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Female Reproduction Physiology Adversely Manipulated by Thyroid Disorders: A Review of Literature

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Abstract: Proper thyroid function is vital to have a healthy reproduction system. Female sex hormones are altered due to hypothyroidism and hyperthyroidism. Female reproduction system is negatively manipulated by both hyperthyroidism and hypothyroidism and menstrual disorders are the ultimate consequences. Hypomenorrhea, polymenorrhea and oligomenorrhea are the clinical manifestation associated with hyperthyroidism and hypothyroidism, respectively. The female infertility is also adversely affected by thyrotoxicosis and myxedema, the clinical presentation of hyper and hypothyroidism. The simultaneous existence of autoimmunity which is present among some portion of pregnant women may aggravate the clinical manifestation of thyroid disorders in female reproductive physiology. Abortion, premature infants, low birth infant, are among clinical presentation of overt hypothyroidism. Auto antibody against thyroid stimulating hormone receptor and eventual hyperthyroidism considered as risk factors which require extra attention while the thyroid disorder is clinically managed during pregnancy to prevent the fetus from abnormal metabolism. The aim of this review is to elaborate the adverse role of hyperthyroidism and hypothyroidism in female reproduction physiology.

Key words: Hyperthyroidism, hypothyroidism, thyroid hormone, female infertility

INTRODUCTION

Thyroid disorders can be divided into hypothyroidism and hyperthyroidism, both with numerous adverse effects and clinical manifestations on many organs within human body. Graves diseases which is the most abundant autoimmune disorders of thyroid gland and it is found to have a different frequency in various part of the world start from 0.4-1.6% with average and about 1% round the globe (Aghini-Lombardi *et al.*, 1999; Tunbridge *et al.*, 1977; Jacobson *et al.*, 1997; Mansourian 2012a-c; Mansourian and Ahmadi, 2010; Mansourian 2010a-e).

Hypothyroidism is another thyroid disorders and it seems the prevalence of hypothyroidism is more frequent among female compared to male and the various studies from many parts of the world indicate that Hashimoto which another type of a thyroid autoimmunity is the important factor for in causing hypothyroidism. The incidence of hypothyroidism as normal cause among female is in directly correlated with age and the prevalence of hypothyroidism in elderly female is about ten times higher compared to younger age in their twenties. World wide studies indicate that the frequency of hypothyroidism is higher is more prevalent more prevalent among female and the ratio getting higher with

increasing chronological age. It seems autoimmunity is the main reason behind hypothyroidism and thyroiditis due to autoimmunity lay behind the most majority of hypothyroidism. Uncontrolled therapy for the hyperthyroidism can also be signaled out among the causative factors of hypothyroidism and fetus functional disorder occur when hyperthyroidism is treated during pregnancy (Tunbridge *et al.*, 1977; Vanderpump *et al.*, 1995; Wang and Crapo, 1997). This review was designed to study the vital role played by thyroid hormones in the female reproductive machinery, accompanied with investigation on the adverse effect of thyroid disorders on the female reproduction physiology.

Hyperthyroidism interfere with female reproduction: The protein responsible for the transportation of female sex hormones, defined as Sex Hormone Binding Globulin (SHBG). The protein responsible for the transportation of female hormones, defined as and also the serum estrogen level concentration are elevated in during hyperthyroidism. Therefore correlation between SHBG and female sex hormones and during a in periodical cycles and pregnancy should be taken into close consideration the correlation between SHBG and female sex hormones is a matter under scrutiny (Akande and Hockaday, 1972a; Ridgway *et al.*, 1975).

The status of androgen the predominately male sex hormones in female is also manipulated due to hyperthyroidism and various form of androgen remain elevated among hyperthyroid female. In addition during the thyrotoxicosis which is given definition for the clinical manifestation of hyperthyroidism, the production of minor form of estrogen including estrone and estriol from male sex hormones are mainly elevated (Krassas, 2005a; Southren *et al.*, 1974; Burrow, 1986). It should be mentioned that the androgen metabolic pathways in female is altered during thyrotoxicosis resulting in the elevation of average male sex hormones in female and with simultaneous increase in the biosynthesis of main sex hormone in female suffering from thyrotoxicosis (Krassas, 2005a; Southren *et al.*, 1974; Burrow, 1986).

