REVIEW

Implications of hypothyroidism in females of reproductive age: a review of current literature

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ABSTRACT

Thyroid disorders are the most common type of endocrine disorder worldwide. Thyroid disorders affect women tenfold more frequently than men. In women of reproductive age, menstrual irregularities, polycystic ovaries, recurrent pregnancy loss, and infertility have been linked to hypothyroidism. A literature search was done between 2000 and 2020 using internet resources such as Pubmed/Medline. The search turned up around 30 unique research publications. Menorrhagia is the most common monthly irregularity, affecting between 27% and 72% of women, followed by oligomenorrhea, which affects between 5% and 26% of women. Hypothyroidism has been linked to PCOS in a range of 21–32% of cases, infertility in a range of 22–32%, and recurrent pregnancy loss in a range of 4–15% of cases, according to previous study. When women with hypothyroidism reach reproductive age, they experience menstrual irregularities, polycystic ovarian syndrome, miscarriages, and infertility. Thyroid function testing should thus be recommended on a routine basis for all women of reproductive age, since it assists in the early diagnosis of hypothyroidism, which may be treated medically with hormones and is very inexpensive. Monthly irregularities such as menorrhagia can be treated without needless surgery, therefore alleviating the load on the healthcare system and society.

Keywords: Reproductive age, Hypothyroidism, menstrual irregularities, PCOS, recurrent pregnancy loss

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INTRODUCTION

According to estimates, 42 million Indians are affected with thyroid illness. The widespread salt iodization initiative in India has improved India's thyroid condition. India is moving from iodine deficit to iodine sufficiency, which will have an impact on thyroid health in the population. The thyroid and auto-immune status of adult Indians is mostly unknown in the post-iodization era. In the industrialised world, 4-5 percent of persons suffer from overt hypothyroidism, whereas 4-15 percent suffers from subclinical hypothyroidism [1-6]. Infertility and abortion have been related to hypothyroidism, which affects 2–4% of adults throughout their reproductive years. Hypothyroidism has been linked to menstrual irregularities, polycystic ovaries, miscarriages, and infertility in women of reproductive age. According to research, women with both overt and subclinical hypothyroidism have been associated to pre-eclampsia, early and recurrent pregnancy loss, stillbirth, breastfeeding failure, and

unfavourable newborn outcomes such as mental retardation and congenital abnormalities [7-11]. The thyroid, along with the pituitary gland, is the body's most essential endocrine organ, affecting growth, metabolism, and all other physiological functions, including reproduction. Because of alterations in the hypothalamic-pituitary-ovarian axis, hypothyroidism has a direct or indirect influence on the reproductive system. TRH caused a malfunction in the luteal phase, resulting in excess oestrogen and amenorrhea, as well as anovulation, which can cause monthly irregularities. Prolactin increases limit GnRH release and elevate FSH relative to LH, resulting in a follicular cyst. It also elevates DHEA levels in the adrenals, which slows follicle maturation. TSH increase causes collagen deposition by causing a spillover effect on FSH receptors. Hypothyroidism impacts peripheral androgen to oestrogen conversion by decreasing SHBG, which leads to aberrant pituitary feedback, resulting in increased peripheral androgen to oestrogen conversion. Oestrogen metabolism is altered when oestradiol and estrone are present. SHBG levels in plasma drop, lowering plasma testosterone and oestradiol, although oestrogen unbound fractions rise [10, 12-14]. The release of progesterone requires synergistic FSH-mediated LH receptors that are thyroid hormone dependent. When progesterone production is inadequate and endometrial development persists, menstrual abnormalities such as menorrhagia, oligomenorrhea, amenorrhea, hypomenorrhea, and polymenorrhagia can occur. By decreasing the coagulation factors vii, viii, ix, and xi, it also causes substantial menstrual blood loss. Heavy menstrual blood loss is an early clinical indication of subclinical hypothyroidism, which can lead to miscarriages. Because of an increased response of gonadotropin to GnRH as a result of higher thyroxine levels, gonadotropin concentration is increased in hyperthyroidism. SHBG rises as a result of hyperthyroidism. Menstrual flow is reduced in hyperthyroidism due to a reduction in factor vii production. The most common menstrual irregularities in hyperthyroidism are oligomenorrhoea and amenorrhoea [15-17].

