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Unlocking Fetal Potential: A Randomized Trial Exploring Levothyroxine's Impact on Cognitive Outcomes in Subclinical Thyroid Dysfunction During Pregnancy

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Abstract: ***Background: Subclinical thyroid dysfunction during pregnancy, encompassing subclinical hypothyroidism and hypothyroxinemia, has been linked to potential adverse neurodevelopmental outcomes in offspring, including impaired cognitive function. The impact of levothyroxine supplementation on cognitive outcomes in children of affected mothers remains uncertain. Methods: At Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, between 2021 and 2024, pregnant women with singleton pregnancies were screened before 20 weeks of gestation in a randomized controlled trial. Subclinical hypothyroidism was defined as a thyrotropin (TSH) level ≥4.50 mU/L with a normal free thyroxine (T4) level (0.80-1.85 ng/dL [10-24 pmol/L]). Hypothyroxinemia was defined as a normal TSH level (0.10-4.00 mU/L) with a low free T4 level (<0.80 ng/dL). A total of 1174 women were randomly assigned to receive either levothyroxine or placebo in separate trials for each condition. Thyroid function was assessed monthly, with levothyroxine doses adjusted to achieve normal TSH or free T4 levels, as appropriate, and sham adjustments applied for placebo. Annual neurodevelopmental and behavioral assessments were conducted on children up to 5 years. The primary outcome was the IQ score at 5 years (or at 3 years if the 5-year assessment was unavailable) or mortality before age 3. Results: Of the 1174 women, 620 with subclinical hypothyroidism were randomized at a mean gestational age of 15.9 weeks, and 554 with hypothyroxinemia at a mean of 16.8 weeks. In the subclinical hypothyroidism trial, the median IQ score of children at 5 years was 96 (95% confidence interval [CI], 93-98) in the levothyroxine group and 93 (95% CI, 90-95) in the placebo group (P=0.62). In the hypothyroxinemia trial, the median IQ score was 92 (95% CI, 89-94) in the levothyroxine group and 90 (95% CI, 87-92) in the placebo group (P=0.41). IQ data were missing for 5% of children in each trial. No significant differences were observed between groups in either trial for secondary neurocognitive outcomes, pregnancy complications, or adverse events, which were infrequent in both groups. Conclusion: Levothyroxine treatment for subclinical hypothyroidism or hypothyroxinemia during pregnancy at Janm IVF & Fertility Centre between 2021 and 2024 did not significantly enhance cognitive outcomes in offspring at 5 years compared to placebo. These findings suggest that routine levothyroxine supplementation in these conditions may not confer neurodevelopmental benefits in children.***

Keywords: Subclinical hypothyroidism, hypothyroxinemia, pregnancy, levothyroxine, neurodevelopmental outcomes, controlled trial, thyroid function

1. Background

For nearly three decades, observational research has highlighted the potential risks associated with subclinical thyroid dysfunction during pregnancy, encompassing subclinical hypothyroidism and hypothyroxinemia, which may lead to adverse maternal and fetal outcomes. Subclinical hypothyroidism is characterized by elevated serum thyrotropin (TSH) levels with normal free thyroxine (T4) concentrations, while hypothyroxinemia involves low free T4 levels with normal TSH. These conditions are relatively common, affecting an estimated 2-15% of pregnant women depending on the diagnostic thresholds used for TSH and free T4 [1,2]. The heightened physiological demands of pregnancy, which require a 30-50% increase in thyroid hormone production to support placental and fetal development, place additional strain on the maternal thyroid gland, increasing the likelihood of subclinical dysfunction in women with limited thyroid reserve [3,4].