Studies showed the Serum Luteinizing Hormone (LH) concentration in thyrotoxic female in average is higher during woman periodical cycle in both follicular and leuteal phase on menstrual period. It seems that by any standard and study procedure LH remain to be higher among women with thyrotoxicosis, but this LH fluctuation may return to reference range of normal following thyrotoxicosis treatment (Akande and Hockaday, 1972b; Akande, 1974; Zahringer *et al.*, 2000).

Other studies indicate that the serum concentration of Follicle Stimulating Hormones (FSH) is not altered as parallel to LH. These parts of female sex hormones alteration due to hyperthyroidism seems to be a controversial area of and still can be considered as a topic with a lot of enthusiastic discussions (Pontikides *et al.*, 1990a, b; Akande, 1974; Tanaka *et al.*, 1981; Distiller *et al.*, 1975; Zahringer *et al.*, 2000).

LH, FH and prolactin are among the crucial hormones which assess the female fertility and thyroid hormone can play important roles in this regards. Any harm to thyroid gland with subsequent to the thyroid hormone abnormality not only adversely affect female reproduction system, but all organs within the human body adversely affected. The findings from interventional studies on hyperthyroid women indicated that LH, FSH and prolactin, are adversely affected with the thyrotoxicosis and it seems with exception of prolactin they are higher compared to control, but studies proved showed the above mentioned hormones return to normal concentration levels following thyroid treatments (Zahringer *et al.*, 2000; Pontikides *et al.*, 1990a).

Studies indicated thyrotoxicosis can interfere with routine metabolic pathways even before the age of puberty among in female and it is believed that thyrotoxicosis may bring forwards the initial age of menstruation. Also there are controversial argument in this regard, particularly when either the menstrual

periodical cycle length duration or the volume related to periodical cycle is a topic for discussion are concerned. Also it seems prenatal hyperthyroidism cannot leave a serious adverse effects on female reproduction system, but care should be taken when thyrotoxicosis is treat during pregnancy to avoid fetus harm machinery (Saxena *et al.*, 1964; Speroff *et al.*, 1983; Warren, 1996).

Hypomenorrhea and hypermenorrhea are the definition are given for about 20% reduction and 20% elevation in the amount of menstrual volume, respectively when compared to the female herself average periodical cycle follow while menorrhagia considered as excessive menstrual flow during menstrual cycle period. Oligomenorrhea, polymenorrhea and amenorrhea are the three definitions which are given to the days between two consecutive periodical cycles. It seems the 28 days can be considered in average as normal periodical cycle, but the duration of more than 35 days and less than 21 days between two consecutive in female menstrual cycle are defined as oligomenorrhea and polymenorrhea, respectively. On the other hand if there is a missed menstrual cycle by more than three month a woman can be labeled as to be in the state of amenorrhea (Speroff *et al.*, 1983; Warren, 1996; Krassas, 2000a). It seems Amenorrhea in female can be considered as prognostic clinical manifestation for the onset of thyrotoxicosis, also there are various reports in this area of female reproductive physiology, including Oligomenorrhea, hypomenorrhea and even also female ovulation cession which all are caused by is the result of hyperthyroidism and its clinical manifestation can be accompanied with abnormality in the including disruption in the female reproduction physiology (Benson and Dailey, 1955; Krassas, 2000a). It is also reported that the females hormones and other biochemical pathology index performed by the, of clinical laboratory are altered adversely as result of result of thyrotoxicosis. The other clinical symptoms of thyrotoxicosis such as nutritional disorders and adverse psychological behaviors which are accompanied with hyperthyroidism and are among the symptoms of thyrotoxicosis, might be behind the abnormalities which are commonly seen in females reproductive pathophysiology (Krassas, 2005a; Benson and Dailey, 1955).

