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Autoimmune Basis of Sub Clinical Hypothyroidism in Pregnancy

Prakruti Dash and Rajlaxmi Tiwari

Abstract

Effects of overt hypothyroidism on pregnancy outcomes and fetal development are well established and treatment protocol is reputable. Subclinical hypothyroidism poses a major health problem in pregnancy. Requirement of iodine increases in pregnancy as demand for synthesis of excess thyroid hormones is there during pregnancy. This is because of fetal dependency on maternal thyroid hormones till 12 weeks of gestation as fetal thyroid tissue is not matured enough to produce adequate hormones for the growing fetus. Hence, dietary iodine deficiency or intake of excess goitrogens in diet can be the major cause of overt and subclinical hypothyroidism in pregnancy. Apart from this autoimmune basis of overt and sub clinical hypothyroidism is also equally important in pregnant women. Data accumulating shows presence of antibodies like anti TPO antibody (anti thyroperoxidase antibody) and anti Tg antibody (anti thyroglobulin antibody) in pregnancy which is associated with increased prevalence of overt and sub clinical hypothyroidism and aggravation of the symptoms associated with it. Studies also document that pregnancy related complications are more prevalent in presence of these autoimmune antibodies. Hence, management of subclinical hypothyroidism in pregnancy also differs in positive and negative cases of anti TPO antibody and anti-Tg antibody.

Keywords: sub-clinical hypothyroidism, pregnancy, obstetric outcome, autoimmunity, anti thyroperoxidase antibody (anti TPO antibody), anti-thyroglobulin antibody (anti Tg antibody), assisted fertilization

1. Introduction

Subclinical hypothyroidism (SCH), frequently observed in pregnancy is defined as high TSH with normal T4 and T3 level. The growing fetus is entirely dependent on mother thyroid hormones in the first 12 weeks; hence, any abnormalities during this period should be detected early and preventive measures initiated as decreased thyroid hormones is known to affect the mother and the fetus adversely.

Presence of anti-TPO antibody is a major risk factor for progression to overt hypothyroidism. After widespread use of fortified Iodine rich food and extra supplementation of iodine in pregnancy, the knowledge and prevalence of autoimmune clinical and subclinical hypothyroidism with presence of various antibodies against thyroid tissues and metabolic factors gains more importance. Adverse obstetric and fetal outcomes particularly attributed to anti TPO antibodies makes its study even more clinically relevant. It is important to know the burden of anti-TPO antibody associated SCH cases due to their differences in management.

Parameter	Changes during pregnancy	Normal values (up to)
TSH	Reaches nadir during first trimester; then plateaus	4.0 mIU/L
T4	Increases in first trimester; then plateaus	150 ng/mL
fT4	Unchanged	30 pg/mL
T3	Increases in first trimester; then plateaus	2 ng/mL
fT3	Unchanged	4 pg/mL

Table 1.
Normal levels of thyroid hormones and TSH in pregnancy [1].

1.1 Anatomical, physiological and biochemical adaption of thyroid gland to pregnancy

A palpable increase in size of the thyroid gland is observed in normal pregnancy which is also associated with a bruit [1]. There is an established increased renal clearance of iodide leading to increased thyroid iodide clearance with associated raised uptake of ¹³¹Iodide by the thyroid glands during pregnancy. This results in a relative iodine deficient status in the pregnant mother. There is also an increase in TBG (thyroid hormone binding globulin) for which total thyroxine exhibits a raised value but free thyroxine and free triiodothyronine (fT3) is mostly normal (**Table 1**).

1.2 Regulation of synthesis of thyroid hormones in pregnancy

The synthesis of thyroid hormones is regulated by HPT axis, i.e., hypothalamus-pituitary-thyroid axis. The TRH released from hypothalamus acts positively on pituitary gland which releases TSH [1]. The TSH in turn stimulates the thyroid gland to synthesize and release T4 and T3. The thyroid gland gives negative feedback signal to hypothalamus and pituitary and thus excess of its synthesis is controlled and regulated. During pregnancy, in addition to the normal regulatory mechanisms, hCG also plays a significant role in regulation of thyroid hormone synthesis. hCG mostly the asialo-hCG fraction secreted from the placenta is known to have weak TSH stimulating action and this plays an important role in maintaining the thyroid hormone levels, whose demand is increased in pregnancy due to fetal dependency on mother's thyroid hormones almost exclusively up to 12 weeks of gestation and hCG acts by contributing to thyrotropic action of placenta. This also results in mild hyperthyroidism status in early pregnancy.

