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Subclinical Hypothyroidism and Pregnancy Loss: A Literature Review

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Abstract

There is a high prevalence of subclinical hypothyroidism (SCH) in pregnancy. It is linked to significant maternal and fetal morbidity and mortality. SCH's effects on pregnancy include increased risks of gestational hypertension and premature rupture of membranes (PROM). Their fetuses and infants had been more likely to suffer from low birth weight (LBW) and intrauterine growth retardation (IUGR). The risk of miscarriage is reported high in various studies for untreated SCH.

SCH is directly associated with increased presence of anti TPO anti bodies in maternal serum.

Early detection and treatment of SCH have witnessed better results in terms of pregnancy outcome.

This review focuses to establish the relationship of increased prevalence of SCH in the developing countries as well as its association with increased anti TPO anti bodies in maternal serum and draw a conclusion which can help narrow down the reasons and provide solution.

This study concluded that SCH is more prevalent in developing countries, either due to iodine deficiency, decreased awareness about this problem or less access to medical facilities. Therefore, it is suggested that females with history of preterm deliveries, previous IUGRs, or miscarriages should undergo screening for subclinical hypothyroidism and Anti TPO antibody levels during their antenatal visits.

Keywords: Subclinical Hypothyroidism; Pregnant Females; Pregnancy Loss

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Introduction

Thyroid hormone regulates the metabolic processes of the body. When you have hypothyroidism, your thyroid produces insufficient thyroid hormone. This can affect many aspects of health, including a healthy pregnancy.

Subclinical hypothyroidism (SCH) is more common than overt clinical hypothyroidism (OH). The etiology is usually autoimmune thyroiditis. Other causes of pregnancy hypothyroidism include postoperative thyroid failure and noncompliance with thyroxine therapy [1].

In hypothyroidism pregnancies, around 2.5% of pregnancies are of subclinical hypothyroidism. During pregnancy, the physiological and hormonal changes increase thyroxin (T4) and triiodothyronine (T3) generation up to 50%, which in return increases a woman's daily iodine demand, while thyroid-stimulating hormone (TSH) levels drop, particularly in the first trimester [1]. Because Human Chorionic Gonadotrophin (HCG) is thyrotrophic, its high levels, particularly in the first trimester, results in low TSH concentrations and therefore cut offs become less. Pregnancy stress emerges as an overt illness in women with insufficient thyroid reserves. Thyroid adaptations are well tolerated in an iodide sufficient area because stored inner thyroid iodide is sufficient; nevertheless, in an iodide deficient location, these physiological adaptations cause significant changes in pregnancy. The rate of detection of SCH in pregnant women, especially in developing countries has not kept pace with the magnitude of the problem [2].

SCH can only be identified based on laboratory test results. Because the symptoms of both SCH and hypothyroidism are non-specific and mirror symptoms that can be associated with changes in lifestyle or those of many other illnesses, such as pregnancy. The effects of SCH in pregnancy include increased risks of gestational hypertension and pre mature rupture of membranes (PROM), and their fetuses and infants had increased risks of Intra uterine growth retardation (IUGR)and Low Birth Weight (LBW) [3].

Prevalence of subclinical hypothyroidism worldwide

The prevalence of SCH in pregnancy in Saudi Arabia was studied by Al Shanqeeti SA, et al. (2018) [4]. It was 50/384 participants, making

it 13%. According to study results in Kashmir, North India done in 2011 by Beenish M, et al. (2017) [3], TSH was within range in 87.4% of subjects and raised in 12.6% of pregnant females. FT4 was within range in 96.2% cases, low in 3.2% and raised in 0.6%. Therefore, the prevalence of subclinical hypothyroidism in pregnant females of Kashmir was 12.6% [2]. Murty NV, et al. (2015) [5], studied the prevalence of SCH in pregnant women in south India and it came out even higher, 16.13%. A study conducted by Yassaee F, et al. (2014) [6], in Tehran, Iran, concluded that the prevalence of SCH was 4.15%. Allan WC, et al. (2000) [7] conducted a report in California to evaluate the prevalence of thyroid deficiencies in pregnant women and discovered that it was 2.5 percent. Vaidya B, et al. (2007) [8], investigated the efficacy of a targeted high risk case finding approach in identifying women with thyroid dysfunction during early pregnancy and discovered thyroid deficiency in 2.4 percent of cases in the United Kingdom. Nadine Johnson discovered it to be 1.9 percent in the Afro-Caribbean cohort [9]. The incidence of transient subclinical hypothyroidism in pregnant females in Japan was found to be 0.19 percent by Kamijo K, et al. (1990) [10].

