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ORIGINAL ARTICLE

Pregnancy Outcomes in Women with Subclinical Hypothyroidism Treated with Levothyroxine

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Abstract

Background: **Subclinical hypothyroidism (SCH) is distinguished by an elevated TSH but normal levels of free triiodothyronine (FT3) and free thyroxine (FT4) (FT4). In terms of pregnancy outcomes, levothyroxine has been linked to improvement in several studies.**

Aim and objectives: **Is to evaluate the treatment influence of levothyroxine therapy on the health of the fetus in pregnant women who have subclinical hypothyroidism.**

Subjects and methods: **This case-control research was performed in Obstetrics and Gynecology department in Al-Hussein and Sayed Galal Hospitals, Al-Azhar University, Started from October 2022 to April 2023. There were two sets of women involved: Group (A) (Case group): Patients were subjected to levothyroxine therapy. Group (B) (Control group): Patients were not subjected to levothyroxine therapy (take placebo).**

Result: **When comparing groups A and B, there was no significant distinction in the outcomes or complications experienced by the mothers in group B. The incidence of low birth weight and Group B had a far greater rate of low Apgar scores than Group A did. Nonetheless, the frequency of unfavorable infant outcomes and Group B had more difficulties than Group A, although the difference was not clinically meaningful.**

Conclusion: **The current study indicated that the rate of low birth weight and low Apgar score might be affected by levothyroxine administration.**

Keywords: Subclinical hypothyroidism, Thyroid hormones, Thyroxine, Triiodothyronine

1. Introduction

Subclinical hypothyroidism (SCH) is distinguished by an elevated TSH but normal levels of free triiodothyronine (FT3) and free thyroxine (FT4) (FT4). There is no more prevalent kind of thyroid dysfunction in pregnancy, with estimates placing the frequency anywhere reliant on research design, from 4 percent to thirteen percent, TSH cutoff values, ethnicity, iodine intake, and dietary habits, among other factors.[1]

High blood thyrotropin (TSH) levels with normal free thyroxine (fT4) levels are the biochemical basis for the diagnosis of subclinical hypothyroidism (SCH). Serum TSH levels above 2.5 mIU/l are considered abnormal throughout the 1st trimester, while levels above 3.0 mIU/l are considered abnormal during the 2nd and 3rd trimesters.[2]

Pregnancy loss, early delivery, gestational hypertension, and low birth weight are only some of the disadvantageous pregnancy outcomes that have been linked to SCH in observational studies comparing euthyroid pregnant women versus those with untreated SCH (LBW).[3] Some studies, however, found no link between SCH and pregnancy problems. These reports may have been affected by publication bias, due to the bias against reporting poor research results. In addition, many studies have looked at the effects of SCH on pregnant women, the majority of them have a low to moderate risk of bias because to issues such limited sample numbers, imprecision in the

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calculations, and lack of control for confounding variables.[1,4]

Several investigations compared the results of pregnancies in which women with SCH were given levothyroxine (LT4) to those in which they were not, and reported a potentially positive benefit for LT4. Furthermore, Levothyroxine's effectiveness in TPOAb-negative pregnant women with subclinical hypothyroidism has only been studied in one randomized clinical trial; the other trials included only TPOAb-positive women or women and men with both types of antibodies.[5]

Many meta-analyses, mostly founded on observational studies have reported a possible increased danger of negatively affected pregnancies in women with SCH[6] emphasizing the undesirable outcomes of levothyroxine therapy rather than its beneficial effects.[7] One meta-analysis based on three trials found that infertile women who took levothyroxine had a considerably decreased rate of miscarriage, albeit these findings cannot be extrapolated to the population as a whole.[8]

Although it is generally agreed that untreated hypothyroidism has a negative impact on pregnancy outcomes and that levothyroxine treatment of these women during pregnancy is highly recommended, there is no agreement on whether or not subclinical hypothyroid (SCH) women should be treated in order to improve pregnancy outcomes.[9]

2. Patients and methods

This case-control research was done at the Obstetrics and Gynecology department in Al-Hussein and Sayed Galal Hospitals, Al-Azhar University. The Study duration Started from October 2022 until April 2023. Study population was 140 women that have mild hypothyroidism during pregnancy.

The Inclusion criteria: pregnant women ranged in age from 18 to 45, and all had to meet the SCH criteria, which were as follows: serum TSH >2.5 mIU/L in the first trimester, >3 mIU/l in the second and third trimesters, but 5 mIU/L with normal levels of FT3 & FT4. Singleton pregnancies and Gestational age: at 1st booking visit between 4 and 8 weeks.