2. Anti-thyroid antibodies to thyroid antigens

2.1 Anti TPO antibody

Polyclonal antibodies directed against some epitopes of thyroperoxidase molecule are present in the blood of some healthy individuals and patients having autoimmune thyroid disorders [1–3]. Anti-TPO antibodies from autoimmune thyroid patients act as competitive inhibitors of enzymatic activity though those from healthy subjects are not seen to block thyroperoxidase [4, 5]. These antibodies mostly belong to IgG class, more often IgG1 and IgG4 subtypes [6]. Prevalence of anti-TPO antibodies are more common than other anti-thyroid antibodies and more symbolic for thyroid hormone imbalance. Excess of oxidative stress markers in blood are seen with anti-TPO antibodies indicating it to be an inducer of oxidative

stress [7]. Apart from hypothyroid patients, anti-TPO antibodies are also detected in Graves' disease patients. These antibodies possess the potential of crossing the placenta barrier to variable extent [8], though its effect on the neonate is debatable.

Few studies document that children born to anti TPO antibody positive pregnant women supposedly suffer from compromised motor and neuropsychological development [9]. There can be behavioral problems, attention deficit disorders in the off springs associated with raised titers of anti TPO antibody in the mothers during pregnancy [10]. Couple of literatures substantiate that children of anti TPO antibody positive mothers have lower brain to body mass ratio, decreased weight of brain and smaller head circumference compared to those of anti TPO antibody negative mothers [11, 12].

As the influence and outcome on off springs of increased anti TPO antibody concentration during pregnancy is of greater significance, longer follow up studies is required to gather more data on this important clinical aspect of neuropsychological development of the children.

2.2 Anti-thyroglobulin antibody

Polyclonal anti thyroglobulin (Tg) antibodies are found in the serum of healthy subjects whereas oligoclonal antibodies are seen in patients having auto immune thyroid disorders. It has been hypothesized that normal blood levels of Tg induce self-tolerance in T cells as low levels of antigens are usually responsible for development of self-tolerance. But this self-tolerance is not seen in case of B cell activity resulting in healthy individuals having very low levels of anti-Tg antibodies which is usually below detection limits. Higher levels of Tg following tissue damage, or due to conformation alteration of the Tg molecule in presence of high iodine levels, or in presence of very high TSH levels, there is alteration in the titers of the anti-Tg antibody. The anti-Tg antibodies are predominantly of IgG4 though minor proportions of IgA and IgM class are also seen. The functional consequence of anti-Tg antibodies is hitherto not known. Circulating antibodies were detected in healthy young subjects and in people >60 years of age to an extent of 10–15%. Presence of anti-Tg antibodies have been documented in auto immune thyroid disorders, Graves' disease and in patients with non-thyroid immune disorders. These antibodies like anti TPO antibodies can cross the placenta barrier but its effects are not very substantially known [1].

2.3 Thyroid hormone receptor antibodies

These antibodies bind to thyroid cell membrane at/near TSH receptor and mimics the action of TSH as "occupied" receptor. This leads to excess thyroxin synthesis by the gland which escapes feedback control mechanisms. It is demonstrated frequently in Grave's disease-also known as long acting thyroid stimulator (LATS) antibodies.

Excess of synthesis of thyroid hormones is known as hyperthyroidism and deficiency leads to hypothyroidism. Both the conditions are associated with deleterious effects to various metabolic processes of the body [1].

3. Thyroid hormones and pregnancy

Thyroid hormones T4 and T3 affect almost every metabolic processes of the body. Pregnancy is considered to be a physiologically altered state of metabolism as the body tries to cater to the needs of the growing fetus. There is an increased need