Symptoms of subclinical hypothyroidism

The history and physical examination in pregnant women with hypothyroidism are comparable to those in non-pregnant women with hypothyroidism. Many women really had no symptoms, while others may have tiredness, constipation, weight gain, and cold intolerance. Dry skin, swollen faces, periorbital edoema, delayed relaxation of deep tendon reflexes, and bradycardia are all possible physical examination findings. Subclinical hypothyroidism may raise the risk of heart failure and coronary artery disease events. Furthermore, middle-aged patients with subclinical hypothyroidism may have cognitive impairment, nonspecific symptoms such as fatigue, and mood changes [1,2].

About 20% of the participants in Beenish M, et al. (2017) [3], in Kashmir, North India, displayed modest hypothyroidism symptoms such as cold intolerance, edoema, and constipation. The History of Preterm births were seen in 6.5 percent of the pregnant study group, while abortions were seen in 5.7 percent. 12.2 percent of those examined were hypertensive, 6.3 percent had palpable thyroid, and 1.2 percent had hung-up reflexes [3].

The effects of subclinical hypothyroidism in pregnancy

The effects of subclinical hypothyroidism in pregnancy includes pregnancy loss, premature rupture of membranes (PROM), premature birth, placental abruption, low birth weight, low Apgar score, increased requirement for caesarian, hypertension in women, higher neonatal mortality, and neuropsychiatric disorders in children [3,4].

Chen LM, et al. (2014) [11], conducted large-scale research in China, discovered that SCH raised the incidence of miscarriage in pregnant women considerably. Furthermore, as serum TSH levels increased, the chance of miscarriage increased, which is consistent with the findings of Benhadi N, et al. (2009) [12] in Amsterdam.

A study conducted in the year 2011 on 902 pregnant females in Kashmir, North India for FT3, FT4, TSH and antiTPO antibody levels, showed that out of total 114 cases of raised TSH, 61 cases were followed, of which 40 were put on thyroxine therapy. Out of these, 8 were lost to follow-up, and amongst the rest 31 deliveries, only 1 aborted i.e., 2.5%. Out of 21 who were not on treatment, 8 were lost to follow-up, 11 delivered i.e., 52.4% and 2 aborted (9.5%) which was statistically significant [3].

Similar findings were reported in a systematic meta-analysis done by Maraka S, et al. (2016) [13], in USA, that pregnancy with SCH is closely associated with a higher foetal mortality (miscarriage rate and stillbirth rate) in a systematic analysis.

However, data from three separate investigations based on particular TSH values, including 7 miscarriage instances in 917 SCH patients and 131 cases in 23,778 healthy participants, revealed no significant difference between SCH subjects and healthy controls (RR = 1.38, 95 percent CI = 0.65-2.96, P = 0.40). There were no significant differences in miscarriage risk between SCH and healthy participants in any of these investigations [13].

Zhang Y, et al. (2017) [14], conducted a meta-analysis in 2017 with 9 relevant cohort studies on patients with subclinical hypothyroidism before 20 weeks of pregnancy and discovered that they have a greater risk of miscarriage. There were seven studies that reported relevant data on the relationship between miscarriage and SCH in the absence of intervention. There were 206 miscarriages among 3137 SCH patients and 399 miscarriages among 17528 euthyroid women.

The meta-analysis results displayed, the prevalence of miscarriage was considerably greater in SCH patients (RR = 1.90, 95 percent CI 1.59-2.27, P). Because the included studies were geographically diverse, additional subgroup analysis based on the different nations was undertaken. The subjects in 7 studies were separated into two as domestic and overseas groups. Subgroup meta-analysis revealed that pregnant women with SCH have a greater risk of miscarriage in both domestic and international populations (RR = 2.00, 95 percent CI 1.61-2.48 vs. RR = 1.69, 95 percent CI 1.25-2.29). There was no heterogeneity in any of the subgroups. A meta-analysis of four studies that reported relevant data on the association between miscarriage and isolated SCH revealed a pooled RR that indicated that there was no statistically significant difference in miscarriage risk between SCH patients who accepted effective treatments and pregnant women who were euthyroid.

Three eligible studies compared the influence of SCH with thyroid auto immunity (TAI) and isolated SCH on the risk of miscarriage. The meta-analysis found that, when compared to isolated SCH, the prevalence of miscarriage risk in TAI patients was considerably higher, with a combined RR = 2.47 (95 percent CI 1.77-3.45, P) [14].

The above results are in discordance with a study conducted by Bernardi LA, et al. (2013) [15], in USA, who found the prevalence of SCH was 55 (19%) of 286 in her Recurrent Early Pregnancy Loss cohort (REPLC).