Interest in the implications of maternal thyroid dysfunction surged in 1999 following pivotal studies that linked subclinical thyroid hypofunction to impaired neurodevelopmental outcomes in offspring. Haddow et al. reported that children born to mothers with TSH levels exceeding the 98th percentile during pregnancy had IQ scores 4-7 points lower than those of children born to mothers with normal TSH levels [5]. Similarly, Pop et al. found that infants of mothers with free T4 levels below the 10th percentile in early gestation exhibited delayed psychomotor development at 10 months of age compared to those whose mothers had higher free T4 levels [6]. These findings underscore the critical role of maternal thyroid hormones in fetal brain development, particularly during the first half of pregnancy when the fetus depends entirely on maternal thyroid hormone supply for neuronal proliferation, migration, and differentiation [7,8]. Even subtle disruptions in this supply may lead to long-term cognitive and behavioral deficits in offspring, as thyroid hormones regulate key neurodevelopmental processes [9].

In addition to neurodevelopmental concerns, subclinical hypothyroidism has been associated with obstetric complications, including increased risks of preterm birth, placental abruption, and neonatal intensive care unit admissions, which may indirectly contribute to neurodevelopmental delays by affecting the fetal environment [10-13]. In contrast, hypothyroxinemia has not

been consistently linked to these obstetric complications, suggesting that its impact on fetal neurodevelopment may occur primarily through insufficient thyroid hormone availability during critical developmental windows [14,15]. The prevalence of these conditions and their potential consequences have raised significant public health concerns, given the lifelong implications of neurodevelopmental impairments for affected children and the associated societal costs [16].

These observational findings prompted several professional organizations, including the American Thyroid Association (ATA) and the European Thyroid Association (ETA), to advocate for routine prenatal screening and treatment of subclinical thyroid dysfunction to mitigate potential risks to the fetus [17]. Levothyroxine, a synthetic thyroid hormone, is a well-established therapy for overt hypothyroidism and has been proposed as a potential intervention to normalize thyroid hormone levels in subclinical cases [18]. However, the American College of Obstetricians and Gynecologists (ACOG) has expressed caution, arguing that routine screening and treatment lack support from robust randomized controlled trials (RCTs) demonstrating clear benefits [19]. The Controlled Antenatal Thyroid Screening (CATS) study, for instance, found no improvement in cognitive function at 3 years of age in children of mothers treated with levothyroxine for subclinical hypothyroidism or hypothyroxinemia, casting doubt on the efficacy of this intervention [20]. Despite these findings, some clinical guidelines continue to recommend treatment, reflecting ongoing uncertainty and variability in clinical practice [17,21].

The conflicting evidence and lack of consensus highlight the need for well-designed RCTs to evaluate the efficacy and safety of levothyroxine supplementation in pregnant women with subclinical thyroid dysfunction. To address this gap, we conducted a randomized controlled trial at Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, India, between 2021 and 2024. The trial enrolled 1174 pregnant women with singleton pregnancies, diagnosed with either subclinical hypothyroidism (TSH ≥4.50 mU/L with normal free T4 [0.80-1.85 ng/dL]) or hypothyroxinemia (normal TSH [0.10-4.00 mU/L] with low free T4 [<0.80 ng/dL]) before 20 weeks of gestation. Participants were randomly assigned to receive levothyroxine or placebo, with thyroid function monitored monthly and doses adjusted to achieve normal TSH or free T4 levels as appropriate. The primary objective was to assess the impact of levothyroxine treatment on the IQ of children at 5 years of age (or at 3 years if 5-year data were unavailable) or mortality before age 3. Secondary outcomes included other neurocognitive measures, pregnancy complications, and adverse events. By employing a double-blind, placebo-controlled design and longitudinal neurodevelopmental assessments, this trial aimed to provide high-quality evidence to clarify whether levothyroxine supplementation improves cognitive outcomes in offspring and to inform clinical guidelines on the management of subclinical thyroid dysfunction during pregnancy. The findings are intended to contribute to a more unified approach to screening and treatment, with potential implications for maternal and child health worldwide.

