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Thyroid Function Tests During First-trimester of Pregnancy: A Review of Literature

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Abstract: This literature review was conducted to summarize the main points of maternal thyroid function tests, with particular attention in the first trimester of pregnancy which accompanied with significant biochemical and metabolic alteration. The evaluation of thyroid function of either hyperthyroidism and hypothyroidism should be assessed by determination of serum Thyroid Stimulating Hormone (TSH), Thyroxine (T4), Triiodothyronine (T3), Iodine and Thyroid Autoantibodies. Glomerular filtration rate is increased during pregnancy; therefor iodine deficiency should be evaluated during the pregnancy to prevent hypothyroidism. The role which can be played by Human Chronic Gonadotropin (hCG) on stimulating the thyroid gland to become over-active was investigated. Serum level of thyroglobulin (Tg) and Thyroxin Binding Globulin (TBG) should be assessed for proper assessments of thyroid gland during pregnancy. Thyroid function tests during first-trimester of pregnancy and particularly the reference interval for thyroid function tests for pregnant women in each region has to be established, to prevent mis-diagnosis and irreversible mental and physical adverse affect for growing fetus.

Key words: Pregnancy, thyroxin, hypothyroid, hyperthyroid, thyroid antibodies

INTRODUCTION

Due to specific conditions related to the pregnancy period, There are various alteration accompanied with this phase of life.

There are a variation of changes required to be occurred due to physiological demands of the growing fetus and the pregnancy itself. The various physiological changes during pregnancy is not only narrowed at thyroid hormonal function tests but due to significant alteration in metabolic processes, many others hormonal change take place during pregnancy to optimize the cellular and molecular demand of maternal and physiological requirements (Kuroka and Takahashi, 2005; Osathanondh *et al.*, 1976; Glinoer and Lemone, 1992; Mandel *et al.*, 1990; Nelson *et al*., 1987; Glinoer *et al.*, 1990, 1992; Burrow, 1993).

The thyroid in the growing fetus during pregnancy demand extraordinary attention, although the thyroid should function properly at any time, in males and females but it seems thyroid function tests are more at risk of abnormality among women particularly during pregnancy period and childbearing age. In addition the first trimester of pregnancy should be under specific and particular medical care, due to fetus physiological demand particularly physical mental and brain developments.

Therefore, evaluation of thyroid function tests during pregnancy is great importance to prevent the above abnormalities (LeBeau and Mandel, 2006; Springer *et al.*, 2009; Hallengren *et al*., 2009).

It should be noted that the proper assessment of thyroid function during pregnancy require the determination of not only the hormone related to the thyroid but also the antibodies raised against the thyroid gland and the iodine requirement of maternal life should be strictly assessed, to prevent the disorder in thyroid hormonal function, tests during maternal life with irreversible side effect particularly to the growing fetus and pregnant women, as well (LaFranchi *et al.*, 2005; Soldin *et al*., 2004).

PHYSIOLOGICAL ALTERATION DURING NORMAL PREGNANCY

Thyroid function tests during normal pregnancy: In normal pregnancy the maternal thyroidal function alter dramatically due to the new condition and requirement of fetus life. Due to the elevated concentration of estrogen during a routine normal pregnancy and its effect on the liver the serum level of Thyroxin Binding Globulin (TBG) increased, the consequence of increasing amount of TBG, lead to elevated concentration of thyroid hormones of thyroxine (T4) and triiodothyronine (T3), in normal pregnancy (Chen and Jhon, 2002; Idris *et al.*, 2005; Kooistra *et al*., 2006).

The iodine requirement during normal pregnancy: The Glomerular Filtration Rate (GFR) and the subsequent increase in renal blood flow, alter the normal clearance of renal iodide to be increased and this normal physiological