The cumulative LIVE BIRTH RATE (LBR) for women with SCH was 27 (69%) of 39 vs 104 (74%) of 141 for euthyroid women. The per-pregnancy LBR for SCH was 34 (49%) of 69 versus 129 (58%) of 221 for euthyroid women. When the LBR was compared between treated and untreated SCH, the cumulative LBR was 17 (71%) of 24 against 10 (67%) of 15. The per-pregnancy LBR for SCH treated over untreated women was 22 (48%) of 46 vs 12 (52%) of 23, respectively. As a result, despite the high frequency of SCH in the REPL cohort, there was no statistically significant difference in subsequent live-birth rate between women with SCH and euthyroid women, or between treated and untreated SCH [15]. In 2017, Uchida S, et al. (2017) [16], studied the Impact of borderline-subclinical hypothyroidism on subsequent pregnancy outcomes in women with unexplained recurrent pregnancy loss.

317 women with a history of recurrent pregnancy loss, RPL,

were included after being tested for antinuclear antibody (ANA), anti-phospholipid syndrome, thrombophilia, uterine abnormalities, hormone problems, and/or chromosomal abnormalities. The women were categorized into two groups: those with borderline-SCH and those with euthyroidism (0.3 TSH 2.5 IU/mL). All of the women had normal serum free thyroxine (T4) levels and did not take levothyroxine before or throughout their subsequent pregnancy.

The pregnancy loss rate (<22 weeks of gestation) tended to be higher in the borderline-SCH than the euthyroid group (29.0%, 9/31 vs 17.9%, 24/134), although not significantly so ($P = 0.16$) [16].

Relevance of Anti TPO antibodies in SCH and pregnancy loss

Gupta A, et al. (2016) [17], studied role of anti-thyroid peroxidase antibodies in adverse pregnancy outcomes, out of 500 women, 18.6% were anti-TPO Ab positive. Number of abortions ≥ 2 was found in 18% and 8% in group B and A whereas preterm delivery was found in 50% and 17% in the two groups respectively. In group B, 48% had increased TSH. Hence she concluded that Anti-TPO Ab presence was significantly associated with preterm deliveries, recurrent abortions, increased maternal and fetal complications.

Many studies have stratified the risk imparted by hypothyroidism according to TPOAb status, and consistently show that this risk is higher in TPOAb positive women. Some data also suggest that the adverse impact associated with maternal TSH levels is apparent at lower TSH elevations in women known to be TPOAb positive compared to women who are TPOAb negative [17].

In 2017, Rajput R, et al. (2017) [18], examined the prevalence of Thyroid Peroxidase Antibody and Pregnancy Outcome in Euthyroid Autoimmune Positive Pregnant Women from a Tertiary Care Center in Haryana, India. TPO antibody positivity was found in 164 (18.9%) of 1030 women with euthyroid condition. TPO Ab positive euthyroid pregnant ladies had considerably lower mean FT4 and TSH levels than TPO Ab negative euthyroid pregnant women. There's no correlation found between maternal age, gestational age, or gravidity and anti TPO antibody levels. Miscarriages occurred in eighteen (12%) of the women in Group 1 and five (3.3%) of the women in Group 2, with the difference being statistically significant (P value of 0.004). Preterm births occurred in 21 (14%) of the women in Group 1 and 5 (3.3%) of the women in Group 2. This was also determined to be statistically significant (p value of 0.001). Other pregnancy-related complications, such as intrauterine death, IUGR, preeclampsia, and PIH, are more common in TPO Ab positive euthyroid pregnant women than in TPO Ab negative euthyroid pregnant women, but the difference is not statistically significant [18].

In 2019, Masoomeh M, et al. (2019) [19], studied the effect of antithyroid peroxidase antibody on pregnancy outcome in euthyroid women and found, of the study population, 21% with anti-TPO antibodies and 3.7% without this antibody had preterm labor. In the control group, 5.7% had spontaneous miscarriage, while 19% in the case group had spontaneous miscarriage. Regarding the occurrence of macrosomia, the difference between the case and control groups was not significant (P = 0.069) [19].

TPOAb positive was not related with an increased risk of poor pregnancy or foetal outcomes in euthyroid women, according to Ning Yuan's 2020 study. After controlling for potential confounding factors, TPOAb-positive euthyroid women pregnant with a female foetus were independently related with preterm births (OR: 4.511, 95 percent CI: 1.075-18.926) [20].

