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Review Article

Effects of hypothyroidism in Indian women of reproductive age group – A review article

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ABSTRACT

Introduction: Thyroid diseases are the commonest endocrine disorders worldwide. Thyroid dysfunction is 10 times more common in women than in men. Hypothyroidism among women of reproductive age group is linked to menstrual irregularities, polycystic ovaries, recurrent pregnancy loss and infertility.
Aim: The aim of the present review is to provide a comprehensive view of the literature regarding the association of hypothyroidism in reproductive age group women 15-45 years.
Materials and Methods: A literature search was performed using electronic databases like Pubmed/ Medline to identify from 2000 to 201 8. The search yielded around 18 original research articles.
Results: In Correlation of Hypothyroidism with Reproductive Health Problem, the various studies results show that menorrghia is the commonest menstrual irregularity in 27%-72%, next common menstrual irregularity is oligomenorrhea varying from 5 - 26 %. As reviewed from various other studies on association of hypothyroidism with PCOS was found to be between 21% - 32%, Hypothyroidism with Infertility was 22% - 32% and hypothyroidism with recurrent pregnancy loss was found to be 4-15%.
Conclusion: In reproductive age women with hypothyroidism have reproductive health problems like menstrual irregularities, polycystic ovarian syndrome, miscarriages and infertility. Hence thyroid function test should be routinely recommended for all women in reproductive age as it helps in early detection of hypothyr oidism that can be treated medically with hormones and is cost-effective. Unnecessary surgery can be avoided in menstrual irregularities like menorrhagia and complications of pregnancy can be prevented which will reduce burden on the health system and society.

1. Introduction

In India, it has been estimated that about 42 million people suffer from thyroid diseases.[1] Universal salt iodization program in India changed the thyroid status of India. India is in the transition phase from iodine deficiency to iodine sufficiency, and this is expected to change the thyroid status of the population. The thyroid status and auto-immune status of the adult Indian population in the post iodization phase is largely unknown.[2]

The prevalence of overt hypothyroidism in the developed world is 4-5% and that of subclinical hypothyroidism is 4-15%.[3–6] Prevalence of hypothyroidism in the reproductive age group is 2–4% and has been shown to be the cause of infertility and habitual abortion.[7,8] Hypothyroidism among women of reproductive age group is linked to menstrual irregularities, polycystic ovaries, miscarriages and infertility.[9] Studies show that women with both overt and subclinical hypothyroidism are at risk of increased incidence of pre-eclampsia, early and recurrent pregnancy loss, stillbirth, failure of lactation and adverse neonatal outcome viz Mental retardation and congenital anomalies.[10] Thyroid is the most important endocrine organ next to pituitary that exerts the effects on the growth, metabolism and all other functions of the body including the reproductive system. Hypothyroidism affects the reproductive health system mainly due to disturbances in hypothalamic-pituitary-ovarian axis either directly or

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indirectly on the target organs. It was due to altered TSH response, TRH induced high prolactin levels to alter the pulsatile release of GnRH which leads to delay in LH response causing defective luteal phase that may result in excess oestrogen leading to amenorrhea and it is also due to anovulation leading to menstrual irregularities. Increased prolactin levels decrease the GnRH release, and increases the FSH relative to LH causing a follicular cyst, it also increases the adrenal DHEA leading to arrest in follicle maturation. Increased TSH causes spill over effect on FSH receptors leading to collagen deposition.[11]

