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Subclinical Hypothyroidism: A Review

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ABSTRACT

Both the mother and the fetus are physiologically stressed out during pregnancy. The second most prevalent endocrine illness among pregnant women, behind diabetes mellitus, is thyroid disease. Several differences in the mother's thyroid function are seen in the complete life cycle of pregnancy, and thyroid dysfunction occurs from the mother's inability to adjust to these physiological changes. The possibility for maternal and fetal outcomes can be extremely high when endocrine abnormalities like Hypothyroidism are present during pregnancy. The fetal development and perinatal outcomes can be significantly impacted by thyroid illness, which is frequent in women of reproductive age. For the first part of pregnancy, the fetus depends on the mother's thyroid hormone, which is essential for optimal fetal neurodevelopment. There is authentication of an association between overt maternal Hypothyroidism and overt maternal hyperthyroidism. With higher obstetrical risks and negative impacts on the offspring's cerebrospinal nervous system expansion, grey matter", and neurocognitive potential. Treatment for overt thyroid disorders improves results. Subclinical maternal hypothyroidism can have a negative impact on a baby's neurocognitive and obstetrical outcomes, despite conflicting findings. Subclinical Hypothyroidism has not yet been successfully treated. Pregnancy-related subclinical hyperthyroidism is easily tolerated. However, new research has revealed no improvement with levothyroxine treatment, indicating that thyroid autoantibodies alone might also affect foetal and neurodevelopmental outcomes.. The fetus may be impacted by several uncommon maternal genetic thyroid conditions, such as a TSH receptor mutation that causes hCG hypersensitivity or"thyroid hormone contrary. The thyroid"perform a key function. For the best care, it is crucial to understand fetal health. Data was gathered from different search engines and databases such as; Google Scholar, Scopus, PubMed, Elsevier, Cochrane, Sage, Medline, and Web of Science. Numerous studies were selected from 2017-2022, using the keywords Subclinical Hypothyroidism, Hypothyroidism, pregnancy, fetal damage, risk factors, current challenges, thyroid hormone, and American thyroid association. The full texts of the retrieved articles were made accessible.

INTRODUCTION

The thyroid gland disease known as subclinical Hypothyroidism (SCH) is distinguished by increased TSH and normal FT3 and FT4 levels. The only approach to detect this illness is through biochemical testing due to the wide variety of clinical presentations. The causes are similar to those of overt Hypothyroidism; the most common is chronic autoimmune thyroiditis (Hashimoto's thyroiditis), characterised by anti-thyroid peroxidase antibodies. Other causes include previous hyperthyroidism, postpartum thyroiditis, subacute thyroiditis, thyroid injury and inflammation from radiation, surgery, medication, and thyroid infiltration. (Khan *et al.*, 2017).

Pregnant women frequently have Hypothyroidism. The detection frequency, particularly in emerging India, for example, has not kept up with the severity of the issue. During pregnancy, the mother's thyroid function changes. There are several causes for these alterations.

Similarly inflation in thyroglobulin due to high-rise estrogen and human chorionic gonadotrophin, inflation in renal losses of iodine due to inflation of glomerular filtration rate, During pregnancy, the need for iodine and the production of thyroid hormone both increase by 50%. This is due to alterations in the peripheral metabolism of maternal thyroid hormone and changes in iodine transport to the placenta (Pokhanna *et al.*, 2017). Pregnancy is a stress test for the thyroid that can lead to Hypothyroidism in women with a low thyroidal reserve or iodine shortage. Subclinical Hypothyroidism affects 2-7% of pregnant women, and overt Hypothyroidism affects 0.22 to 2.5% (Sakr & Sakr, 2020) (Mandel, 2004), (Syamala *et al.*). Retardation in neurodevelopment is a result of maternal Hypothyroidism, particularly in the first trimester, and hinders cognitive growth (Wade & Mandel, 2018), ((Aravelli *et al.*, 2022; Malti).