The Exclusion criteria: Positive thyroid peroxidase Ab, Chronic diseases (hypertension, diabetes … etc.) and Multiple pregnancies.

All women were separated into two groups after satisfying the inclusion and exclusion criteria: Group A (Case group): cases who were subjected to levothyroxine therapy and Group B (Control group): Patients who were not subjected to levothyroxine therapy (would take placebo).

2.1. Study procedures

All patients underwent the subsequent procedures: History taking, Estimation of gestational age and Laboratory investigations.

2.2. Statistical analysis

SPSS (Statistical Program for the Social Sciences) software, version 23.0, was utilized for tabulating and statistically analyzing the collected data. The median, first- and third-interquartile ranges, and range widths were computed for numerical non-parametric data, while the mean, standard deviation, range width, and least and max value were computed for numerical parametric data.

Inferential analysis was performed on quantitative variables utilizing independent *t*-test for 2 categories with parametric data and the Mann Whitney U for two groups with non-parametric data. Inferential analysis of qualitative data was performed using the Chi-square test for independent groups. A *P* value of less than 0.050 was judged statistically significant. A study's *p* value indicates how likely it is that the results were produced by random chance.

3. Results

Table 1 demonstrates no significant age, BMI, or parity differences within the two groups.

By comparing routine laboratory measures taken during the booking visit, neither of the differences between the two groups were significantly different, Table 2.

The groups showed no statistically significant changes in all laboratory measurements, Table 3.

As can be seen in Table 4, there is a statistically significant difference between the two groups tested in terms of TSH on the 2nd and 3rd visits. In addition, only in group A did TSH levels decrease noticeably.

There was no discernible difference between groups A and B in terms of maternal outcome or complications as shown in Table 5, Fig. 1.

Table 6 shows that low birth weight and Group B had much more low Apgar scores than group A. However, Overall neonatal outcomes/complications were somewhat higher in group B than group A but not statistically significant Fig. 2.

4. Discussion

Subclinical hypothyroidism (SCH) is the most frequent thyroid malfunction during pregnancy, with a prevalence incidence of 3.5%–14 %. When

Table 1. Comparison of the two groups' demographic information.

	Group A ($N = 70$)	Group B ($N = 70$)	t	P
Age (years) Mean ± SD	27.45 ± 3.24	28.17 ± 3.66	1.1	0.283
<30 years	48 (68.6 %)	45 (64.3 %)	0.288	0.591
>30 years	22 (31.4 %)	25 (35.7 %)		
BMI (kg/m^2) Mean ± SD	26.82 ± 1.69	27.32 ± 1.88	1.65	0.102
<25 kg/m^2	13 (18.6 %)	14 (20 %)	1.22	0.544
25–30 kg/m^2	32 (45.7 %)	37 (52.9 %)		
>30 kg/m^2	25 (35.7 %)	19 (27.1 %)		
Parity				
Primi	37 (52.9 %)	34 (48.6 %)	0.257	0.612
Multi	33 (47.1 %)	36 (51.4 %)		

Table 2. Comparison of laboratory parameters between the two study populations during the booking visit.

	Group A ($N = 70$)	Group B ($N = 70$)	t	P
Hb (g/dl)Mean ± SD	11.19 ± 2.11	10.42 ± 2.53	0.085	0.933
TLC (x 10^3/l)Mean ± SD	8.15 ± 2.32	8.23 ± 2.35	0.131	0.897
PLT (x 10^3/l)Mean ± SD	215.54 ± 57.76	207.14 ± 61.22	0.537	0.593
ALT (U/l)Mean ± SD	39.22 ± 10.65	38.25 ± 9.31	0.574	0.567
AST (U/l)Mean ± SD	37.82 ± 8.56	35.84 ± 7.73	1.44	0.153
Creatinine (mg/dl) Mean ± SD	1.06 ± 0.268	1.1 ± 0.315	0.809	0.420
Urea (mg/dl)Mean ± SD	32.62 ± 5.83	34.28 ± 7.31	0.956	0.343
RBS (mg/dl)Mean ± SD	137.75 ± 25.41	141.96 ± 27.65	0.604	0.549
Albumin (g/dl)Mean ± SD	3.71 ± 0.823	3.64 ± 0.904	0.479	0.633

Table 3. Distribution of thyroid function in between the two groups of research.