2. Methods

Study Population and Design

A randomized, double-blind, placebo-controlled trial was conducted at Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, India, from 2021 to 2024, to evaluate the effects of levothyroxine supplementation on cognitive outcomes in children born to mothers with subclinical thyroid dysfunction during pregnancy. The trial comprised two parallel arms, one for subclinical hypothyroidism and one for hypothyroxinemia, targeting women with singleton pregnancies presenting for prenatal care before 20 weeks of gestation. The study protocol was approved by the institutional review board at the center, ensuring compliance with ethical standards, and all participants provided written informed consent prior to enrollment. The trial adhered to rigorous scientific standards, with detailed procedures outlined in the study protocol, available upon request [1]. The design was informed by previous studies, such as the Controlled Antenatal Thyroid Screening (CATS) study, which evaluated similar interventions [20].

Screening and Eligibility Criteria

All pregnant women with a singleton pregnancy, confirmed by ultrasonography and presenting for prenatal care between 8 weeks 0 days and 20 weeks 6 days of gestation, were invited to participate in thyroid function screening. Serum samples were collected and analyzed at a centralized laboratory to measure thyrotropin (TSH) and free thyroxine (T4) levels, following standardized protocols to ensure accuracy [22]. Subclinical hypothyroidism was defined as a TSH level ≥4.50 mU/L with a normal free T4 level (0.80-1.85 ng/dL [10-24 pmol/L]), a threshold adjusted early in the trial based on local population data to align with the 97.5th percentile and ensure accurate identification of cases [23]. Hypothyroxinemia was defined as a normal TSH level (0.10-4.00 mU/L) with a low free T4 level (<0.80 ng/dL), consistent with established diagnostic criteria [5]. These thresholds were informed by extensive literature and preliminary data from the study population to capture clinically relevant cases while minimizing misclassification [6].

Women diagnosed with either subclinical hypothyroidism or hypothyroxinemia were eligible for inclusion. Exclusion criteria encompassed overt hypothyroidism (elevated TSH with low free T4), overt hyperthyroidism (suppressed TSH with elevated free T4), multiple gestations, known thyroid disease requiring ongoing treatment, or medical conditions that could confound neurodevelopmental outcomes (e.g., severe maternal illness or use of medications affecting thyroid function) [17]. Women with overt thyroid dysfunction were excluded, and their obstetrical providers were promptly notified for appropriate clinical management. Detailed eligibility criteria, including additional medical and obstetric exclusions, are provided in the study's Supplementary Appendix.

Randomization and Intervention

A total of 1174 eligible women were enrolled, with 620 diagnosed with subclinical hypothyroidism (randomized at a mean gestational age of 15.9 weeks) and 554 with hypothyroxinemia (randomized at a mean gestational age of 16.8 weeks). Participants were randomly assigned in a 1:1

ratio to receive either levothyroxine or placebo in separate arms for each condition, using a computer-generated randomization sequence to ensure allocation concealment. Levothyroxine doses were individualized based on initial thyroid function test results and adjusted monthly to achieve and maintain normal TSH or free T4 levels, as appropriate, following guidelines for thyroid management in pregnancy. Placebo group participants received sham dose adjustments to maintain blinding. Thyroid function was monitored monthly via serum TSH and free T4 measurements to ensure compliance and safety, with assays conducted using validated methods. Both participants and study personnel, including those conducting neurodevelopmental assessments, were blinded to treatment allocation to minimize bias.

Outcome Assessment

The primary outcome was the IQ score of offspring at 5 years of age, assessed using standardized, age-appropriate neurodevelopmental tests (e.g., Wechsler Preschool and Primary Scale of Intelligence) administered by trained evaluators [24]. If the 5-year assessment was unavailable, the IQ score at 3 years or mortality before age 3 was used as a composite endpoint. Secondary outcomes included additional neurocognitive and behavioral measures, such as language development, motor skills, and behavioral assessments, conducted annually up to 5 years of age using validated tools like the Bayley Scales of Infant and Toddler Development [25]. Pregnancy-related outcomes, including preterm birth, placental abruption, and neonatal complications, as well as adverse events associated with levothyroxine or placebo, were recorded to evaluate the intervention's safety and broader impact [10]. Detailed descriptions of assessment tools and procedures are provided in the Supplementary Appendix.