Making a clinical diagnosis of hypothyroidism during pregnancy is difficult due to nonspecific features that may be masked by already present obstetric symptoms. Thyroid function testing is therefore required for the diagnosis of subclinical Hypothyroidism. Since Hypothyroidism is easily managed by early diagnosis and medication, this could lessen the burden of unfavorable maternal and fetal outcomes, which are extremely frequently seen.

Screening should ideally be done during prenatal testing or after a pregnancy is confirmed. There aren't any national

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guidelines for treating thyroid dysfunction, and there are few statistics on its prevalence during pregnancy in India. The study aims to assess the prevalence and consequences of thyroid malfunction, particularly Hypothyroidism in pregnancy.

According to reports, the prevalence of SCH is 4–10% in adults. However, this varies according to the population, with more instances occurring in regions with enough iodine (Canaris *et al.*, 2000). Even more patients who take thyroid drugs are affected (Abdurazzakova, 2021). Like other thyroid conditions, SCH is more prevalent in women than males and worsens with age. Every year, it's likely that 2-5% of SCH patients will develop overt Hypothyroidism (Abdurazzakova, 2021). According to the increase in serum TSH levels, there are typically two types of SCH: mildly raised TSH levels (4.0–10.0 m IU/L) and severely increased TSH values (>10 m IU/L). However, the lower limit of TSH that should be utilised is still debatable, with numerous studies employing different cutoffs. Most SCH patients (4–10 m IU/L) have lesser levels of elevated TSH (Kim *et al.*, 2017).

A collection of conditions known as thyroid diseases damage the thyroid gland. The thyroid is a tiny, butterfly-shaped gland that produces thyroid hormones on the front of your neck (Cooper & Biondi, 2012). Nearly every organ in your body, including your heartbeat, is impacted by thyroid hormones because they regulate how your body uses energy (Farling, 2000).

Sometimes the thyroid produces these hormones in excess or insufficiently. Hyperthyroidism, a condition in which your body produces too much thyroid hormone, can make numerous bodily processes faster. The term hyper denotes an overactive thyroid. Learn more about pregnancy-related hyperthyroidism. Hypothyroidism, or having too little thyroid hormone, can slow down many bodily processes. Hypo denotes the under activity of the thyroid. Learn more about pregnancy-related Hypothyroidism (Mullur *et al.*, 2014). Thyroid hormones part in central nervous system development (Morreale de Escobar *et al.*, 2000). Since the fetus does not begin manufacturing thyroid hormone until weeks 16 to 20, the maternal thyroid is the only source of thyroid hormone in the early stages of pregnancy (Morreale de Escobar *et al.*, 2000).

By having frequent thyroid function testing and taking any medications your doctor prescribes, you can still have a safe pregnancy and preserve the health of your unborn child if you have thyroid issues (Shahid *et al.*, 2018).

Pregnancy is crucial for women since it involves significant physiological changes. Today, it has been discovered that fetal programming has consequences beyond fetal development; as a result, poor prenatal programming significantly impacts the development of most chronic diseases that threaten human life (Huang *et al.*, 2017).

One of the most frequent endocrine abnormalities during pregnancy is thyroid disease. The relationship between maternal thyroid dysfunction during pregnancy and unfavorable pregnancy outcomes and long-term health effects has drawn much attention over the past two decades (Korevaar *et al.*, 2017). Understanding variations in thyroid function and the effects of thyroid disease during pregnancy is extremely important, given the significance of thyroid hormones for a healthy pregnancy and fetal development. Numerous short- and long-term negative effects on the health of the mother and fetus are associated with overt thyroid problems. When detected and addressed at an early enough stage, the majority of these complications can be avoided. Uncertainty exists over whether maternal subclinical Hypothyroidism affects pregnancy or the subsequent cognitive growth of their offspring.