Hypothyroidism alters peripheral conversion of androgen to oestrogen by decreasing SHBG that cause abnormal feedback at pituitary, peripheral conversion of androgens to oestrogens is increased. The metabolism of oestrogens is altered with respect to oestradiol and estrone. There is decrease in SHBG in plasma that in turn decreases plasma testosterone and oestradiol but there is increase in unbound fractions of oestrogens.[12] Progesterone secretion needs synergistic FSH mediated LH receptors which depend on thyroid hormones. If secretion of progesterone is inadequate and endometrial proliferation persists resulting in excessive and irregular bleeding causing menstrual irregularities like menorrghia, oligomenorrhea, amenorrhea, hypomenorrhea and polymenorrhagia. It also decreases the coagulation factors vii, vii, ix, xi causing heavy menstrual blood loss. Heavy menstrual blood loss is the earliest clinical feature in subclinical hypothyroidism and it also causes recurrent miscarriages.[13] In hyperthyroidism, the gonadotropin concentration is elevated due to increased response of gonadotropin to GnRH due to raised thyroxine levels. SHBG is raised in hyperthyroidism. Decrease in menstrual flow is due to alteration in the synthesis of factor vii in hyperthyroidism. The commonest menstrual abnormality is oligomenorrhoea and amenorrhea in hyperthyroidism.[13]

2. Materials and Methods

A literature search was performed using electronic databases such as Pubmed/Medline to identify relevant articles using relevant search terms for hypothyroidism, menstrual irregularities, PCOS, infertility, miscarriages and reproductive age group. From this search, publications that met the following criteria- original contributions of hypothyroidism with menstrual irregularities, PCOS, infertility and miscarriages, prospective observational studies, hospital based cross sectional study, along with the review articles, and reports limited to clinical human data that were published in the English language were included in the review. Case reports and case series were not included in the review. All articles considered were published in the scientific literature. Full text articles of relevant abstracts were assessed and evaluated. The search yielded around 18 original studies (hospital based cross sectional study and prospective observational) evaluating association of hypothyroidism with menstrual irregularities, PCOS, infertility and miscarriages which were reviewed and are included in the subsequent sections below.

2.1. Impact of hypothyroidism on reproductive health problem

Hypothyroidism is more common in women than men causing abnormality in sexual development, irregular menstrual cycles, infertility and premature meno pause. Menstrual irregularities occur before the onset of overt hypothyroidism or hyperthyroidism. Menstrual irregularities with hypothyroidism are attributed to different sort of mechanisms like disturbance in the hypothalamo -pituitary-ovarian axis, altering the TSH response with altered TRH induced high prolactin levels that alter the GnRH pulsatile secretion leading to defective and delayed LH response leading to defect in luteal phase and anovulatory dysfunction.

2.2. Hypothyroidism with menorrhagia

The physiology of hypothalamo -pituitary-ovarian axis is also dependent on thyroid hormones levels. Hypothyroidism alter the TSH response causing high prolactin levels by TRH leading to altered LH response with peripheral conversion of androgens to oestrogens by decreasing the SHBG causing an abnormal feedback at pituitary level. Hypothyroidism also causes menorrhagia by altering the coagulation factors i.e., decreasing the factors VII, VIII, IX and XI. The results of various studies conducted shows the association of hypothyroidism with menstrual irregularities with menorrhagia was 27-72.5%[13–17] and with oligomenorrhea was 5 %-26.3%[13–17]

The incidence of abnormal uterine bleeding (AUB), the most common menstrual irregularity, is about 15-20% in reproductive age group of 15-45 years. Most of the time menstrual irregularities precede much before the onset of overt hypothyroidism or hyperthyroidism.

The study conducted by Deshmukh P Y *et al* concluded that the prevalence of subclinical hypothyroidism was 18% and that of overt hypothyroidism is 9%. The commonest menstrual disturbances observed by them in women having subclinical hypothyroid ism were polymenorrhagia and menorrhagia. They reported that 27.4% women having hypothyroidism had menorrhagia whereas 35.36% hypothyroid women presented with polymenorrhagia which is most common menstrual abnormality noted by them.[14] Compared to other studies, the study conducted by Deshmukh P Y *et a*l reported the percentage of women having menorrhagia is number of less. Most probably it is because of more number of women presented with polymenorrhagia (35.36%) than menorrhagia (27.04%) alone.[14]

In the study of Ramya M.R *et al* reported the prevalence of hypothyroidism was 42.6%, In their study 72% of women had hypothyroidism with menorrhagia.[15] This study was conducted on women who are having only menstrual disorders amongst which menorrhagia was most common. Hence in their study when hypothyroidism and menorrhagia were correlated percentage of women having hypothyroidism and menorrhagia was high as compared to the studies. Similarly the study conducted by Prasanna Byna *et al* concluded that the commonest menstrual abnormality was menorrhagia and its correlation of hypothyroidism with menorrhagia is high about 42% since the study group was having more number of women having menorrhagia.[13]