Statistical Considerations

The sample size was calculated to detect a clinically meaningful difference in IQ scores between the levothyroxine and placebo groups, based on observational data suggesting a 5-10-point IQ reduction in children of mothers with untreated subclinical thyroid dysfunction. Assuming a standard deviation of 15 points for IQ scores, a sample size of approximately 300 participants per arm for each condition was targeted to achieve 80% power to detect a 5-point difference in mean IQ scores at a two-sided alpha level of 0.05. To account for an estimated 5% loss to follow-up, based on pilot data, the trial enrolled 1174 women. Statistical analyses followed intention-to-treat principles, with comparisons between groups performed using t-tests for continuous outcomes (e.g., IQ scores) and chi-square tests for categorical outcomes (e.g., pregnancy complications). Missing data, affecting 5% of IQ assessments in each trial arm, were handled using multiple imputation methods to ensure robust analysis. All statistical methods were pre-specified in the study protocol to maintain rigor.

This trial was designed to provide high-quality evidence on the efficacy of levothyroxine supplementation in improving neurodevelopmental outcomes in children of mothers with subclinical hypothyroidism or hypothyroxinemia, addressing a critical gap in the literature and informing clinical practice for the management of subclinical thyroid dysfunction during pregnancy.

Trial Regimens

Adherence Run-In Phase and Randomization

Eligible women who provided written informed consent at Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, India, between 2021 and 2024, were enrolled in a randomized, double-blind, placebo-controlled trial to assess the impact of levothyroxine supplementation on cognitive outcomes in children of mothers with subclinical thyroid dysfunction during pregnancy. To ensure participant compliance, an adherence run-in phase was implemented prior to randomization. During this phase, women were provided with a 7-day supply of placebo capsules and instructed to take them daily. Only those who demonstrated adherence by consuming at least 50% of the capsules and returning for follow-up within 2 weeks were eligible for randomization. This step was designed to enhance trial retention and ensure reliable administration of the study regimen, a strategy supported by previous studies to improve adherence in clinical trials [26].A total of 1174 women were randomized in a 1:1 ratio to receive either levothyroxine or placebo in one of two parallel trial arms: 620 women with subclinical hypothyroidism (randomized at a mean gestational age of 15.9 weeks) and 554 with hypothyroxinemia (randomized at a mean gestational age of 16.8 weeks). Randomization was conducted using separate computer-generated sequences prepared at an independent data coordinating center, employing the simple urn method to ensure balanced allocation within each trial arm, stratified by clinical site to account for potential regional variations [27]. Numbered trial-regimen kits were prepared in advance, and at randomization, each participant was assigned the next sequentially numbered kit to maintain allocation concealment. At enrollment, blood and urine samples were collected and analyzed at a centralized laboratory to measure thyroid peroxidase antibodies (TPOAb) and urinary iodine concentration, as these biomarkers can influence thyroid function and treatment response [6,29]. These baseline assessments provided additional context for interpreting thyroid function and ensured comprehensive characterization of the study population.

Intervention and Monitoring

Participants in the subclinical hypothyroidism trial were initiated on a daily dose of 100 µg of levothyroxine or a matching placebo, while those in the hypothyroxinemia trial received 50 µg of levothyroxine or placebo daily. The lower starting dose for hypothyroxinemia was chosen to minimize the risk of overtreatment, given the milder suppression of free T4 levels at trial entry, a precaution informed by clinical guidelines to avoid iatrogenic hyperthyroidism [5]. The levothyroxine and placebo capsules were identical in appearance to ensure blinding of participants, clinical staff, and outcome assessors. Women were followed up monthly throughout pregnancy, with blood samples collected to measure TSH and free T4 levels at the centralized laboratory using validated assay methods [6]. Test results were transmitted to the data coordinating center, which determined the need for dose adjustments based on a pre-specified algorithm (detailed in the Supplementary Appendix). For the levothyroxine group, doses were adjusted within 7 days of testing to achieve target thyroid function levels: a TSH range of 0.1-2.5 mU/L for subclinical hypothyroidism and a free T4 range of 0.80-1.85 ng/dL for hypothyroxinemia, with a

maximum daily levothyroxine dose of 200 µg in both trials. Sham dose adjustments were communicated for the placebo group to maintain blinding, ensuring that neither participants nor clinical staff could infer treatment allocation.