Various studies elaborate the fact that the extend in which hyperthyroidism may not adversely affect the female reproductive pathophysiology are not completely similarly and there are some studies coming with showing different frequency in the onset of oligomenorrhea, amenorrhea, polymenorrhea, hypomenorrhea, hypermenorrhea. The comprehensive conclusion out all these controversial findings is that female reproductive

physiology is deeply upset by the hyperthyroidism gland in female. Thyrotoxicosis is also accompanied with menstrual and other reproductive disturbances in females, also as thyroid return to normal functioning the adverse effect of thyrotoxicosis may be can be cleared off (Goldsmith *et al.*, 1952; Joshi *et al.*, 1993; Benson and Dailey, 1955; Tanaka *et al.*, 1981; Krassas *et al.*, 1994, 1999).

The prevalence of fertility has was set up to be around 10-15% and it seems the ratio of infertility among female and male according what is been established is almost equal to about 30% and 35% for male and female, respectively. In spite of what was mentioned there are other unexplained reason for infertility as well. The definition for infertility which is explained from various studies come from the fact of not being conceived following the first year in spite of desire for pregnancy. Beside hormonal disturbances, physiologically there are many other reasons for female infertility (Poppe *et al.*, 2007a; Evers, 2002; Mosher and Pratt, 1991; Wang *et al.*, 2003; Gnoth *et al.*, 2003; Healy *et al.*, 1994; Schenken and Guzick, 1997; Lunenfeld and Insler, 1974).

There are various study any way which have found a correlation between the clinical manifestation of hyperthyroidism and infertility and it is most certain that thyrotoxicosis which is a definition for the clinical manifestation of hyperthyroidism play an definite role in female infertility (Joshi *et al.*, 1993; Goldsmith *et al.*, 1952). Hormonal studies during periodical cycle are also partly in favor of adverse role of thyrotoxicosis for the onset of infertility in females (Pontikides *et al.*, 1990a). Laboratory studies indicated the frequency of infertility among hyperthyroid infertile women remain high and the incidence of infertility shown to be even higher in female with thyroid autoimmunity as positive stimulator of hyperthyroidism for to the thyroid which can be considered the onset of hyperthyroidism, the incidence of infertility shown to be even higher (Poppe *et al.*, 2002, 2008a, b).

The adverse effect of therapeutic regiment in particular radioactive iodine therapy should be taken into consideration when it is recommended for thyrotoxic female to prevent the side effect which may arises due to such its application on the reproductive physiology in female fertile age (Safa *et al.*, 1975; Krassas, 2000a).

How hypothyroidism affect female reproduction system:

Various biochemical changes including hormonal alteration are accompanied in female following hypothyroidism. Some hormone clearance such as including estrone are is reduced and some while the

biochemical pathways leading to some other unwanted female hormones are elevated increased (Redmond, 2004; Longcope *et al.*, 1990).

Mexedema is definition which is given for the clinical manifestation of during hypothyroidism and during such clinical presentation the clearance of some estrogens the in female hormone can be elevated. The reduction in the amount of Sex Hormone Binding Globuline (SHBG), is among other biochemical alteration which eventually will be ended up with female hormone abnormality, also the condition is reversed following hypothyroid treatments. SHBG reduction followed by androgen, estrogen fluctuation in female, resulting in a drop in total testosterone and estrogen, but it seems the free hormones concentrations are elevated. In addition to female gonad disturbances, studies indicated some manipulation in the hypothalamus-pituitary axis happen and the normal physiological interrelation which is existed between them are altered resulting in the in coordination of relation between gonadotropin releasing hormone and luteinizing hormone which are hypothalamuses and pituitary hormones, respectively. As result of such irregularity there are studies indicating a rise in thyrotropin releasing hormones from hypothalamuses with subsequent elevation in the concentration of thyroid stimulating hormone and prolactin which are released from pituitary. All the previous metabolic disorders are return to normal following hypothyroid treatments (Redmond, 2004; Longcope *et al.*, 1990; Gallagher *et al.*, 1966; Gordon and Southren, 1977; Larsen *et al.*, 1998; Marino *et al.*, 2006; Valenti *et al.*, 1984; Honbo *et al.*, 1978).