condition well happened during early phase of pregnancy. The latter physiological condition, indicate the additional demand of iodine during pregnancy in the diet to protect the maternal and also to provide the iodine required by fetus thyroid, which become gradually active at the end of first trimester of pregnancy. On condition the dietary regiment is not well supplement with enough iodine during early phase of pregnancy, the inadequate thyroid hormones concentration of maternal and fetal hormones level, lead to some abnormality in the thyroid glands of pregnant women and the fetus, with ultimate enlargement of maternal thyroid gland to produce enough thyroid hormones. The iodine is an important factor for the thyroid proper function not only in pregnancies but also for non pregnant women and men as well. The author and colleagues worked and reviewed the pattern of urinary iodine with results indicating there are iodine deficient subjects still are present. It is absolutely clear that pregnancy aggravate the clinical manifestation of iodine deficiency during pregnancy (Crooks *et al*., 1969; Glinoer and Lemone, 1992; Glinore *et al*., 1995; Levy *et al*., 1980; Nelson *et al*., 1987; Liberman *et al*., 1998; Halnan, 1958; Dworkin *et al*., 1966; Mansourian *et al*., 2007).

The stimulation of maternal thyroid gland during normal pregnancy by human Chorionic Gondatropin (hCG): The hCG is a glycoprotein produced during pregnancy by placenta, to some extend is identical to molecular structure of Thyroid Stimulating Hormone (TSH). Thyroid stimulating hormone produced by the pituitary gland released into blood circulation. The target tissue for TSH is thyroid gland. The TSH is synthesized in pituitary in response to the Thyrotropin Releasing Hormone (CRH) produced in the hypothalamus. At the time TSH reached the thyroid gland, it binds to its receptor on the thyroid membrane, activating the receptor, finally an enzyme called Adenylate Cyclase activated on the thyroid gland and cyclic AMP (cAMP) is produced cAMP, subsequently activate the enzymes which are required for thyroid hormone synthesis and process, such as Iodine entry into thyroid gland by active transport through activation of soduim-potasium pump which are required for the production of thyroxin (T4) and triiodo-thyronine (T3). The hCG hormon due to structural similarity to the TSH, now with its elevated concentration particularly during first-trimester of pregnancy can bind to the TSH receptor and subsequently switch on, all the activities within the thyroid gland to synthesis the thyroid hormones T4 and T3 during early stage of pregnancy and T4 and T3 maternal serum are elevated and the extra demand for thyroid hormones naturally are produced and pregnant women consume the elevated T4 and T3 for the normal requirement of thyroid hormones during pregnancy. Due to what was mentioned earlier, thyroid over-activity during normal pregnancy is logical requirement of this phase of maternal life. It is due to this fact, that thyroid function should be assessed by referring to the normal reference range intervals of thyroid hormone during pregnancy, in addition each trimester of pregnancy should have its own normal reference range separately (Yoshimura and Hershaman, 1995; Glinoer *et al*., 1993; Pekonen *et al*., 1988; Hershman, 1992, 1994; Fantz *et al*., 1999; Merz, 1996; Smits *et al*., 2002).

Nausea and vomiting-hyperemesis gravidarum during pregnancy: Various studies reported, that cases with nausea and vomiting, due to the over-activity of thyroid gland. The author of this review and his colleagues in a study reported that T4 Level elevated among 56.6% of their pregnant women with nausea and vomiting when compared with control pregnant women without nausea and vomiting. it means that elevated T4 during pregnancy might be responsible for such a disorder during pregnancy period (Shahmohammdi *et al*., 2008; Verberg *et al*., 2005; Bouilln *et al*., 1982).

When nausea and vomiting continues in excessive amount and the period and duration of nausea and vomiting prolonged resulting in dehydration and weight loss, with subsequent requirement for hospitalization of pregnant women, hyperemesis gravidarum is the pathological definition for this latter condition, which accompanied with elevated level of hCG and suppressed serum TSH level and elevated T4 concentration which is believed would be the result of excessive amount of hCG production in some pregnancies.

Vomiting can be considered as a normal cause of pregnancy, but hyperemesis gravidarum which may be accompanied with coincidence of less than 1%, is a pathological case among pregnant women (Mestman *et al*., 1995; Glinoer, 1998a, b; Verberg *et al*., 2005; Al-yatama *et al*., 2002).

Although, hyperemesis grovidarum condition during pregnancy accompanied with hyperthyroidism and is believed that hCG may be responsible, but it is reported that hyperemesis gravidarum accompanied with some pregnancies are the direct results of thyroid autoantibodies of Graves disease which is predominately responsible for hyperemesis gravidarum in some pregnancies (Tan *et al*., 2002; Bishnoi and Sachmechi, 1996; Kirshon *et al*., 1988; Goodwin *et al*., 1992a, b, 1997; Lao *et al*., 1987; Dozeman *et al*., 1983; Goodwin *et al*., 1997; Glinoer, 1998; Mori *et al*., 1998; Bouilln *et al*., 1982).