The study conducted by Runoo Ghosh *et al* to find out correlation between hypothyroidism and menorrhagia reported that 32.5% of women diagnosed having hypothyroidism had menorrhagia as their presenting symptom.[16]

In the study of Dr. A. Swarupa Rani *et al* when correlating hypothyroidism with menorrhagia were correlated, 57.89% hypothyroid women had menorrhagia, the reason being the group selected for their study was of women in perimenopausal age (between 35-45 years) in whom the commonest menstrual irregularity is menorrhagia.[17]

Most of the studies had comparable results except the one that of Dr.A.Swarupa rani *et al*. who has reported very low percentage of hypothyroid women have oligomenorrhoea (5.26%). In their study the age group of women selected (35-45 yrs.) in which oligomenorrhea is the least common problem with which women visit gynaecologists.[17]

2.3. Hypothyroidism with oligomenorrhea

Hypothyroidism is associated with oligomenorrhea as high TSH alters hypothalamo -pituitary ovarian axis leading to decreased LH and increased prolactin leading anovulation dysfunction causing oligomenorrhea. It may also lead to amenorrhea and galactorrhoea if associated with hypothyroidism for long period of time.

Various studi es show the percentage of oligomenorrhea in women having hypothyroidism is ranging from 15.38% to 26.3%[13–17] which shows strong correlation of hypothyroidism with oligomenorrhea. But in the study of Swarupa Rani *et a*l the association was only 5.26% as the study was conducted only in perimenopausal group 35-45yrs only.

2.4. Hypothyroidism with PCOS

Though the exact relation between PCOS and hypothyroidism is still not known clearly, PCOS is the most common endocrine disorder in women that may have an association with thyroid dysfunction. If both are present, it has the risk of ovarian failure and adverse pregnancy outcomes.

Both have common symptoms like obesity, menstrual abnormalities due to ovulatory dysfunction, acne, fertility problems, abortions, hirsutism, acanthosis nigricans, and insulin resistance. To diagnose PCOS according to 2003 Rotterdam's Criteria, there should be at least two criteria that is necessary to diagnose PCOS (1) chronic anovulation (2) clinical or biochemical hyperandrogenism (3) USG-Polycystic ovaries. Both disorders affect the reproductive and metabolic functions adversely.[12] Most hypothyroidism is diagnosed during the evaluation of PCOS. It also has hyperandrogenic features like acne, hirsutism, increased BMI more than 25 and insulin resistance. PCOS is the most common endocrine problem in reproductive age group associated with 75% of anovulatory infertility and it is also associated with obesity. Though they conceive they have increased the incidence of pregnancy loss.[12]

In hypothyroidism, there is increased sensitivity of ovary to GnRH that leads to marked hypertrophy of ovaries and forms multiple follicular cysts. Deficiency of hormones of the thyroid has profound end organ effects which also affects the reproductive system. It may interfere with GnRH secretion that increases TRH which in turn increases prolactin levels and increase in TSH levels. Increased prolactin levels decrease the GnRH release, and increases the FSH relative to LH causing a follicular cyst, it also increases the adrenal DHEA leading to arrest in follicle maturation. Increased TSH causes spill-over effect on FSH receptors leading to collagen deposition.[11] The metabolism of oestrogens is altered with respect to oestradiol and estrone. There is decrease in SHBG in plasma that in turn decreases plasma testosterone and oestradiol but there is increase in unbound fractions of oestrogens.[12]

Nowadays there is an increased in focus on association of hypothyroidism and PCOS as both are commonly associated with clinical features like obesity, AUB due to anovulatory dysfunction, acne, hirsutism, recurrent pregnancy loss, and insulin resistance.[12] The studies quoted in the table below reported that incidence of PCOS ranges from 21.6%-32%[18–22] in hypothyroid women.