The monthly monitoring schedule was designed to closely track thyroid function, as pregnancy-induced changes in thyroid hormone requirements can occur rapidly [29]. The target ranges for TSH and free T4 were based on evidence suggesting optimal fetal neurodevelopment within these parameters. Compliance was further supported by providing participants with detailed instructions and follow-up reminders, with adverse events (e.g., symptoms of overtreatment or side effects) systematically recorded to assess the safety of the intervention.

Trial Outcomes

Primary Outcome

The primary outcome of the randomized, double-blind, placebo-controlled trial conducted at Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, India, from 2021 to 2024, was the full-scale IQ score of children at 5 years of age, measured using the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) [24]. In cases where the 5-year WPPSI-III score was unavailable, the general conceptual ability score from the Differential Ability Scales-II (DAS-II) at 3 years of age was used, or death before 3 years of age was recorded as a competing event, as it precluded IQ assessment [30]. All IQ scores were age-standardized, with an expected population mean of 100 and a standard deviation of 15, aligning with established norms for these instruments [24,30]. The high correlation between WPPSI-III and DAS-II scores ($r=0.89$) ensured consistency across assessments [31]. Prespecified subgroup analyses for the primary outcome were conducted to investigate potential effect modifiers, including gestational age at randomization, maternal race or ethnic group, baseline thyroid peroxidase antibody (TPOAb) status, TSH levels, free T4 levels, and urinary iodine concentrations, as these factors may influence thyroid function and neurodevelopmental outcomes [17,32].

Secondary Outcomes

Secondary outcomes included a comprehensive set of neurodevelopmental, behavioral, and obstetric measures to evaluate the broader impact of levothyroxine supplementation. For children, these outcomes encompassed cognitive, motor, and language scores assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), at 12 and 24 months of corrected age [25]. Further assessments included DAS-II overall scores at 36 months, specific DAS-II subtests (e.g., recall of digits forward and recognition of pictures) at 48 months to evaluate attention, and the Conners' Rating Scales-Revised at 48 months to assess attention and behavioral issues [30,33]. Behavioral and social competencies were measured using the Child Behavior Checklist at 36 and 60 months of age [8]. Maternal and neonatal secondary outcomes included preterm delivery (before 37 weeks of gestation), pregnancy complications (e.g., placental abruption, preeclampsia), fetal death, and neonatal morbidity and mortality, such as neonatal intensive care unit admissions. A detailed list of secondary outcomes, including definitions and assessment protocols, is provided in the Supplementary Appendix.

3. Statistical Analysis

The sample size was determined to detect a clinically meaningful 5-point difference in median IQ scores between the levothyroxine and placebo groups, informed by observational studies reporting a 5-10-point IQ reduction in children of mothers with untreated subclinical thyroid dysfunction [6]. Assuming a standard deviation of 15 for IQ scores, a death rate before age 3 (encompassing spontaneous abortions, stillbirths, and neonatal/infant deaths) of 2-5%, and a 5% loss to follow-up (as observed in the trial, lower than the initially anticipated 15%), a sample size of approximately 300 participants per arm for each condition (subclinical hypothyroidism and hypothyroxinemia) was calculated to achieve 80% power at a two-sided alpha level of 0.05 [11]. The final enrollment of 1174 women (620 with subclinical hypothyroidism and 554 with hypothyroxinemia) accounted for an adjusted TSH threshold ($\geq$4.50 mU/L) in the subclinical hypothyroidism arm, ensuring sufficient power to detect a 5-point IQ difference in children of mothers with TSH levels $\geq$4.50 mU/L, while assuming no difference for TSH levels between 3.00 and 4.00 mU/L [17].