There are other reports, which indicated the excessive amount of hCG produced during some pregnancy and the stimulation of TSH receptor and in turn the production excessive amount thyroid hormone during some pregnancies which can be the reasons for the clinical manifestation of hyperemesis gravidarum during pregnancy (Yoshimura *et al*., 1993; Yoshimura and Hershman, 1995).

The status of Thyroxin Binding Globulin (TBG) during Pregnancy: The TBG is a protein synthesized in the liver and transport thyroid hormones in blood circulation in human in general. During normal case of pregnancy the serum level of total T4 and total T3 are increased which are partly due to elevated amount of TBG, which is mainly produced by the liver on The effect of female hormones concentration of estrogen which is elevated during pregnancy and it can modify the synthesis of TBG by the liver. There are many reports arguing the reason of elevated of T4 and T3 during pregnancy are partly due to direct effect of elevation of TBG in maternal blood (Golinor, 1997; Skjoldebrand *et al*., 1982; Guillamue *et al*., 1985; Glinoer *et al*., 1990).

The serum thyroglobulin concentration during pregnancy: Thyroglobulin is a large idonized glycomacromolecular weight protein of about 5000 amino acids, this macroprotein contain, 115 tyrosine residues an aromatic amino acids which are part of this large protein. T4 and T3 are synthesized on the tyrosine residual of thyroglobulin. Thyroglobulin concentration is increased during any thyroid lesion and hyperactivity during pregnancy, which reflect the over-activity of thyroid gland during a normal pregnancy (Glinoer, 2004; Bartalena, 1990; Zigman *et al*., 2003).

The auto-antibodies raised against thyroid gland during pregnancy: The hyperthyroidism, during the routine pregnancy and its pathological cause which is responsible for, nausea and vomiting (Shahmohammdi *et al*., 2008) and its severe form hyperemesis gravidarum, at some point can be caused by auto-immunity against thyroid gland. These auto-antibodies, can be raised against TSH receptor, peroxides enzyme and thyroglobulin itself. Due to the above facts, the thyroid auto-antibodies maternal serum concentration should be assessed to diagnose the Grave disease, which may be responsible for metabolic disorder during pregnancy, mainly of hyperemesis gravidarum, by checking the serum level of thyroid auto-antibodies (Weetman and McGregor, 1984; Fausett and Branch, 2000).

During a normal pregnancy the pregnant women immune system go through a tremendous changes to adapt itself, to fetus, which can be considered as a antigen determinants as whole, there are some arguments, that the induction of autoimmunity in maternal physiological system, partially related to fetus itself, which is considered as a outsider to the pregnant women immune system. During a normal pregnancy, the immune system of pregnant women adapt itself, with the new condition and there is not a serious adverse side effect of immune system against pregnant women, during a normal pregnancy (Imaizumi *et al*., 2001). It should be noted that due to what was mentioned above and in case the immune system was not able to adjust itself, subsequently, thyroid auto-antibodies are elevated during pregnancy and growing fetus can release enough antigens to stimulate the immune system of pregnant women and maternal immune system, subsequently produce enough antibodies stimulate the maternal thyroid and inducing the thyroid abnormalities afterward.

HYPERTHYROIDISM AND HYPOTHYROIDISM DURING PREGNANCY

Hyperthyroidism: The main core of what was mentioned in this review, up to this point, were about the hyperthyroidism during pregnancy, Factors predominantly responsible mainly are, thyroid auto-immune disease, which is Graves diseases and only a minor cases of hyperthyroidism related to excessive amount of hCG which may stimulate TSH receptor and overproduce T4 and T3, with above metabolic disorder of pregnancy and in some cases it will end up with pregnancy termination as sudden abortion (Glinoer, 1999).