Hypothyroidism for female child bearing age might be accompanied with disorder in periodical cycle and various menstrual abnormality ranging from oligomenorrhea, amenorrhea, polymenorrhea Menorrhagia (Kutteh *et al.*, 1999; Ansell, 1996).

Extensive investigation emphasizes on the adverse role which is laid behind the clinical symptoms of hypothyroidism on the menstrual disturbances in females. The pattern of abnormalities is not evenly distributed, but various forms of menstrual disturbances have been manifested during hypothyroidism.

The female periodical cycle abnormalities seems to be much higher in hypothyroid patients and studies indicate that also the general belief put the amenorrhea is at higher prevalence, but it seems that oligomenorrhea also are prevailed not to be less than amenorrhea.

Studies indicated that even hypothyroids which occur due to the therapeutic treatment of hyperthyroidism can be followed by disorders in menstrual cycle in the affected subjects (Goldsmith *et al.*, 1952; Joshi *et al.*, 1993; Ansell, 1996; Benson and Dailey, 1955; Scott and Mussey, 1964; Joshi *et al.*, 1993; Kutteh *et al.*, 1999).

Subclinical hypothyroidism is form of a thyroid disorder which is presented with normal thyroid hormones of thyroxine (T4) and triiodothyronine (T3), but with elevated thyroid stimulating hormone (TSH). The correlation between subclinical hypothyroidism and infertility also is rare but it is a matter for consideration in some cases of infertility (Bals-Pratsch *et al.*, 1997; Gerhard *et al.*, 1991; Shalev *et al.*, 1994; Grassi *et al.*, 2001; Arojoki *et al.*, 2000; Raber *et al.*, 2003; Abalovich *et al.*, 2007; Poppe *et al.*, 2008a, 2006; Bohnet *et al.*, 1981; Krassas 2005b; Poppe *et al.*, 2002).

Intensive studies about the role of overt hypothyroidism in inducing infertility have been carried out and all in agreement for a role for hypothyroidism in female infertility in some respect. Those female suffering from myxedema, the clinical feature of hypothyroidism, are presented with various form of infertility problem ranging from disorder in ovulation and abnormality in the amount of corpus luteum, produced during a periodical cycle and other menstrual abnormalities (Goldsmith *et al.*, 1952; Joshi *et al.*, 1993).

With all controversial findings in the relation which is existed between hypothyroidism and infertility in female child bearing age, but various studies in this area of physiology indicate there are some kind of correlation between hypothyroidism and infertility of any form. This physiological disturbances in female infertility are elaborated in many studies, also the real concern in this area of research come from the fact that many hypothyroid patient may had been diagnosed and possibly the infertility as medical case might not be dealt with simultaneously with hypothyroidism (Poppe *et al.*, 2007a; Arojoki *et al.*, 2000; Poppe *et al.*, 2006; Zollner *et al.*, 2001).

Mexedema which is the clinical manifestation on hypothyroidism exert hormonal abnormality on female to the extent of causing infertility, the female sex hormones the estrogens, the elevation of prolactin, The abnormality in the proper secretion of Luteinizing Hormone (LH) which is due to disruption of gonadotropin releasing hormone-luteinizing hormone axis and in fact the irregularity in the hypothalamus-pituitary axis can play an important adverse effect on female hormonal disorder with subsequent infertility in female.