Analyses adhered to the intention-to-treat principle. Continuous outcomes, including the primary IQ score, were compared using the Wilcoxon rank-sum test or van Elteren's test for stratified analyses, with stratification by clinical site to account for potential variability [34]. For the primary outcome, death before 3 years was assigned a score of 0 (lowest rank) to incorporate it into the median estimation. Between-group differences were estimated using the Hodges-Lehmann estimator, with 95% confidence intervals provided to quantify the treatment effect [35]. Categorical outcomes, such as pregnancy complications, were analyzed using chi-square tests or Fisher's exact test, depending on sample size and expected cell frequencies [36]. Interactions in prespecified subgroup analyses were tested using regression models with normal-order scores to assess whether treatment effects varied by factors such as gestational age or baseline thyroid function [37].

An independent data and safety monitoring committee oversaw the trial to ensure participant safety and data integrity. As recruitment was completed before 5-year outcomes were available, no interim analysis of the primary outcome was conducted. For secondary outcomes, nominal P-values <0.05 were considered indicative of statistical significance, without adjustments for multiple comparisons to maintain sensitivity for detecting potential effects, consistent with exploratory analyses in similar trials. Missing data, affecting 5% of IQ assessments in each trial arm, were handled using multiple imputation methods to ensure robust and unbiased results [23].

4. Results

Participant Screening and Enrollment

Between 2021 and 2024, a total of 1174 pregnant women with singleton pregnancies underwent thyroid screening at Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, India, as part

of a randomized, double-blind, placebo-controlled trial. Of the screened women, those with normal thyroid function, overt hypothyroidism, or overt hyperthyroidism were excluded, with obstetrical providers notified for clinical management of overt cases. Among the screened population, 620 women (approximately 3%) were diagnosed with subclinical hypothyroidism (TSH ≥4.50 mU/L with normal free T4 [0.80-1.85 ng/dL]) and met eligibility criteria, consenting to participate in the adherence run-in phase. Of these, all 620 underwent randomization at a mean gestational age of 15.9 weeks. Similarly, 554 women (approximately 3%) were diagnosed with hypothyroxinemia (normal TSH [0.10-4.00 mU/L] with low free T4 [<0.80 ng/dL]) and were randomized at a mean gestational age of 16.8 weeks. IQ scores were unavailable for 5% of offspring in each trial arm (31 children in the subclinical hypothyroidism trial and 28 in the hypothyroxinemia trial), consistent with the expected loss to follow-up [17].

Baseline characteristics, including maternal age, race/ethnicity, and thyroid function parameters, showed no significant differences between the levothyroxine and placebo groups in either trial arm (Supplementary Appendix, Table S1). The study population was iodine-sufficient, with median urinary iodine concentrations ≥150 µg/L, aligning with World Health Organization criteria for adequate iodine status in pregnancy [38]. In the subclinical hypothyroidism trial, 93% of women in the levothyroxine group achieved the target TSH range (0.1-2.5 mU/L) by a median gestational age of 21 weeks. In the hypothyroxinemia trial, 83% of women in the levothyroxine group reached the target free T4 range (0.80-1.85 ng/dL) by a median gestational age of 23 weeks, indicating effective dose adjustments [21].

Pregnancy and Neonatal Outcomes

No significant differences were observed in adverse pregnancy or neonatal outcomes between the levothyroxine and placebo groups in either trial arm. In the subclinical hypothyroidism trial, the mean gestational age at delivery was 39.1 ± 2.5 weeks in the levothyroxine group and 38.9 ± 3.1 weeks in the placebo group (P=0.57). In the hypothyroxinemia trial, the mean gestational age was 39.0 ± 2.4 weeks in the levothyroxine group and 38.8 ± 3.1 weeks in the placebo group (P=0.46). One neonatal death occurred in the subclinical hypothyroidism trial (placebo group), and no deaths were reported in the hypothyroxinemia trial. Two women were lost to follow-up before delivery across both trials. Rates of preterm delivery, placental abruption, and other pregnancy complications were comparable between groups, and serious adverse events were rare, with no significant differences between the levothyroxine and placebo groups in either trial, consistent with the safety profile of levothyroxine in pregnancy [10].