Comparison of treated and untreated cases of subclinical hypothyroidism on pregnancy outcome

Maraka S (2017) [21], studied a total of 5405 women with subclinical hypothyroidism in the United States in 2014; 843 (15.6 percent) actually started levothyroxine treatment with an average dose of 50 µg, 7 (0.8 percent) with thyroid extract formulation, and 4 (0.5 percent) with a combination of levothyroxine and liothyronine. The remaining 4562 women (84.4%) were not treated with thyroid hormone. The proportion of women treated grew from 12% in 2010 to 19% in 2014. Of the 843 women treated, 719 (85.3%) had at least one follow-up TSH test, and 130 (18.0%) had a TSH levels greater than 3 mU/L. Treatment was linked to a lower chance of miscarriage but an increased risk of premature birth, diabetes, high blood pressure throughout pregnancy, and fast heart rates [21].

Casey BM, et al. (2017) [22], studied the treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. He mainly focused on the cognitive ability of the baby born. A total of 677 women with subclinical hypothyroidism were randomly assigned at a mean of 16.7 weeks of gestation, and 526 women with hypothyroxinemia were randomly assigned at a mean of 17.8 weeks of gestation. The median IQ score of the children in the subclinical hypothyroidism study was 97 (95 percent Confidence interval, 94 to 99) in the levothyroxine group and 94 (95 percent CI, 92 to 96) in the placebo group (P=0.71) [22].

In 2021, Bein M, et al. (2021) [23], conducted a meta-analysis of Levothyroxine and the risk of poor pregnancy outcomes in women with subclinical hypothyroidism. He reviewed the available information on the use of levothyroxine in the treatment of SCH during pregnancy. He discovered that using levothyroxine among women with SCH was related with a lower incidence of pregnancy loss and neonatal mortality compared to not using it. Despite the scarcity of available data, there is evidence that levothyroxine medication is connected with improved foetal outcomes, such as decreased foetal discomfort and macrosomia. We found no links between levothyroxine treatment and other negative pregnancy, labour, and delivery, or postpartum outcomes. Finally, there was no evidence of a link between levothyroxine use during pregnancy and children's cognitive outcomes. Nevertheless, there was variation among the included studies in terms of study participants and initiation of levothyroxine [23].

Rao M, et al. (2019) [24], discovered that levothyroxine medication was related with a lower incidence of pregnancy loss and preterm birth in women with SCH and thyroid autoimmune illness as compared to women who did not get treatment. In a subgroup analysis of women with SCH, levothyroxine medication was linked with a lower risk of pregnancy loss compared to no treatment (RR: 0.43; 95 percent CI: 0.26-0.72), but no relation was seen between levothyroxine treatment and preterm birth (RR: 0.67; 95 percent CI: 0.41-1.12) [24].

Nazarpour S, et al. (2019) [25], conducted a meta-analysis comparing women with SCH during pregnancy who were treated with levothyroxine to women who weren't treated/euthyroid. In a subgroup study, they examined women with SCH who were treated with levothyroxine discovered a lower risk of pregnancy loss linked with levothyroxine medication (odds ratio: 0.78; 95 percent CI: 0.66-0.94) [25].

Ju R, et al. (2016) [26], discovered that starting levothyroxine during the first trimester reduced the risk of PROM, gestational diabetes, postpartum haemorrhage, gestational hypertension, and foetal macrosomia compared to women who started levothyroxine

later in the pregnancy [26]. Zhao L, et al. (2018) [27], also found that starting levothyroxine in the first trimester was associated with a lower risk of adverse pregnancy outcomes (i.e., premature labour, pregnancy loss, post-partum haemorrhage, and low birth weight) compared to starting treatment in the second trimester (incidence of pregnancy complications among women treated in the first trimester versus second trimester: 3/31 versus 13/31; p = 0.004) [27].

Conclusion

Contemplating on the overall discussion, it appears that SCH is more prevalent in developing countries, either due to iodine deficiency, low awareness about this problem or less access to medical facilities [4,5]. Whatever being the reason, it's obvious by going through the reviews, that females with history of preterm deliveries, previous IUGRs, or miscarriages should undergo screening for subclinical hypothyroidism along with Anti TPO antibody status, even if they exhibit subtle or no symptoms of hypothyroidism [16-18]. Studies have shown that the deleterious maternal outcomes, in terms of PIH, preeclampsia, PPH, PROM, preterm deliveries, as well as neonatal morbidity in terms of IUGR, macrosomia, fetal deaths and reduced IQ level of babies, can be considerably reduced, particularly if treatment is started in the first trimester [21,23, and 26]. Therefore, a strategy needs to be planned to screen all pregnant women, especially in their first and second trimester for SCH and treat them effectively even if its borderline SCH [16], to avoid maternal or neonatal morbidity and mortality as it is an easily preventable problem, only if identified and corrected at the right time.

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Conflicts of Interest

The authors declare that they have no competing interest.

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