IMPACT OF HYPOTHYROIDISM ON REPRODUCTIVE HEALTH PROBLEM

Hypothyroidism affects more women than males, causing abnormal sexual development, irregular menstrual cycles, infertility, and early menopause. Menstrual irregularities may occur prior to the onset of overt hypothyroidism or hyperthyroidism. Menstrual irregularities in hypothyroidism are caused by a number of factors, including disruption of the hypothalamo-pituitary-ovarian axis, changes in the TSH response due to altered TRH-induced high prolactin levels, changes in GnRH pulsatile secretion, and a defective and delayed LH response, all of which result in luteal phase defect and anovulatory dysfunction [15, 18].

Hypothyroidism with menorrhagia

The physiology of the hypothalamo-pituitary-ovarian axis is affected by thyroid hormone levels. Hypothyroidism changes the TSH response by causing high prolactin levels via TRH, leading in an altered LH response with peripheral conversion of androgens to oestrogens via decreasing SHBG, culminating in a pituitary feedback loop. Hypothyroidism,

which affects coagulation factors VII, VIII, IX, and XI, leading them to diminish, can also induce menorrhagia. According to the findings of numerous studies, hypothyroidism is associated to monthly abnormalities in 27-72.5 percent of cases of menorrhagia and 5% to 26.3 percent of instances of oligomenorrhea. Abnormal uterine bleeding (AUB) is the most frequent monthly irregularity, affecting around 15-20 percent of women between the ages of 15 and 45. Long before overt hypothyroidism or hyperthyroidism presents itself, menstrual irregularities are common [15, 19-23]. Subclinical hypothyroidism affects 18% of adults, whereas overt hypothyroidism affects 9% of the population, according to Deshmukh P Y et al.'s study. In women with subclinical hypothyroidism, polymenorrhagia and menorrhagia were the most common monthly abnormalities. Menorrhagia was found in 27.4% of hypothyroid women, whereas polymenorrhagia was found in 35.36 percent of hypothyroid women. Deshmukh P Y et al. discovered a decreased percentage of women with menorrhagia in compared to previous studies. Polymenorrhagia affects 35.36 percent more women than menorrhagia (27.04 percent) [19, 23].

Another study discovered that hypothyroidism affects 42.6 percent of the population. Hypothyroidism and menorrhagia were found in 72% of the women in their research. The ladies in this research experienced just menstrual issues, the most common of which was menorrhagia. As a consequence, when they connected hypothyroidism and menorrhagia in their study, the percentage of women with hypothyroidism and menorrhagia was greater than in prior studies. [24]. Likewise, Byna et al discovered that menorrhagia was the most common monthly irregularity, with a strong link between hypothyroidism and menorrhagia (42 percent) since the research group had a larger percentage of women with menorrhagia [15]. Menorrhagia was the presenting symptom in 32.5 percent of hypothyroidism patients, according to a study done by Ghosh et al to establish the relationship between hypothyroidism and menorrhagia [21, 25]. In a research by Rani et al., hypothyroidism and menorrhagia were linked, and 57.89 percent of hypothyroid women had menorrhagia. This is because the women in their study were in perimenopausal age (between 35 and 45 years), when menorrhagia is the most frequent monthly irregularity. The bulk of the studies showed comparable results, with the exception of Rani et al's research, which indicated a comparatively low number of hypothyroid women with oligomenorrhoea (5.26 percent). Women in the study ranged in age from 35 to 45, and oligomenorrhea was the least prevalent reason for visits to gynaecologists [26, 27].

Hypothyroidism with oligomenorrhea

Hypothyroidism is associated with oligomenorrhea because increased TSH disturbs the hypothalamo-pituitary-ovarian axis, leading in a decrease in LH and an increase in prolactin, which results in anovulation dysfunction and oligomenorrhea. When used in conjunction with hypothyroidism over an extended period of time, it might result in amenorrhea and galactorrhoea. According to many studies, the percentage of women experiencing oligomenorrhea as a result of hypothyroidism ranges between 15.38 and 26.3 percent 13–17, showing a definite relationship between

hypothyroidism and oligomenorrhea. However, the relationship was only 5.26 percent in the study by Swarupa Rani et al., since the investigation was confined to perimenopausal women aged 35 to 45 years [26, 28, 29].