Hypothyroidism: Although, the prevalence of hypothyroidism during pregnancy is higher compared to hyperthyroidism 0.7 vs 0.2%, but the metabolic disorder accompanied by hyperthyroidism such as hyperemesis gravidarum are much more stressful, for pregnant women, in case the hyperthyroidism which is not treated, the fetus faces eventual death. Hypothyroidism during pregnancy mainly occur, due to iodine deficiency of maternal regiment and autoimmunity, which is called Hashimato, thyroiditis, low birth weight and mental retardation are part of hypothyroidism side effect (Dendrinos *et al*., 2000; Glinoer, 2000; Netto *et al*., 2004).

Thyroid hormone assessment in hyperthyroidsm and hypothyroidism: Also clinical manifestation detected by the clinician is vital, but medical diagnostic laboratory can help in diagnosing whether the patient is in state of either

hypothyroidism or hypothyroidism. The TSH is a single laboratory test which can give a clear outcome of thyroid function test, also the measurement of T4, is critical and it is clearly indicated. In earlier study by author and the findings on the state of nausea and vomiting among pregnant women, the measurement of T4 even was more important to diagnose the patients clinical cause (Shahmohammdi *et al*., 2008). The TSH is a hormone which can evaluate the thyroid function and it also recommended by the American thyroid association, as the most important single test of thyroid assessment (Surks *et al*., 1990).

The measurement of T4, T3 and the determination of auto-antibodies raised against thyroid enzymes and thyroglobulin are also recommended (Dendrinos *et al*., 2000; Glinoer, 2000; Netto *et al*., 2004). In case of high TSH and low T4 and T3, hypothyroidism is and when TSH is low accompanied with elevated T4 and T3 the, hyperthyroidism are detected, respectively. Although, there are cases with normal T4 and T3 but elevated TSH which the subjects on clinical examination are euthyroid, but from laboratory point of view are categorized as hypothyroid patients, but the definition for such subjects are termed as subclinical hypothyroidism. It probably mean such patients do not exhibit the full clinical syndrome of hypothyroidism. A study on women subclinical hypothyroidism patients was carried out by the author et al., on the state of serum lipid alteration of subclinical patients women and it was found that in subclinical hypothyroidism there is an association of dyslipidemia, among women. In present study we found more women are in state of sub clinical hypothyroid disorder than men (Mansourian *et al*., 2008), subsequently we argue that it is clear that pregnancy aggravate the disorder even further.

The other concern for hypothyroid patients as it was mentioned is the dyslipidemia and lipid alteration among sub clinically hypothyroid patients with adverse effect of arthrosclerosis, which can be considered as alarming risk factor and need particular attention for pregnant women at a time when pregnancy accompanied with some particular complications itself. The author in a review of literature found the lipid disorder among subclinical hypothyroid patients. Abnormal elevation of total cholesterol and LDL- Cholestrol are common findings in most reported studies (Mansourian, 2010). The other basic point which can be focused on hypothyroid patients is the level of lipid per- oxidations and free radical productions which can cause tissue injury and other abnormality. In separate study we examined the elevated lipid per-oxidations among hypothyroid patients and we found that hypothyroidism accompanied with free radical production, (Marjani *et al*., 2008). On the base of latter findings we argue that free radical production during pregnancy also should have been taken seriously to prevent damage to the growing fetus and maternal tissues as well. The Graves disease and Hashimato thyroiditis, the two well known thyroid auto-immune disorder are the stimulator of causing the hyper and hypothyroidism, respectively which should also has to be taken into account for pregnant women and fetus. (Amino *et al*., 1976, 1977, 1982; Jansson *et al*., 1984; Bech *et al*., 1991; Mckenzie and Zakarija, 1989; McKenzie and Zakarija, 1992; Roti and Emerson, 1992; Rasmussen *et al*., 1990; Zakarija and Mckenzie, 1983; Janssen *et al*., 1984). The auto-antibodies measurements are among laboratory tests which can clearly explain partly the thyroid disorder during pregnancies.

The thyroxin produced by thyroid gland is vital for the proper physiological function of fetus, especially for the growing physical and mental development and above all brain proper development require sufficient amount of thyroxin. In addition if pregnant women is on levothyroxin, to compensate for thyroxin deficiency, it should be remembered that, the pregnant women will need extra amount of thyroid replacement therapy than before for the sake of herself and her well being of growing fetus (Glinoer, 1998a, b).