Practical Issues

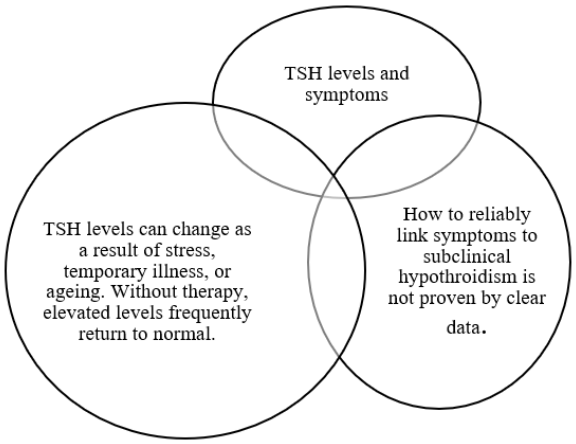

Figure 1: Shows TSH levels and their symptoms

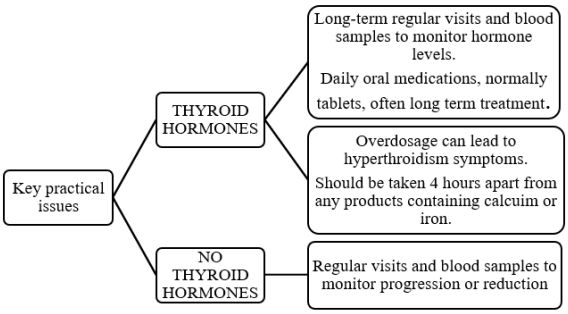

Figure 2: Shows the key practical issues with Thyroid hormones and with no thyroid hormones

METHODOLOGY

To indicate the treatment outcomes of Subclinical Hypothyroidism in different age groups and in during pregnancy, several recent studies, review articles, prospective studies, cross-sectional studies, and literature reviews, all published and peer-reviewed, were searched and considered. The area of search was based on how effective is treatment with thyroxine in preventing morbidity in different age groups, treatment of infertility due to subclinical Hypothyroidism, prevention of fetal loss, and fetal brain damage.

This article is a review. Thus not all information on thyroid

illness and its implications on fetuses has been provided are contained in this. We have included observational studies and all significant, pertinent big trials to highlight the overall conclusions. Although we tried to incorporate the largest and most pertinent research, it is important to keep in mind that the tiny, hopeful observational studies were likely chosen due to publication bias.

Physiology of Thyroid During Pregnancy

Due to the increased metabolic demands during pregnancy, the thyroid gland undergoes considerable physiologic changes that affect its form and function. Depending on baseline iodine supplies, the thyroid expands by 0–30% in size when iodine requirements rise. (Berghout & Wiersinga, 1998), (Vannucchi *et al.*, 2017). Thyroid binding globulins (TBG), in particular, rise 2- to 2.5-fold in response to increased serum estrogen (Sorrenti *et al.*, 2021). The thyroid gland must produce more thyroid hormone to resist standard extent of available thyroid hormone in response. Additionally, human chorionic gonadotropin (hCG) is released prematurely in pregnancy. It has an alpha subunit one is comparable to thyroid stimulating hormone's (TSH) alpha subunit, this causes the thyroid gland to be directly stimulated, a rise in free thyroid hormone, and a reduction of TSH in the first trimester of pregnancy(ERDOĞAN *et al.*, 2022; Glinoer *et al.*, 1993). This is assumed to happen so the fetus receives enough available thyroid hormone to by pass the placenta. Inlarged TBG, hCG stimulation, renal excretion, and transplacental transit of available thyroxine (FT4) cause a nearly 50% rise in thyroid hormone production during the first trimester (LeBeau & Mandel, 2006).