Hypothyroidism with PCOS

Although the precise association between PCOS and hypothyroidism is uncertain, PCOS is the most common endocrine disorder in women that may be associated with thyroid problems. If all factors are present, there is a risk of ovarian failure and an unsuccessful pregnancy. Obesity, ovarian dysfunction, acne, infertility problems, abortions, hirsutism, acanthosisnigricans, and insulin resistance are all common symptoms. PCOS must fulfil at least two criteria as out in the 2003 Rotterdam Criteria: (1) prolonged anovulation (2) clinical or biochemical hyperandrogenism (3) polycystic ovaries as determined by USG. Both of these situations are detrimental to reproductive and metabolic functions. Most cases of hypothyroidism are identified during a PCOS evaluation. Acne, hirsutism, a BMI more than 25, and insulin resistance are all considered to be hyperandrogenic. PCOS is the most prevalent endocrine disease in females of reproductive age, accounting for 75% of anovulatory infertility and obesity. They have raised the rate of miscarriage, despite the fact that they conceive [10]. Hypothyroidism results in increased ovarian sensitivity to GnRH, which results in substantial ovarian hypertrophy and the development of many follicular cysts. Thyroid hormone insufficiency has a detrimental effect on the reproductive system and is associated with severe end organ complications. It may inhibit the production of GnRH, which increases TRH, which increases prolactin levels and TSH. Increased prolactin levels inhibit the release of GnRH and elevate FSH relative to LH, leading in the formation of a follicular cyst. Additionally, it increases adrenal DHEA, halting follicular maturation. Increased TSH has a spillover impact on FSH receptors, resulting in the deposition of collagen. Oestrogen metabolism is altered in response to oestradiol and estrone. There is a drop in plasma SHBG, which results in a fall in testosterone and oestradiol levels, but an increase in oestrogen unbound fractions [10]. Obesity, AUB owing to anovulatory dysfunction, acne, hirsutism, recurrent miscarriage, and insulin resistance are all common clinical manifestations of hypothyroidism and PCOS. According to the studies summarised below, the prevalence of PCOS in hypothyroid women is between 21.6 and 32%. Two investigations done by Qun-Yu et al. and Arun Mathew et al. compared PCOS women to normal controls. Both studies discovered that PCOS patients had a 32% and a 24% prevalence of hypothyroidism, respectively [30-32].

Hypothyroidism with Infertility

The hypothalamus pituitary adrenogenital axis is maintained in balance, as is fertility. Thyroid illness, as a result, may lead to infertility. Thyroid disorders have been related to a number of difficulties affecting women of reproductive age, including delayed puberty, monthly abnormalities, and repeated miscarriages. Hypothyroidism is the most frequent endocrine condition associated with infertility; others include hyperthyroidism, PCOS, diabetes mellitus, and Cushing's

syndrome. Ovulatory failure, luteal phase defects, a prolactin surge, and sex hormone abnormalities all appear to be associated with hypothyroidism and decreased fertility. TRH production is increased, stimulating the pituitary to produce TSH and oestrogen, which might disrupt ovulation. Ovarian dysfunction is produced by an abnormally high amount of oestrogen, which interrupts the mid-cycle preovulatory FSH and LH production, resulting in ovarian dysfunction. By decreasing SHBG and boosting production, it impairs ovarian function [20, 22, 33]. When hypothyroidism is present from birth, it decreases the number of primordial and Graafian follicles, resulting in abnormal folliculogenesis and the lack of the corpus luteum. Reduced LH secretion is considered to be the result of a shift in GnRH release, which has a luteolytic effect and influences folliculogenesis, oestrogen production, and ovulation. As a result, thyroid function is important for fertility, maintaining pregnancy, and avoiding recurrent pregnancy loss. Reduced fertility, recurrent abortions, stillbirth, an increased incidence of gestational hypertension, anaemia, abruptio placenta, PPH, and preterm birth, LBW, impaired cognitive development, and learning disabilities in neonates are all adverse pregnancy outcomes caused by hypothyroidism and autoimmune thyroid disease. According to studies, autoimmune thyroiditis affects 4% of young girls, with up to 15% of those at risk harbouring antibodies against the thyroid. According to studies, there is a strong relationship between thyroid immunity and infertility, miscarriage, and thyroid disorders during pregnancy and postpartum. Thyroid vehicle antibodies have a TSH-structured but TSH-independent action. As a result, auto immune thyroiditis should be diagnosed and treated in infertile and EPL patients. There is an increase in TRH in hypothyroidism, which produces TSH and prolactin. Thus, hyperprolactinemia is a cause of infertility and PCOS. Vitamin D deficiency is considered to be associated with an increased risk of autoimmune disorders. According to studies, low vitamin D levels are associated with thyroid autoimmunity. Infertility and miscarriage are associated with thyroid insufficiency, indicating a potential interaction with thyroid autoimmunity in the setting of infertility. Autoantibodies against thyroid hormone have an effect on the zonapellucida, placental antigens, and the chorionic receptor. According to numerous studies, hypothyroidism is associated with infertility in 22% to 32% of persons [31, 34-38].