of thyroid hormones in pregnancy as the developing fetus is completely dependent on maternal thyroid hormones till 12 weeks of gestation. Hence, the gland becomes over stimulated and hyperactive to secrete more T4 and T3 to meet the increased demand and this is brought about through hypothalamus-pituitary-thyroid axis regulatory mechanisms. Thyroxin and TBG (thyroid binding globulins) levels rise in pregnancy along with a simultaneous decrease in TSH (thyroid stimulating hormone) level [13]. A placental deiodinase enzyme also results in more thyroid hormone synthesis in pregnancy [14–16]. hCG is known to have a TSH stimulating effect and hence attributes to raise the thyroid hormone synthesis to meet the increased demand via its thyrotrophic effect [17]. Absolute fetal dependency on mother's thyroid hormones can result in adverse obstetric and fetal outcome if the increased demand for T4 and T3 is not met adequately in the first 12 weeks of gestation [18]. There has also been documented evidences that proper placental development is also dependent on thyroid hormones and lack of it can result in improper placenta formation [19] with adverse obstetric outcomes like abruptio placentae, preeclampsia, miscarriages, preterm delivery, low birth weight (LBW), IUGR (intrauterine growth retardation) and small for gestational age babies (SGA) [20–22]. Impaired intellectual development of off springs of hyper/hypothyroid mothers has also been documented [23].

3.1 Thyroid hormones and its effects on obstetric outcome

Various studies have registered in their findings that placenta has strong affinity for T3 and is dependent on thyroid hormones for its growth. Triiodothyronine/ T3 is plays a significant role in placental trophoblastic growth by its likely effect on growth factors like EGF (epidermal growth factor) and hormone like 17 beta estradiol [19, 24, 25]. Small for gestational age babies (SGA) and intra uterine growth retardation of fetus (IUGR) are most likely results of impaired growth of placental trophoblasts [26, 27]. Fetal thyroid hormones have been found to be decreased in IUGR babies compared to gestation matched normal fetal serum. Inflammation associated with impaired uteroplacental circulation are registered to be causative factors for development of serious disorders like eclampsia and preeclampsia in pregnancy. These situations are also documented to be associated with increased oxidative stress by various studies [28]. Hence various studies now put inflammation under major focus in development of preeclampsia and pre-term labor in pregnancy. Thyroid hormones act on DNA and regulate expression of various genes which also includes genes associated with inflammation. As inflammation is now considered to be an important causative factor for development of pre-eclampsia, thyroid hormones are also corroborated by various studies to be responsible for this [29]. Analysis of maternal and cord blood has validated this hypothesis and revealed a low T4 with raised TSH level in preeclampsia cases which has also been linked with placental inadequacy.

Various studies have also found an association of gestational diabetes mellitus (GDM) with impaired thyroid status. Inverse correlation between metformin and TSH value further strengthens this association. Thus, screening of all pregnant women for thyroid function along with anti TPO antibody measurement has been advised by many studies, particularly in “at risk” cases of GDM [30–33]. Both thyroid dysfunction and diabetes mellitus are known to adversely affect obstetric and fetal outcome and now gradually gathering data proves that very often both the conditions coexist in pregnancy depicting an association between them and hence early screening, intervention and timely management is advocated by various studies [34–37].

3.2 Pregnancy and clinical/subclinical hypothyroidism

The need for iodine increases in pregnancy (daily requirement of iodine –150–200 µg/day, 250 µg/day in pregnancy) leading to an iodine deficient status if not adequately supplemented. Apart from iodine deficiency, the other most common factor for thyroid hormone deficiency has been attributed to anti-TPO antibodies. Hypothyroidism is registered to be more prevalent in Asian countries compared to their Western counterparts. As such thyroid disorders have wide geographical variations attributed to dietary factors, level of various goitrogens in diet and their consumption level, deficiencies of micronutrients like selenium, iron and most importantly iodine. Autoimmune thyroid diseases are also more prevalent in Asian countries and accumulating literatures suggest it to be more substantial in Indian population with greater prevalence of anti TPO antibody positivity.

High TSH level with normal T4 level is known as subclinical hypothyroidism (SCH). Subclinical hypothyroidism is one of the most common type of thyroid dysfunction that is found to be associated with pregnancy [38, 39]. The increased need of thyroid hormones to meet the extra demand by the growing fetus in the first 12 weeks of gestation is dealt by hCG due to its thyrotrophic action as discussed earlier and also via hypothalamus-pituitary-thyroid axis regulation which usually results in small painless enlargement, i.e., goiter formation in pregnant women [1]. This also results in increased need of iodine in pregnancy.