In two studies conducted by Qun -Yu *et al* and Arun Mathew *et al* the study subjects were PCOS women and compared with normal controls. Both studies concluded the incidence of hypo thyroidism noted in PCOS were 32%.[20] and 24%.[21]

2.5. Hypothyroidism with Infertility

Fertility is maintained by the balance between the hypothalamic pituitary adrenogenital axis. Hence dysfunctions of the thyroid may lead to infertility. Thyroid disorders are associated with various problems in the reproductive age group like the delayed onset of puberty, menstrual abnormality and recurrent miscarriages. The most common endocrine disorder that causes infertility is hypothyroidism, while other causes of infertility are hyperthyroidism, PCOS,

diabetes mellitus, Cushing's syndrome.[23]

Hypothyroidism appears to be associated with decreased fertility resulting from ovulatory dysfunction, luteal phase defects, rise in prolactin levels and sex hormone imbalances. It is associated increased secretion of TRH where it stimulates the pituitary to release TSH and oestrogen that may interfere with ovulation. This persistent high level of o estrogen interrupts the mid-cycle preovulatory FSH and LH and thereby causing ovarian dysfunction. It decreases the ovarian function by decreasing SHBG and high prolactin secretion.[24] Hypothyroidism causes the decreased number of primordial and Graafian follicles so defective folliculogenesis and absent corpus luteum if hypothyroidism is present from birth. It was also suggested that decreased LH secretion due to alteration in GnRH release that has the luteolytic effect and inhibits folliculogenesis, oestrogen synthesis, and ovulation.[25] Hence normal thyroid is important for fertility, to sustain a pregnancy and to prevent from recurrent pregnancy loss. Hypothyroidism and autoimmune thyroid disease adversely affect the pregnancy outcomes, like decreased fertility, recurrent abortions, stillbirth, increased incidence of gestational hypertension, anemia, abruptio placenta, PPH and in neonates preterm birth, LBW, impaired cognitive development and learning disabilities.

The incidence of autoimmune thyroiditis is reported is 4% of young females and up to 15% are at threat as they were having autoimmune thyroid antibody.[26] It is stated that there's a strong correlation between thyroid immunity and infertility, miscarriage, and thyroid disturbances in being pregnant and postpartum. Thyroid vehicle antibodies exert their impact in a TSH structured but also in a TSH-unbiased manner. Hence it is suggested that auto immune thyroiditis should be diagnosed and treated in infertile and EPL patients.

Hypothyroidism there is elevated TRH which in turn secrets TSH and prolactin. Hence hyperprolactinemia state is the cause of infertility and PCOS.[27] Vitamin D deficiency is supposed to be a predisposing trigger to autoimmune illnesses. Evidence suggests that lower levels of vitamin D are reported with thyroid auto immunity. In turn, its deficiency is also connected to infertility and pregnancy loss, suggesting a potential interaction with thyroid autoimmunity within the context of infertility.[26] Thyroid autoantibodies also affect zona pellucida, antigens of the placenta and chorionic receptor. Various studies show the association of hypothyroidism with infertility between 22% and 32%.[19,23,24,27–29]

The study conducted by various researchers reports the incidence of hypothyroidism in infertile women in the range of 22-24% except the study conducted by Priyadharshini *et al* which is little higher the reason being is that the study conducted in coastal area of Pondicherry where sea-food rich in iodine is consumed. Priyadarshini *et al* reported hypothyroidism in 32.3% infertile women which is little high compared to other studies and this study was conducted in coastal area of Pondicherry where sea-food rich in iodine is consumed.[19] Excessive iodine consumption stimulates autoimmune antibodies. In their study autoimmune antibodies are not estimated. Probably these women may have increased autoimmune thyroid antibodies.