Iodine and Conception

Iodine is a crucial element of thyroid hormones, and pregnant women need more of it. Iodine shortage is linked to thyroid malfunction, affecting fetal development (Zimmermann, 2016). Today, it is generally acknowledged that severe maternal iodine deficiency can have negative effects on both the mother and the baby, including miscarriage and conditions including Hypothyroidism and goiter and stillbirth; for the newborn, including neonatal mortality; and for the child, including stunted growth, cretinism, and poor brain development (Delange, 2007). In societies with severe iodine deficiency, iodine supplementation is advised as a treatment for maternal Hypothyroidism, and there is strong evidence that it improves clinical outcomes, such as rates of cretinism and infant mortality (Li *et al.*, 2016). Concerns have lately been voiced over the UK and other affluent nations iodine intake requirements for pregnant and childbearing women. Some formerly believed to be iodine-rich regions were mild to moderately iodine deficient (Zimmermann, 2007). Additionally, recent research from the large longitudinal AVON project in the UK has indicated a linear relationship between mild-to-moderate maternal iodine shortage and worse cognition in children between the ages of eight and nine (Bath *et al.*, 2013). Despite the positive evidence, it is debatable whether pregnant women from areas with mild to moderate iodine deficiency should take iodine supplements. Concerning supplements, not all of the research used rigorous techniques (Bath & Rayman, 2013). These studies have suggested that iodine supplementation in populations with mild-to-moderate iodine deficiency may have some positive effects on maternal newborn serum thyroglobulin and thyroid volume (i.e., a smaller increase), though data on thyroid function are inconsistent, and there is a lack of hard evidence regarding long-term effects like pregnancy outcomes, childhood neurodevelopment, and growth (Zimmermann, 2007). Some research suggests that starting iodine supplementation sooner can lead to better results (Taylor *et al.*, 2014).

The American Thyroid Association's guidelines for diagnosing and treating thyroid disorders during pregnancy and postpartum served as the reference ranges for the test values used in this study. Regulation 14.2 of the ATA recommendations, states that the following normal reference ranges should be used in the laboratory in the absence of trimester-specific TSH reference ranges in the laboratory.

"1st Trimester- 0.1 to 2.5 m IU/L",
"2nd Trimester- 0.2 to 3m IU/L",
"3rd Trimester- 0.3 to 3m IU/L".

Standard free t4 volume is 0.7 to 1.8ng/ml
The free t3 volume is 1.7 to 4.2 pg/ml.

Thyroid Physiology in Fetus

In her opening remarks, Dr. Morreale de Escobar discussed the various neurodevelopmental consequences in infants born in regions with endemic iodine shortages and children born with inherited Hypothyroidism. Infants born to mothers severely deficient in iodine risk developing neurologic cretinism, which can cause psychological issues, deafness, mutism, squinting quadriplegia. If these mental defective infants acquire enough iodine, their thyroid function will be completely normal at birth. On the other hand, infants with inherited Hypothyroidism are hypothyroid at birth and are thought to have been so while still in utero. However, babies born to moms who are iodine insufficient will suffer acute, irreparable brain damage originating by an event that occurred during the 1st half of pregnancy, but neonates born with inherited Hypothyroidism, if discovered and medicate in advance, will have a positive result for their neurodevelopment. Understanding fetal thyroid development and possible maternal thyroid rise to the fetus is necessary to explain these disparities, particularly in the first half of pregnancy, before the foetus develops any significant thyroid hormone (Eng & Lam, 2020).

First Trimester

Fetal thyroid hormone levels are determined by fetal coelomic fluid and serum.

The existence of thyroid hormone in the fetus during the 1st trimester has been shown in fetal coelomic fluid at

six weeks and fetal serums at twelve weeks of gestation, which are probably of maternal genesis (Contempré *et al*., 1993).

Thyroid hormone levels in the circulation of the fetus continue to rise throughout pregnancy, as sum-up here:

1. At 12 weeks gestation, the average foetal serum T4 level is about 26 nmol/L, and at term, it is 128 nmol/L. Foetal serum-free T4 (fT4) levels climb over the course of pregnancy, with a mean value of around 1.3 pmol/L at 12 weeks and 25.7 pmol/L at duration. (Jansen *et al*., 2019).
2. The total triiodothyronine (T3) and free T3 concentrations in fetal serum remain low until 30 weeks of gestation due to the placental inner deiodination process of T4 to reverse triiodothyronine (rT3) and increase slowly from roughly 0.09 nmol/L at the 12th gestational week to 0.68 nmol/L at birth.
3. TBG concentrations also increase noticeably, rising from 5 mg/L during 12 weeks gestation to about 25 mg/L at delivery, with higher concentrations in babies than in adults.