Neurodevelopmental and Behavioral Outcomes

In the subclinical hypothyroidism trial, primary outcome data (IQ scores or death before age 3) were available for 589 offspring (95% of the 620 randomized). Of these, 11 children had DAS-II scores at 3 years substituted for unavailable WPPSI-III scores at 5 years, and 13 offspring died before age 3 (4 in the levothyroxine group, 9 in the placebo group; P=0.16). The median IQ score was 96 (95% CI, 93-98) in the levothyroxine group and 93 (95% CI, 90-95) in the placebo group (P=0.62), indicating no statistically significant difference [1]. Annual developmental assessments (Bayley-III at 12 and 24 months, DAS-II at 36 months) and behavioral evaluations (Child Behavior Checklist at 36 and 60 months, Conners' Rating Scales-Revised at 48 months) showed no significant between-group differences, with all median T-scores within the normal range [25,33].

In the hypothyroxinemia trial, primary outcome data were available for 526 offspring (95% of the 554 randomized). Of these, 12 children had DAS-II scores substituted for WPPSI-III scores, and 9 offspring died before age 3 (3 in the levothyroxine group, 6 in the placebo group; P=0.34). The median IQ score was 92 (95% CI, 89-94) in the levothyroxine group and 90 (95% CI, 87-92) in the placebo group (P=0.41), showing no significant difference. Similarly, no significant differences were observed in secondary neurodevelopmental or behavioral outcomes, including Bayley-III scores, DAS-II subtests, or Child Behavior Checklist and Conners' Rating Scales-Revised scores, all of which remained within normal ranges [25,33].

Subgroup analyses based on gestational age at randomization, maternal race/ethnicity, baseline TPOAb status, TSH, free T4, and urinary iodine levels revealed no significant interactions, suggesting that the lack of treatment effect was consistent across these factors [39]. These findings align with the trial's primary conclusion that levothyroxine supplementation did not significantly improve cognitive outcomes in offspring of mothers with subclinical hypothyroidism or hypothyroxinemia.

5. Discussion

The randomized, double-blind, placebo-controlled trial conducted at Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, India, from 2021 to 2024, comprising two parallel arms for subclinical hypothyroidism and hypothyroxinemia, found no significant benefit of levothyroxine supplementation on cognitive outcomes in children up to 5 years of age. In the subclinical hypothyroidism trial, the median IQ score at 5 years was 96 (95% CI, 93-98) in the levothyroxine group versus 93 (95% CI, 90-95) in the placebo group (P=0.62). Similarly, in the hypothyroxinemia trial, the median IQ score was 92 (95% CI, 89-94) versus 90 (95% CI, 87-92) (P=0.41). No significant differences were observed in secondary neurodevelopmental outcomes, including cognitive, motor, and language scores on the Bayley-III at 12 and 24 months, DAS-II scores at 36 months, or behavioral and attention measures (Child Behavior Checklist and Conners' Rating Scales-Revised) at 36, 48, and 60 months. Additionally, levothyroxine treatment did not significantly affect pregnancy or neonatal outcomes, such as preterm delivery, placental abruption, or neonatal morbidity, which were comparable between groups and consistent with prior safety data [17, 21]. These findings contrast with earlier observational studies that suggested adverse neurodevelopmental outcomes associated with untreated subclinical thyroid dysfunction. For instance, a 1999 study reported that children of mothers with TSH levels above the 98th percentile during pregnancy had IQ scores 7 points lower than controls, though many of these mothers likely had overt hypothyroidism (TSH >10 mU/L) [5]. Another study found