Hypothyroidism with recurrent pregnancy loss

Hypothyroidism is associated with recurrent pregnancy loss as a result of luteal phase irregularities, ovulatory dysfunction, and autoimmune thyroiditis caused by anti-TPO antibodies. Even moderate hypothyroidism might result in recurrent pregnancy loss. Anti-TPO antibodies have been demonstrated to be positive in patients with overt and subclinical hypothyroidism. The prevalence of hypothyroidism in coastal areas is unclear. If the females are discovered to be hypothyroid, it is highly improbable that it is due to a deficiency of iodine, as they consume iodine-rich water. It is conceivable that this is due to autoimmune thyroiditis, and so all of these individuals will need to be tested for thyroid autoantibodies. According to the study, administering iodine to individuals with

endemic goitre results in the generation of thyroid autoantibodies and a rise in intrathyroidal lymphocytic infiltrations. After iodine removal, thyroid autoantibodies and lymphocytic infiltration decrease. Another factor is oxidative stress, which results in thyroid cell necrosis and autoantigen formation. As a result, iodine intake has been associated with the development of autoimmune thyroiditis and thyrocyte death. Thyroid problems and autoimmunity are more prevalent in reproductive-aged women, leading in poor pregnancy outcomes. Pregnancy itself is associated with immunologic alterations, most notably the transition of lymphocytes from helper-1 to helper-2 cells. Thyroid autoimmunity increases the chance of miscarriage, and thyroxine therapy appears to be ineffective. By 14 weeks of pregnancy, thyroid peroxidase antibodies are associated with an increased risk of recurrent miscarriages and thyroid dysfunction throughout pregnancy in 10% of women. 3. Postpartum thyroiditis develops. Despite having normal thyroid function, pregnant women with autoimmune thyroiditis (AITD) had a greater risk of miscarriage in the first trimester than those without AITD. Autoimmunity Thyroiditis does not impair normal blastocyst implantation during pregnancy in women, but it does raise the risk of miscarriage. Gonadotropin levels are normal in hypothyroidism. As a result, gonadotropins may aid in the differentiation of primary from secondary hypothyroidism [20, 39, 40].

Due to TRH's stimulatory effect, which results in excessive prolactin production, a small increase in prolactin levels may occur in primary hypothyroidism. Numerous studies have discovered a connection between hypothyroidism and pregnancy loss of between 4% and 15%. The incidence in the study conducted by Rao et al. was lower than in previous investigations, at just 4.2 percent, due to the fact that it was a case-control study comparing patients and controls with or without recurrent pregnancy loss. According to Shreshta et al., 's the prevalence of hypothyroidism with elevated TSH was 36.79 percent, with 14.56 percent of those who had recurrent miscarriages having hypothyroidism. Due to the high occurrence of subclinical hypothyroidism and the fact that the majority of patients remained symptomless during the SCH stage, the incidence was somewhat greater than in previous study. Within one year of initiating thyroxine hormone replacement treatment, 44.3% became pregnant, indicating that hypothyroidism can be treated with thyroxine and hence recurrent abortion may be cured and prevented. Gahlawat et al. reported an incidence of hypothyroidism associated with recurrent pregnancy loss of 13%, which is lower than the current study because the previous study considered only recurrent pregnancy with elevated TSH in the first trimester, whereas the current study considered both recurrent miscarriages and early single spontaneous abortion [20, 33, 40-44].

CONCLUSION

Numerous studies have discovered a relationship between hypothyroidism and menstrual abnormalities such as menorrhagia, oligomenorrhea, hypomenorrhea, and polymenorrhagia. Menorrhagia is the most common kind of menstrual irregularity. As a result, thyroid disorders in women of reproductive age have been associated with reproductive health problems such as irregular

menstruation, polycystic ovarian syndrome, miscarriages, and infertility. Thyroid function testing should be suggested frequently for all women of reproductive age, since it assists in the early diagnosis of hypothyroidism, which may be treated medically with hormones. Additionally, it is financially effective, since needless surgery for menorrhagia is avoided, pregnancy problems are averted, and the burden on society is decreased. Subclinical hypothyroidism can be prevented from developing to overt hypothyroidism by early identification and treatment, as well as diligent follow-up.

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