The research team led by Dr. Morreale de Escobar concluded that the levels of thyroid hormone-binding proteins in fetal fluids and serum is extremely low and independent of the maternal thyroid state. Before midgestation, most maternal T4 and T3 enter these compartments in the free form, causing levels to rise to physiologically important levels.

They suspect there is proof that these maternal hormones play a significant role in fetal evolution, notably in the neurological structure, as is explained below. They also emphasize the importance of placental barrier to stop free T4 and particularly T3 from entering the fetal tissues at extent, can be hazardous.

Iodothyronine Deiodinases in Fetuses

Physiology of the fetal thyroid Thyroid hormones (TH) is produced by the mother during early pregnancy. Despite being first noticed at 10–12 weeks, fetal TH and hypothalamic-pituitary maturation do not start to rise until 18–20 weeks. The main fetal deiodinase that activates thyroid function is deiodinase type 2, or D2, which becomes more active by the end of the first trimester and enhances thyroid receptor occupancy with T3. Apo-TRs: thyroid hormone receptors that are not occupied.

Second and Third Trimester

Thyroid Hormone Levels in Serum

Around 18 to 20 weeks of gestation, the pituitary-portal vascular system fully develops, and fetal thyroid hormone secretion starts. Foetal serum T4 rises without involvement of maternal-fetal vascular connections from a mean of around 2 g/dL (26 nmol/L) at 12 weeks to 10 g/dL (138 nmol/L) at term in samples obtained via cordocentesis. (Ziegler *et al*., 2022). The rise in hepatic fabrication of serum TBG and, to a minor extent, the stimulation of fetal thyroidal T4 production by TSH are both responsible for the rise in serum T4. From a mean of roughly 0.1 ng/dL (1.3 pmol/L) at 12 weeks to 2.0 ng/dL (25.7 pmol/L) at term, fetal serum Due to placental type 3 or 5-deiodinase 3 (5-D3) venture, which changes T4 to reverse triiodothyronine (rT3) and T3 to reverse T2, the increase in fetal serum and free T3 levels is significantly less. Foetal serum T3 levels range from 6 ng/dL (0.09 nmol/L) at 12 weeks to 45 ng/dL (0.68 nmol/L) at term. Adult values of euthyroid persons serum TSH levels are particularly execessive than in the maternal circulation, rising progressively from 4 mU/L at 12 weeks to 8 mU/L at term. It is well thought out that the genesis and evolution purpose of this foetal TSH remain unknown. Because of intrauterine levels of free T4, it appears that the development of the hypothalamic-pituitary-thyroid compact and negative response is not finished prior a few months after birth. of free T4 and TSH are favourably related up to delivery. The fact that intrauterine FT4 levels are significantly greater than the one found in age-paired preterm babies leads to the perspective that maternal transfer of T4 continues to donate remarkably to the hormones accessible to foetal tissues (Ares *et al*., 1997), (Morreale de Escobar, 1998).

Hypothyroidism

Primary maternal Hypothyroidism is characterised as a high TSH level throughout pregnancy without uncommon exceptions such as thyroid hormone resistance, pituitary tumors that secrete TSH, and a few cases of central Hypothyroidism with physiologically inactive TSH (Zimmermann, 2007).

Hypothyroidism and the Results of Pregnancy (Overt Hypothyroidism)

Overt hypothyroidism has been associated with preterm birth, prenatal hypertension, placental abruption, low birth weight, postpartum hemorrhage, perinatal morbidity, and mortality. (Wasserstrum & Ananla, 1995). In overt Hypothyroidism, the probability of preterm birth was higher (or 1.19, P 0.00001), according to a synopsis of 14th cohort studies and one case-control study (Sheehan *et al*., 2015). The risk of problems was greatly reduced by earlier treatment of overt Hypothyroidism and normalisation of thyroid function during pregnancy (Leung *et al*., 1993).