Hence, endemic areas of iodine deficiency have shown a higher prevalence of clinical or subclinical hypothyroidism in general and in particular in pregnant women. Because of increased thyroid hormone production, increased renal iodine excretion, and fetal iodine requirements, dietary iodine requirements are higher in pregnancy than they are for non-pregnant adults. The requirement of iodine is 250 µg/day in pregnancy. Recommendation by American Thyroid Association (ATA) is women who are planning pregnancy or currently pregnant, should supplement their diet with a daily oral supplement that contains 150 µg of iodine in the form of potassium iodide [40]. This should optimally start 3 months in advance of planned pregnancy.

3.3 Hypothyroidism and autoimmunity in pregnancy

However, apart from iodine deficiency, the other most significant cause of hypothyroidism in recent times is presence of anti thyroperoxidase antibody, i.e., anti TPO antibody and anti Tg (anti thyroglobulin) antibody in the serum. The thyroperoxidase enzyme as described above is highly essential for oxidation of trapped iodine and its incorporation into tyrosine molecule for synthesis of thyroxine. Anti TPO antibody destroys the thyroperoxidase enzyme and hence prevents the iodination of tyrosine molecule and overall synthesis of thyroxine is hampered resulting in hypothyroidism. This autoimmune basis of hypothyroidism is now more relevant after iodine deficiency has been tackled by fortification of food products with iodine/with iodine supplementation as potassium iodide. In pregnancy, immune regulatory cytokines and cells are present in the mother's circulatory system and accumulate in the decidua and can modify autoimmune responses influencing the symptoms of autoimmune disease [41].

Presence of anti-TPO antibody is a major risk factor for progression to overt hypothyroidism. Various studies reveal a prevalence of 2–17% of euthyroid pregnant women being anti-TPO antibody positive. Still data from Indian scenario is extremely limited. TPO antibodies are able to cross the placenta. At the time of delivery, cord blood anti TPO Ab levels strongly correlate with third-trimester

maternal anti TPO antibody concentrations [8]. However, concrete documentation of maternal passage of either anti TPO antibodies or anti Tg antibodies affecting the fetal thyroid function is still debatable [9–12].

It has been documented that euthyroid pregnant women who are positive for thyroid peroxidase autoantibody (anti TPO antibody) also are at increased risk of various complications of pregnancy including miscarriage, preterm birth, pregnancy-induced hypertension (PIH), intrauterine death (IUD), and intrauterine growth retardation (IUGR) [42, 43].

A number of etiologies have been hypothesized as the cause of the relationship between various pregnancy related complications like miscarriage, IUGR, pre-eclampsia, pre term delivery and autoimmune thyroid antibodies. To enumerate a few: (a) prior presence of a restrained degree of hypothyroidism, (b) thyroid antibodies reflecting an immunological imbalance inclining towards auto immunity in the pregnant female, (c) direct effects of thyroid autoantibodies on the placenta or the fertilized ovum. The above hypotheses have been corroborated by the observation of higher levels of TSH within the normal range noted in various meta-analysis studies indicating a milder degree of thyroid failure in euthyroid pregnant women with thyroid auto antibodies positivity [41, 44–46].

3.4 Autoimmune hypothyroidism and development of goiter in pregnancy

Pregnancy is considered to be a goitrogenic status, particularly in the Iodine deficiency scenario. Increased need of thyroid hormones, TSH simulating actions of beta HCG with super added iodine deficiency actually leads to volumetric increase in the gland and not just vascular engorgement which also has been biochemically corroborated by observations of high serum Thyroglobulin levels, more T3 secretion and small rise in basal TSH level at delivery. Studies supports that there is actual goiter formation in pregnancy which can be tackled to a measurable extent by adequate iodine supplementation [47].

Presence of anti TPO antibodies is mostly associated with Hashimoto's thyroiditis, Graves' disease, nodular goiter and thyroid carcinoma [1]. Anti TPO antibody positivity in pregnancy is mostly associated with overt or subclinical hypothyroidism during pregnancy sometimes associated with a goiter which is often painless. Post-delivery, there are incidences of postpartum thyroiditis with a milder form of Graves' disease lacking the typical symptomatic features which after a few months, changes to hypothyroidism and development of small painless goiter [1, 48, 49].

4. Reference limits for diagnosis of hypothyroidism in pregnancy

It is important to know the burden of anti-TPO antibody associated SCH cases due to their differences in management. This is even more important in case of pregnant women as presence of anti TPO antibody makes them more vulnerable to clinical hypothyroidism and hence its detection at early pregnancy helps in its better management. The management for pregnant women with subclinical hypothyroidism with anti TPO Ab positive and negative differs from each other.

