DB, O'Neill TW, Pendleton N, Bartfai G, Boonen S, Casanueva FF, Finn JD. Thyroid hormones and male sexual function. International journal of andrology. 2012 Oct;35(5):668-79.
3. Handelsman DJ, Turtle JR. Testicular damage after radioactive iodine (I-131) therapy for thyroid cancer. Clinical endocrinology. 1983 May;18(5):465-72.
4. Hernandez JC, Garcia JM, Garcia Diez LC. Primary hypothyroidism and human spermatogenesis. Archives of Andrology. 1990 Jan 1;25(1):21-7.
5. Krajewska-Kulak E, Sengupta P. Thyroid function in male infertility. Frontiers in endocrinology. 2013 Nov 13;4:174.
6. Krassas GE, Perros P. Thyroid disease and male reproductive function. Journal of endocrinological investigation. 2003 Apr 1;26(4):372-80.
7. Krassas GE, Pontikides N. Male reproductive function in relation with thyroid alterations. Best Practice & Research Clinical Endocrinology & Metabolism. 2004 Jun 1;18(2):183-95.
8. Lotti F, Maseroli E, Fralassi N, Degl'Innocenti S, Boni L, Baldi E, Maggi M. Is thyroid hormones evaluation of clinical value in the work-up of males of infertile couples?. Human Reproduction. 2016 Jan 11;31(3):518-29.
9. Nikoobakht MR, Aloosh M, Nikoobakht N, Mehrsay A, Biniaz F, Karjalian MA. The role of hypothyroidism in male infertility and erectile dysfunction. Urology journal. 2012 Feb 27;9(1):405-9.
10. Singh R, Hamada AJ, Agarwal A. Thyroid hormones in male reproduction and fertility. Open Reprod Sci J. 2011;3:98-104.
11. Trummer H, Ramschak-Schwarzer S, Haas J, Habermann H, Pummer K, Leb G. Thyroid hormones and thyroid antibodies in infertile males. Fertility and sterility. 2001 Aug 1;76(2):254-7
12. Wajner SM, Wagner MS, Maia AL. Clinical implications of altered thyroid status in male testicular function. Arquivos Brasileiros de Endocrinologia & Metabologia. 2009 Nov;53(8):976-82.
13. Wortsman J, Rosner W, Dufau ML. Abnormal testicular function in men with primary hypothyroidism. The American journal of medicine. 1987 Feb 1;82(2):207-12.

Key Message

- Thyroid disease is a common condition in the reproductive medicine setting due to the complex interplay between the hypothalamo-pituitary axis and the thyroid gland.
- Thyroid hormones play an important part in normal reproductive function both through
  1. direct effects on the ovaries
  2. indirectly by multiple interactions with other reproductive hormones
- Screening for thyroid disease (TSH, Free T4 and TPO anti bodies) should be considered in women presenting with subfertility and recurrent early pregnancy loss.
- Abnormalities in thyroid function, including hyperthyroidism an 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.
- When thyroid dysfunction is detected, treatment is able to normalizes PRL and LH levels, restore normal fertility and reduce the risk and requirement for ART
- 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 sub-fertile women and reduce early pregnancy loss.
- Treatment required preceding and after COH
  - COS is an important stress factor for thyroid function
  - When AITD is present, the impact of COH on the thyroid function is more severe and depends on the pre-COH serum TSH and FT4 value
- Those treated with levothyroxine daily had normalized mid progesterone secretion and 20% became pregnant
- The benefits of L-T4 replacement in euthyroid women with AITD both pre-conceptually and during pregnancy remain a grey area and further research is needed to confirm benefit.
- Thyrotoxicosis produces abnormalities in seminal parameters, mainly sperm motility, whereas hypothyroidism has abnormalities in sperm morphology
- Presence of semen abnormality warrants thyroid evaluation in the male