Subclinical Hypothyroidism

Poor perinatal outcomes could also be made more likely by subclinical Hypothyroidism (Maraka *et al*., 2016). According to a synopsis of 18 cohort studies, women's with subclinical Hypothyroidism had a inflated risk of miscarriage (RR 2.01), placental abruption (RR 2.14), preterm membrane breach (RR 1.43), and infant death (RR 2.58) (Maraka *et al*., 2016). Contrarily, a study of 10,990 patients found no increase in unfavorable pregnancy outcomes in the 483 (4.4%) women who had subclinical Hypothyroidism (TSH >97.5% , FT4 2.5-97.5%) (Rosario *et al*., 2018). The variations in these studies findings could be attributed to the various

ways subclinical Hypothyroidism has been defined and the presence or absence of TPO antibodies. The subclinical hypothyroidism definition used in the meta-analysis varied between research studies; some adjusted for TPO status while others did not (Maraka *et al*., 2016). Positive antibodies raise the likelihood of complications for women with subclinical hypothyroidism", and 30- 60% of pregnant women with high TSH have greater levels of TPO antibodies (Mansouri *et al*., 2017). As was previously mentioned, a meta-analysis of three randomised trials that examined the influence of levothyroxine medication for subclinical Hypothyroidism did'nt find any differences in obstetrical consequences after 3, 5, or 9 years of persue.

To summarise, gestational hypertension, squat birth weight, and premature delivery are all increased by overt maternal Hypothyroidism. Treatment, particularly in the early stages of pregnancy, helps reduce these risks. Although the evidence is mixed, maternal subclinical Hy Additionally, the treatment's results have not yet been observed. This may not come as a surprise given the biological improbability that even a very slight thyroid dysfunction would cause like a wide variety of unfavourable pregnancy outcomes.pothyroidism may also negatively impact obstetrical consequences.

There are conflicting recommendations about when to start treating subclinical Hypothyroidism. Currently, the American Thyroid Association advises starting treatment. When a pregnant woman has subclinical Hypothyroidism, her TSH should be less than 4.0 mIU/L when the pregnancy-certain reference value is not accessible to their community, 2.5 mIU/L if she has negative TPO antibodies", and more than that if she has positive TPO antibodies (Anagnostis *et al*., 2017). The American College of Obstetricians and Gynaecologists states that there is no evidence that subclinical Hypothyroidism can be identified or treated and makes no recommendations about its management; pregnant women with subclinical Hypothyroidism have better baby outcomes (Obstetricians ACo, 2015). The Royal Australian and New Zealand College of Obstetricians and Gynaecologists advises against testing for TPO antibodies or subclinical Hypothyroidism and against using levothyroxine to treat subclinical Hypothyroidism during pregnancy (James-McAlpine, 2019). The treatment of subclinical Hypothyroidism in the course of pregnancy can not be necessary, according to the findings of more recent investigations.

DISCUSSION

One of the most prevalent endocrine conditions in pregnant women is thyroid disease, which negatively affects both the mother and the fetus. The initial antenatal visit's universal screening aids in identifying thyroid problems in pregnancy. Thyroid dysfunction should ideally be screened for before conception because any hypothyroid status can be treated before trying for a baby. This clinical study's primary goal was to ascertain the frequency of thyroid problems in pregnancy. Geographical differences in the prevalence of Hypothyroidism during pregnancy are significant. According to data from Western nations, subclinical Hypothyroidism affects an estimated 2.5% of people, and overt Hypothyroidism complicates up to 0.3% of pregnancies (AKBAŞ & ÇARLIOĞLU, 2020). In India, pregnancy-related Hypothyroidism is significantly more common than in Western nations. We still have iodine deficiency in many areas of India. Therefore prevalence varies greatly between different states. Iodine deficiency is the most typical cause of Hypothyroidism in pregnancy in underdeveloped nations like India.