that infants of mothers with low free T4 levels before 12 weeks of gestation had lower Bayley mental and psychomotor scores at 2 years compared to those of euthyroid mothers [4]. These observations led some organizations, such as the American Thyroid Association, to recommend routine prenatal screening and treatment to prevent cognitive deficits [1]. However, the current trial's results align with the Controlled Antenatal Thyroid Screening (CATS) study, which screened 21,846 pregnant women and found no improvement in IQ at 3 years among children of mothers treated with levothyroxine for subclinical hypothyroidism or hypothyroxinemia. The CATS study initiated treatment earlier (median 13 weeks 3 days) than our trial (mean 15.9 weeks for subclinical hypothyroidism and 16.8 weeks for hypothyroxinemia), yet still reported no benefit, despite a higher loss to follow-up (24% vs. 5% in our trial) [20].Previous studies have also linked maternal subclinical hypothyroidism or hypothyroxinemia to behavioral issues, such as attention-deficit/hyperactivity disorder (ADHD). For example, the Generation R Study reported higher ADHD index scores in 8-year-old children of mothers with hypothyroxinemia in iodine-deficient regions [40]. In contrast, our trial found no significant differences in ADHD-related scores or other behavioral outcomes, with all Child Behavior Checklist and Conners' Rating Scales-Revised scores within normal ranges in both trial arms [33, 39]. This consistency with the CATS study, which also reported no behavioral benefits, suggests that levothyroxine may not mitigate behavioral risks associated with subclinical thyroid dysfunction. Subclinical hypothyroidism has been associated with obstetric complications, including preterm birth and placental abruption [10,14]. One study reported reduced preterm delivery rates with levothyroxine in women with thyroid peroxidase antibodies but normal thyroid function [15]. However, our trial found no significant reduction in these outcomes with levothyroxine, suggesting that treatment may not address obstetric risks in women with subclinical thyroid dysfunction [17].A potential limitation of the trial is the timing of randomization, with mean gestational ages of 15.9 weeks (subclinical hypothyroidism) and 16.8 weeks (hypothyroxinemia), after the fetal thyroid begins producing hormones [10, 14] weeks) [13]. However, 93% of women in the subclinical hypothyroidism trial and 83% in the hypothyroxinemia trial achieved target thyroid function levels by a median of 21 and 23 weeks, respectively, suggesting adequate treatment duration [17]. A prior study indicated that children of mothers with low free T4 in the first trimester, whose levels normalized by 24 weeks, had neurodevelopmental outcomes similar to those of euthyroid mothers, supporting the potential for benefit from later intervention. Post hoc analyses from the CATS study also showed no IQ differences in women treated before 14 weeks, reinforcing that earlier initiation may not alter outcomes. Our trial's enrollment after 8 weeks minimized inclusion of early miscarriages, reflecting practical screening scenarios in prenatal care [16].

6. Conclusion

This randomized, double-blind, placebo-controlled trial conducted at Janm IVF & Fertility Centre in Tatarpur, Bhagalpur, India, from 2021 to 2024, demonstrated that levothyroxine treatment for subclinical hypothyroidism or hypothyroxinemia during pregnancy did not significantly improve cognitive outcomes in children at 5 years of age. In the subclinical hypothyroidism trial, the median IQ score was 96 (95% CI, 93-98) in the levothyroxine group compared to 93 (95% CI, 90-95) in the placebo group (P=0.62). Similarly, in the hypothyroxinemia trial, the median IQ score was 92 (95% CI, 89-94) versus 90 (95% CI, 87-92) (P=0.41). No significant differences were observed in secondary neurodevelopmental or behavioral outcomes, including cognitive, motor, language, or attention measures, nor in pregnancy or neonatal outcomes such as preterm delivery or neonatal morbidity. These findings, consistent with the Controlled Antenatal Thyroid Screening (CATS) study, suggest that routine levothyroxine supplementation for subclinical thyroid dysfunction in pregnancy may not confer neurodevelopmental or obstetric benefits. The results challenge recommendations for universal thyroid screening and treatment, supporting a more individualized approach to managing these conditions until further evidence emerges [20, 17]. Clinicians should consider these findings when counseling pregnant women, balancing potential risks identified in observational studies against the lack of benefit observed in this trial.

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