Setting the reference limits for thyroid hormones and TSH in pregnancy is a debatable fact due to different laboratories giving different values and there is gross geographical variation too. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and Postpartum (ATA 2011) recommends a trimester specific range of TSH in pregnancy which is lower than in normal adult, i.e., first trimester: 0.1–2.5 mIU/L, second trimester: 0.2–3.0 mIU/L, third trimester: 0.3–3.0 mIU/L [40]. However, the recent guidelines

	TSH value	T4/T3	Anti TPO	Therapy with LT4
1	Within the pregnancy-specific reference range or <4.0 mIU/L (if specific reference range unavailable)	Normal	Negative	Not recommended
2	TSH >10.0 mU/L	Normal	Negative	Strong recommendation
3	TSH >2.5 mU/L and below the upper limit of the pregnancy-specific reference range	Normal	Positive	Weak recommendation
4	TSH greater than the upper limit of the pregnancy-specific reference range but below 10.0 mU/L	Normal	Negative	Weak recommendation
5	TSH greater than pregnancy-specific reference range or >4.0 mIU/L (if specific reference range unavailable)	Normal	Positive	Strong recommendation

Table 2.
Recommendations by ATA 2017 guidelines regarding management of sub clinical hypothyroidism in pregnancy [50].

of ATA recommend “When available, population- and trimester-specific reference ranges for serum TSH during pregnancy should be defined by a provider’s institute or laboratory and should represent the typical population for whom care is provided. Reference ranges should be defined in healthy anti TPO Ab-negative pregnant women with optimal iodine intake and without thyroid illness. If internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of ~4.0 mIU/L may be used” (ATA-2017) [50]. In the absence of accredited trimester specific reference ranges for thyroid hormones and TSH levels in pregnancy in India, the current practice is to use the reference limits set by ATA as per 2017 guidelines [50].

4.1 Management of overt and subclinical hypothyroidism in pregnancy

Recent guidelines of ATA recommends regular monitoring of thyroid status in women with overt and subclinical hypothyroidism (treated or untreated) or those at risk for hypothyroidism (e.g., patients who are euthyroid but anti TPO antibody or anti Tg antibody positive, post-hemithyroidectomy, or treated with radioactive iodine) with a serum TSH measurement approximately every 4 weeks until completion of second trimester and at least once near 30 weeks gestation [50]. Sub clinical hypothyroidism in anti TPO antibody negative and positive cases in pregnancy are differently managed with levothyroxine (LT4) as per the recommendations of ATA 2017 guidelines [50] (**Table 2**).

5. Thyroid auto antibodies and assisted fertilization

Recently, some researchers speculated that assisted conception in women positive for anti-thyroid antibodies had poor outcome of *in vitro* fertilization, even if they were euthyroid. Studies do document that anti thyroid antibodies positive patients had low fertilization rate, implantation rate, and pregnancy rate and high abortion rate. Regarding the question how these antibodies interfered with fertilization, embryo development as well as implantation potential still remains unanswered. The hypothesis is that the antibodies may bind to either the surface of the egg and/or embryo and interfere with fertilization and subsequent embryo

development. Alternatively, the presence of the auto antibodies in the endometrial tissue may exert detrimental effect on embryo implantation leading to early pregnancy loss [51–54].

6. Conclusion

More and more evidences worldwide have pointed towards anti TPO antibody to be associated with clinical and subclinical hypothyroidism with adverse obstetric and fetal outcomes. As the management differs for subclinical hypothyroidism in anti TPO antibody positive and negative pregnant women hence more studies should be undertaken pertinent to different geographical areas regarding the prevalence of autoantibodies and their effect on pregnancy and on the off springs in the long term. The trimester specific reference ranges for different areas should also be specified with larger cohort of studies particularly for countries like India where there are wide geographical and ethnic variations. The area where there is severe lacking of data with respect to India is regarding the effects of autoimmune sub-clinical hypothyroidism on the obstetric, fetal outcomes and most importantly on the off springs in the long run. Hence, longer follow-up studies with larger cohorts is necessary to gather more evidences regarding this important endocrinal disorder in pregnancy in India.

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