According to the study, 6.8% of people had Hypothyroidism, with 0.7% having overt Hypothyroidism and 6.1% having subclinical Hypothyroidism. Subclinical Hypothyroidism was shown to be prevalent in 633 people in the Indian population in a prior study, which was carried out in 2010 (Sahu *et al*., 2010). Our data is on par with recent research on prevalence. According to the statistics gathered, pregnant women have a high frequency of Hypothyroidism, which necessitates rapid intervention. This high prevalence may be caused by multiple pregnancies, adolescent pregnancies, the low nutritional content of local foods, malnutrition and iodine deficiency, poor socioeconomic conditions of the local population, and high physiological demand during the growing years. In addition to iodine shortage, environmental factors may contribute to the prevalence of Hypothyroidism in the area.

Compared to the West, Asian countries were found to have a higher prevalence of Hypothyroidism. The prevalence of Hypothyroidism was considerably higher in the high-risk group than in the non-high-risk group in a huge Chinese research study that collectively 2899 pregnant women (10.9 vs. 7.0%, P = 0.008) (Ayyar, 2011).

According to a Chinese study, goitrogens are present in the food, as evidance from India, and micronutrient deficiencies, like those in selenium or iron, might result in Hypothyroidism and goiter (Marwaha *et al*., 2003) (Teng *et al*., 2011), (Das *et al*., 2011).

Therefore, it is hypothesized that India and Asia have greater rates of Hypothyroidism during pregnancy. In India, Hypothyroidism is also not consistently prevalent (Gayathri *et al*., 2009). Bandela *et al.* 10% of people in Andhra Pradesh reported having SCH.

2.8% of people had SCH, according to Gayathri *et al.* TSH's varying upper limit cutoffs could contribute to this discrepancy (Unnikruishnan *et al*., 2013).

Rate of Live Births Per Cycle

"Using data from nine studies involving 4396 women, Busnelli *et al.* discovered that women with positive TAI had lower LBR than women with negative TAI (OR 0.73, 95% CI [0.54-0.99], p14.04). The pooled effect estimate was also obtained using a random effect (notmod0.64, 950.64,90.42-0.99], p 14.05).Werhofer *et al.* discovered that low TSH levels were linked to a higher likelihood of getting pregnant (13.9%) as opposed to

high TSH levels, which were linked to a lower likelihood of getting pregnant (5%); however, the authors note that statistical analysis of the link between baseline TSH levels and pregnancy potential was not possible in their study because of the small sample size (2-0.99], p. 14.05).“Werhofer *et al.*’s”observation towards upgraded pregnancy potential in the presence of low-normal TSH levels (13.9%) compared to the high-normal TSH group (5%), but the authors note that statistical analysis of the effect of baseline TSH levels on pregnancy potential was not possible in their research study due to the least number of pregnancies’.

CONCLUSION

To prevent harmful results for the mother and fetus, thyroid dysfunction during pregnancy must be identified and treated early. Both overt Hypothyroidism need to be properly managed. Levothyroxine is frequently used to treat subclinical Hypothyroidism; however, its ability to improve maternal or fetal outcomes has not been conclusively demonstrated. Treatment for subclinical hyperthyroidism is typically unnecessary, although it should be remembered that nonthyroidal disease or pregnant thyrotoxicosis are both possibilities. Although monitoring studies with euthyroid women who had thyroid autoantibodies showed worse maternal and fetal outcomes, there is currently insufficient evidence to show that these outcomes are improved by thyroxine supplementation. More RCTs are required to examine the effects of treating pregnant euthyroid women with autoimmune thyroid disease, subclinical hypothyroidism, and isolated hypothyroxinemia. A secure basis for practise is provided by current practise guidelines, and they are strikingly similar and differing in significant ways that generally point to gaps in our present understanding of thyroid problems in pregnancy.

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