Also gonadotropin releasing hormone, luteinizing releasing hormone and follicle stimulating hormones are the essential hormones in female fertility, but the thyroid hormones, play an important role in the optimum state of female fertility. Thyroid hormone substitute-hormonal therapy can reverse the negative effects of hypothyroidism and studies indicate how female serum hormones concentration return to normal following

thyroid start function properly (Krassas, 2000a; Cramer *et al.*, 2003; Krassas, 2000b; Redmond, 2004).

The immune system behave out of range in some individual and it facts female compared to male are more prone to autoimmunity, but this type of thyroid disorder may remain undiagnosed without any sign and symptoms when thyroid function are assessed. Various studies indicate on the adverse correlation of autoimmunity with female fertilization (Poppe *et al.*, 2007a, b).

It seems there is a close relation between thyroid autoantibody and female infertility and this fact have been explained in many studies (Krassas *et al.*, 2008; Kaprara and Krassas, 2008; Wilson *et al.*, 1975; Roussev *et al.*, 1996; Geva *et al.*, 1997).

Also the relation between infertility and auto immunity to the thyroid is already have been established, but still there some controversy in this area of research in the homogeneity of fact findings (Kaider *et al.*, 1999; Reimand *et al.*, 2001; Janssen *et al.*, 2004; Petta *et al.*, 2007; Van Voorhis and Stovall, 1997; Cecconi *et al.*, 1999; Maruo *et al.*, 1991; Poppe *et al.*, 2008b; Poppe *et al.*, 2002; Abalovich *et al.*, 2007; Krassas 2000a, b).

The coordination of thyroid hormone and female estrogen hormones are essential for the optimum biochemical-physiological pathways leading to a proper menstrual cycles in female. It seems a healthy thyroid gland with adequate amount of thyroid hormones with and combination of a healthy hypothalamus-pituitary axis is a pre-condition for a proper female fertility. Therefore Leuteinizing Hormones (LH), Follicle Stimulating Hormone (FSH) which are the central core in female ovarian production will behave optimally when they are combined with thyroid hormones on female reproduction machinery. As result of Females estrogen and estradiol production in particular and its subsequent affect on liver which is followed by increase concentration of Thyroxine Binding Globuline (TBG). The elevation in the concentration of TBG which is a transporter protein carrying the large amount of circulating thyroxine (T4) and triiodothyronine (T3) which in theory can leave the pregnant women hypothyroid during pregnancy, but the healthy female they can be counter acted the scenario through the necessary amount of thyroid hormones biosynthesis by in thyroid gland .Thyroid hormones assessment are therefore should be included in laboratory examination during pregnancy to avoid any harm to the growing fetus (Bartalena, 1990; Alexander *et al.*, 2004; Lee *et al.*, 2009; Wakim *et al.*, 1993).

The major role played by thyroid hormone in female fertility and pregnancy come from various studies on assisted pregnancies. following the thyroid hormones statues and its requirements. At initial stage and also

during pregnancy period thyroid hormones are strongly required which all indicate the tendency towards hypothyroidism in female during pregnancy if remain unattended and unchecked. following . The evaluation of related thyroid hormones and Thyroid Stimulating Hormone (TSH) which is in fact a pituitary hormone reveal the possible incidence of hypothyroidism during pregnancy. It seems most certain that the elevation in the amount of female sex hormone and estardiol in particular is behind this thyroid hormone fluctuation and that is due to the direct effect of estrogen on liver to produce an even excess amount of TBG. This later manifestation followed by eventual binding of free thyroid hormone in the circulation to TBG, although the healthy pregnant woman overcome it if is put on proper dietary regiment including enough amount of iodine (Muller *et al.*, 2000; Poppe *et al.*, 2004).

The thyroxine concentration is elevated during early pregnancy and studies indicated the elevated concentration of Human Chorionic Gonadotropin (HCG) following early conception is the stimulator for the thyroid stimulation leading into increased amount of thyroid hormones.