The medical squeal of hyper and hypothyroidism, profoundly well established. There are various adverse effect of for either of thyroid disorders. The examples can be from pregnancy abortion, fetus death and, infertility, low birth weight, mental retardation in hyper-and hypothyroidism respectively (Seely and Burrow, 1991; Grodstein *et al*., 1993; Peterson, 1994).

Thyroid function during first-trimester of pregnancy: Hormonal changes during first trimester of pregnancy and steady elevation of Stradiol and other estrogen during the first trimester of pregnancy and their effect on the liver make the few fold increase in the concentration of TBG. It has been shown that the TBG serum level increases at early stage of pregnancy, thyroxin the main hormone of thyroid gland has a high affinity for the TBG and T4 is mainly bound to this protein, which is synthesized within the liver and in early pregnancy its concentration increased. This physiological process, modify the T4 concentration. and total thyroxin level increased at early stage of first-trimester of pregnancy (Ain *et al*., 1987; Kumar *et al*., 2003; Shahmohammdi *et al*., 2008).

Induced hyperthyroidism due to a combined action of estrogen hormone on the liver on producing TBG and

hCG action on thyroid gland to produce extra T4 and T3. The author of this review and his colleagues have carried out an study on the role of thyroid hormone during the first trimester of pregnancy and they found induced hyper thyroidism, which cause more pregnant women, to have morning sickness and nausea and vomiting (Shahmohammdi *et al*., 2008). In other study we found 56.6% of pregnant women demonstrated elevated T4 and shown to have nausea and vomiting in compare to 33.3% of control which showed to have elevated T4. we concluded that the induced elevation of T4 may be responsible for the morning sickness, nausea and vomiting of first-trimester of pregnancy, this finding is in agreement with many other studies in different part of the world (Al-Yatama *et al.*, 2002; Caffrey, 2000; Haddow *et al.*, 2008; Sheehan, 2007).

Laboratory assessment of thyroid function test during early stage of pregnancy and measurement of TSH, T4,T3,TBG, hCG and thyroid auto- antibodies, all help the clinician to properly address a pregnant women with hyperthyroidism. In our study also we found elevated serum T4, but on the other hand TSH was not suppressed to the level that match T4. The TSH level during the first trimester of pregnancy should be assessed carefully, although there are contradictory findings on the level of T4, which has been reported by many authors (Mansourian *et al*., 2010; Burrow, 1993; Glinoer, 1997; Boss and Kingstone, 1979; Kurtz *et al*., 1979; Harada *et al*., 1979; Malkasian and Mayberry, 1970).

There are strong arguments, that the induced hyperthyroidism during early stage of pregnancy is responsible for the nausea and vomiting and its sever form hyperemesis gravidarum (Shahmohammdi *et al*., 2008; Mazzaferri, 1997; Goodwin *et al*., 1992a, b).

There are also other arguments about the state of hyperthyroidism during pregnancy. As it is well established, pregnancy is a physiological condition with profound alteration of many hormones required for the new physiological condition. There are universally agreed on the need of thyroxin replacement when pregnant women do not synthesis enough thyroxin, which is outmost importance for the growing fetus and pregnant women as well (Springer *et al*., 2009; Chen and Jhon, 2002; Idris *et al*., 2005). Although, there are many reports advising for the proper evaluation of thyroid function tests during early stage of pregnancy, to avoid, the risk involved with hypothyroidism (Striker *et al*., 2007) but one should remember that the extra requirement of T4 during pregnancy and elevated T4 according to the reference range of manufacturer kit, for non pregnant women may cause some irreversible damage to the growing fetus if the treatment for hyperthyroid start which it is in fact are the extra requirements of thyroid hormone for pregnant women and the fetus. In our earlier work we found if the reference intervals for pregnant women not established, there would be a negative adverse effects on pregnant women and the fetus as well (Mansourian *et al*., 2010).