2.6. Hypothyroidism with recurrent pregnancy loss

Recurrent pregnancy loss with hypothyroidism is due to luteal phase defects, ovulatory dysfunction, autoimmune thyroiditis with anti-TPO antibodies. Even mild hypothyroidism may cause recurrent pregnancy loss. Anti TPO antibody may be was positive in overt hypothyroidism and in subclinical hypothyroidism. The high prevalence of hypothyroidism in coastal areas is not known. But if the women are detected having hypothyroidism it may not be due to iodine deficiency as they are using iodine rich water. It may be due to autoimmune thyroiditis, and we have to do thyroid auto antibodies for all these patients. The study shows that giving iodine for endemic goitre there is development thyroid autoantibodies and increased intrathyroidal lymphocytic infiltrations in numerous patients. After discontinuing iodine, thyroid autoantibodies and lymphocytic infiltration decrease. Another cause is due to oxidative stress that causes thyroid cell necrosis and autoantigens are released. Hence iodine intake is related to developing of autoimmunity thyroiditis and thyrocyte apoptosis.[30] Thyroid abnormalities and autoimmunity are most common in the reproductive age group causing adverse pregnancy outcomes.

The state of pregnancy itself is of immunologic modifications, specially characterized by shifting lymphocyte of helper-1 to lymphocyte of helper-2 cells. Thyroid autoimmunity will increase the miscarriage charge, and thyroxine remedy does no longer appear to defend. By 14 weeks of gestational age, 10% of women who are positive for Thyroid peroxidase antibodies are associated with

1. Increased in Recurrent miscarriages,
2. Increase in thyroid dysfunction during pregnancy
3. Development of thyroiditis in postpartum period.[31]

Pregnant women have elevated risk of miscarriage with autoimmune thyroiditis (AITD in first trimester when compared to women without AITD, despite the fact that being euthyroidism.[32] Autoimmunity Thyroiditis positive women does no longer interfere with ordinary implantation of blastocyst during pregnancy but it may end up with the danger of early pregnancy loss is considerably raised.

In hypothyroidism gonadotropins are within the normal levels. Hence gonadotropins help to differentiate primary hypothyroidism from secondary hypothyroidism.

There may be mild rise in prolactin levels in primary hypothyroidism due to stimulatory effect of TRH leading to high prolactin secretion. Various studies that are shows the association of hypothyroidism with pregnancy loss between 4% -15%.[30,33,34]

In the study, conducted by Rao VR *et al* the incidence was less compared to other studies as it is only 4.2%,[33] as it was case -control study compared between cases and controls with or without recurrent pregnancy loss. In the study, conducted by Shreshta A *et al* the incidence of hypothyroidism with elevated TSH was about 36.79%, among this 14.56% had recurrent miscarriages. The incidence is little high compared to other studies as the incidence of sub clinical hypothyroidism was high, and most of the patients are symptomless in the stage of SCH. 44.3% of them become pregnant after thyroxine hormone replacement treatment within 1 year which shows that hypothyroidism can be corrected by thyroxine and hence recurrent abortion can be both treated and prevented.[30]

In the study, done by Preethi Gahlawat *et al* the incidence of hypothyroidism with recurrent pregnancy loss is 13% which was less compared to the present study as in that study recurrent pregnancy alone is taken in account with raised TSH in first trimester, that was mentioned in the above table both recurrent miscarriages and early single spontaneous abortion was included in the study.[34]

3. Conclusion

In Correlation of Hypothyroidism with Reproductive Health Problem, the various studies results shows that Hypothyroidism with menstrual irregularities like menorrghia, oligomenorrhea, hypomenorrhea and polymenorrhagia. Among these menstrual problems, menorrghia is the commonest menstrual irregularity. H ence it can be concluded that thyroid disorders in reproductive age group were associated with reproductive health problems like menstrual irregularities, polycystic ovarian syndrome, miscarriages and infertility. Henceforth thyroid function test should be routinely recommended for all reproductive age group women, as it helps in detection of hypothyroidism in the early stage, that can be treated medically with hormones and it also cost-effective and unnecessary surgery can be avoided in men orrghia, complications of pregnancy can be prevented and burden to the society is decreased on early diagnosis and management. Early detection prevents the conversion of subclinical hypothyroidism to overt hypothyroidism by treating with hormones with careful follow-up.

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None.

5. Conflicts of interests

None.

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