The role of thyroid hormone in pregnancy: Pregnancy is a period with tremendous metabolic fluctuation and requirements with ultimate major effects on thyroid gland. In general women are more prone to thyroid abnormality and hypothyroidism in particular and specifically during female fertile age. The role of thyroid on the healthy pregnancy and the close association which is exited between pregnant woman and growing fetus are the topic of intensive investigation for the sake of pregnant woman and more specifically for the fetus. Thyroid produce the two most important hormones which dearly are needed for growing fetus as well as the well being of maternal physiology. Thyroid gland should also adapt itself with the crucial period of pregnancy and in fact thyroid hormones in fact I dictate the physiological changes which accompanied with pregnancy in general and at least During each trimester of pregnancy thyroid gland should also adapt itself with this crucial period of pregnancy and in fact thyroid hormones in fact dictate the physiological changes which accompanied with pregnancy in general and at least particularly during each trimester of pregnancy (Glinoe, 1997; Glinoe, 2005; Mansourian, 2011c; Mansourian *et al.*, 2011; Shahmohammdi *et al.*, 2008; Mansourian *et al.*, 2010a, b).

Thyroid binding globulin is a protein synthesized in the liver and its concentration can be elevated by rising estrogens during pregnancy, as result serum thyroxin concentration is elevated, particularly in early stage of

pregnancy. As result of such biochemical modification thyroid hormone should biosynthesis extra amount of thyroid hormones up to the middle of pregnancy to overcome the female new physiological presentation and the requirement of thyroid hormones.

A healthy pregnant woman can adopt herself with this scenario and thyroid in pregnancy produce an extra amount of thyroid hormones on condition of a healthy thyroid gland in combination of enough iodine an essential element in the thyroid hormone structure.

In addition the pregnancy is a physiological period which can be associated with various thyroid malfunctions (Glinoe, 2005; Glinoe, 2007; Pearce, 2009; Bartalena, 1990; Mansourian, 2011 a-d).

Iodine requirements for thyroid hormones biosynthesis is widely investigated and insufficient iodine particularly during pregnancy exert its adverse effect eventually on thyroid to produce enough thyroxin on expenses of elevated Thyroid Stimulating Hormone (TSH). As result the thyroid gland enlarged by the excess amount of TSH which is also produced by the pituitary for the sake of suppressed thyroxin, but it is able to enlarge the thyroid gland leading to goiter presentation (Glinoe, 2005, 2007; Pearce, 2009; Mansourian *et al.*, 2007; Mansourian *et al.*, 2008; Mansourian, 2011c). It is also strongly recommended the pregnant women should be carefully assessed for thyroid hormones, due to the extra demand for thyroid hormones during this crucial times for the sake of fetus and its pregnancy mother. The serum concentration of TSH, T4, T3, are the least thyroid parameters which should be evaluated during pregnancy to have a clear picture of a healthy fetus and maternal life. The normal range for thyroid hormones during pregnancy are altered and when thyroid hormones are assessed those specific values should be taken into consideration. Pregnancy itself might have an adverse effect on thyroid function, leaving the pregnant woman with subclinical, overt hypo and hyperthyroidism. It seems autoimmunity to the thyroid during pregnancy is the major cause for hypothyroidism in particular (Glinoe and Spencer, 2010; Glinoe, 2009; Mansourian, 2010a-e; Mansourian and Ahmadi, 2010).

CONCLUSION

It seems thyroid disorders of any form have the adverse effect on the fertilization. The fluctuation in the amount of sex hormone binding globuline and female hormones have a close correlation with thyroid abnormality. Hyperthyroidism and hypothyroidism both cause menstrual disorders, comprises of polymenorrhea and oligomenorrhea, respectively. It seems both type of

thyroid disorders including overt and subclinical exerting the same adverse effects on female infertility. The autoimmunity to the thyroid also is accompanied with female infertility. Also it is for certain but thyroid malfunction during pregnancy if remain untreated can be followed by various disorders for fetus, pregnant woman and the outcome of pregnancy.

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