It means, not every pregnant women which demonstrate elevated T4 she is really in state of hyperthyroidism but, it is the new physiological condition and the metabolic regulation of pregnant women which realized and on that base, extra thyroxin requirement is requested, T4 is elevated, not for the sake of hyperthyroidism, but for the sake growing fetus demand and the maternal new physiological conditions, therefore the establishment of reference intervals and the methodology of thyroid hormone measurements in each region is a great importance (Dash *et al*., 2005). We argue that if the maternal serum thyroxin level, is at normal level it should be taken seriously into account, whether the pregnant women is being, practically at hypothyroid state, if not and the pregnant women are treated for hypothyroidism which is not in real term present, then the fetus is faced with irreversible mental and physical damage.

Therefore, the reference intervals for each society should be established, to prevent the missdiagnosis. Some times the laboratory findings and recommendation to the clinician can be miss -leading if the laboratory test result properly not presented and the normal range of thyroid hormone on each region is not established. In addition to the methodology of laboratory manufacture kit, environmental factors, ethnicity, nutritional habits in each region should to be also taken for further consideration for any laboratory test results considered by clinicians for managements of pregnant women, otherwise, according to the laboratory findings to treat, a hyperthyroidism which was not a real, subsequently end up with hypothyroidism which may have irreversible damages to mental, brain and physical functions of growing fetus (Roti and Emerson, 1992; Springer *et al*., 2009; Dash *et al*., 2005).

In our study on pregnant women in our region we found an unacceptable results of 48 and 10% of our pregnant women remained in hyperthyroid state according to T4 and TSH level and reference interval of manufacture of laboratory kit which according to our opinion can not be accepted and be corrected because the pregnant women in present study were apparently healthy

subjects (Mansourian *et al*., 2010) and if the clinician was going to treat the present disorder, ultimately, we would have pregnant women in hyperthyroid state. On the base latter findings even the pregnant women with normal T4 and TSH on the manufacture kit should be taken under repeated laboratory tests and laboratory findings should be compared with pregnant women reference intervals and not with reference interval of non-pregnant women which for sure can mislead the clinicians and medical team on the outcome of pregnancy.

It has been reported that 10.6% of potential misclassifications of thyroid function test were found when the non-pregnant women thyroid reference intervals were used for pregnant women, which should be taken seriously for the pregnancy outcome with unvalued reference range for pregnant women (Panesar *et al*., 2001; Morreale de Escobar *et al*., 2004; Brent, 2007; Haddow *et al*., 2004; Stricker *et al*., 2007).

CONCLUSIONS

The main points concluded from this review of literature are as follow:

- Pregnancy is a physiological condition for women with varieties of new biochemical and metabolically changes. Significant alteration happens in the maternal thyroid gland with eventual effect on the growing fetus
- Iodine deficiency may occur during new physiological condition of pregnancy due to increased glomerular filtration rate and this clearance happen at a time when the maternal and growing fetus Iodine requirement are higher at any time than before
- The evaluation of thyroid function test during pregnancy and particularly in the first- trimester of pregnancy is of great importance due to extra requirement of thyroxin for growing fetus
- The role played by human choronic gonadotropin (hCG) and the stimulatory effect of hCG on TSH receptor should be investigated to assess the extra thyroxin produced by thyroid gland by the hCG stimulatory action
- Hyper and hypothyroidism during pregnancy should be evaluated carefully and assessed properly to avoid the irreversible adverse effects on the growing fetus and pregnant mothers
- The determination of serum TSH, T4, T3, Iodine, thyroid auto-antibodies should be investigated properly
- Nausea and vomiting (morning sickness) and its sever form hyperemesis gravidarum during early stage of pregnancy which might be due to hyperactivity of thyroid gland and its causative factors should be evaluated carefully to protect the pregnancy outcome
- The status of TBG, a protein responsible for thyroxin transport should be assessed, it is usually elevated with subsequent elevation of total thyroid hormones
- The concentration of thyroglobuline during pregnancy should be evaluated to assess for any thyroid injury and over activity of thyroid gland
- Hyper and hypothyroidism during pregnancy should be diagnosed to avoid adverse side effect on the maternal and fetus physiology
- Thyroid function test during the first-trimester of pregnancy should be assessed carefully to prevent the irreversible consequences and damages on pregnancy outcome in the early stage of fetus formation
- Above all the reference intervals of thyroid hormone for pregnant women in each region should be determined to prevent misdiagnosis of such vital stage of life for growing fetus and pregnant women new physiological demands

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