	Group A ($N = 70$)	Group B ($N = 70$)	T	P
TSH (mIU/l)Mean ± SD	5.63 ± 1.77	5.38 ± 1.46	0.912	0.364
Free T_4 (ng/dl)Mean ± SD	1.36 ± 0.624	1.23 ± 0.522	1.34	0.183
Free T_3 (pg/ml)Mean ± SD	2.29 ± 0.783	2.35 ± 0.812	0.445	0.657

Table 4. Follow up measure of TSH distribution between the two studied groups.

	Group A ($N = 70$)	Group B ($N = 70$)	T	P
TSH at 1st visit (mIU/l) Mean ± SD	5.63 ± 1.77	5.38 ± 1.46	0.912	0.364
TSH at 2nd visit (mIU/l) Mean ± SD	3.84 ± 1.31	5.56 ± 1.52	**7**	<0.001
TSH at 3rd visit (mIU/l) Mean ± SD	2.51 ± 0.916	5.28 ± 1.24	**15**	<0.001

Table 5. Comparison of the two groups with respect to maternal outcome.

	Group A ($N = 70$) N (%)	Group B ($N = 70$) N (%)	χ^2	P
Preeclampsia	2 (2.9)	3 (4.3)	0.207	0.649
Eclampsia	0 (–)	1 (1.4)	1.01	0.318
Placental abruption	0 (–)	1 (1.4)	1.01	0.318
Placenta previa	0 (–)	2 (2.9)	2.03	0.154
GDM	3 (4.3)	7 (10)	1.72	0.190
Gestational HTN	7 (10)	6 (8.6)	0.085	0.771
PROM	8 (11.4)	7 (10)	0.075	0.785
Miscarriage	4 (5.7)	6 (8.6)	0.431	0.512
Postpartum hemorrhage	1 (1.4)	2 (2.9)	0.341	0.560

testing thyroid function, SCH is defined by an increased serum thyrotropin (TSH) but a normal free thyroxine (FT4) level. Thyroid function is influenced by environmental circumstances, ethnicity, iodine consumption, and genetic vulnerability and so may vary amongst groups. Thyroid dysfunction in the

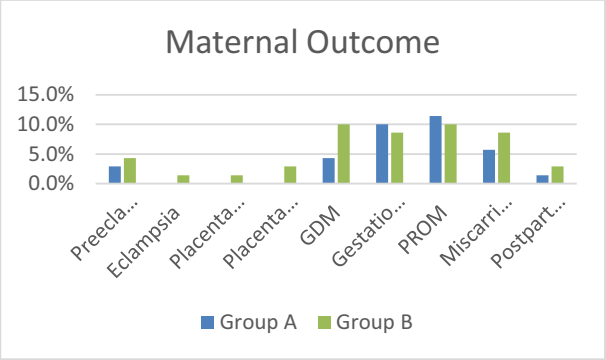

Fig. 1. Shows comparison of the maternal outcome in group A and B.

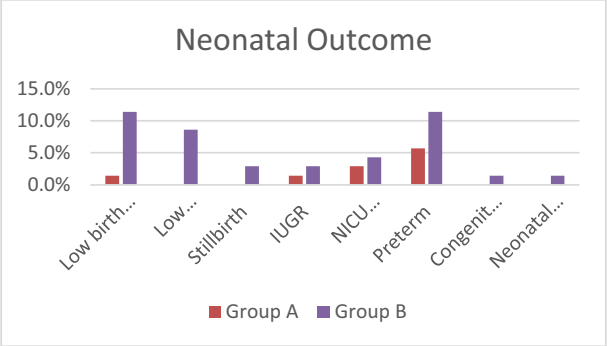

Fig. 2. Shows comparison of the neonatal outcome in group A and B.

first trimester of pregnancy should be diagnosed using a population-based TSH reference range, with 4.0 mIU/L as the top reference limit in the absence of such a range as provided by the American Thyroid Association (ATA) in their 2017 guidelines.[10]

As regard demographic data: Age, BMI, and parity are not statistically different between the two groups.

In the study of[8] they stated that SCH-TPOAb (negative for thyroid peroxidase antibody) A total of 183 females were assigned at random to receive LT4 treatment (group A) or to serve as a control (group B), and their findings corroborated ours. Women without euthyroid TPOAb ($n = 1028$) were used as a comparison group (group C). Subjects in groups A, B, and C had mean (SD) ages of 27.0 (5.3), 26.9 (4.7), and 27.1 (5.2) and BMIs of 25.8 (4.9), 26.0 (4.6), and 24.8 (4.6), respectively.

Similarly[5] demonstrated that neither trial found any differences between the levothyroxine and placebo groups at baseline.

The current study showed that when comparing regular laboratory parameters among the opposing groups, there is no discernible difference. TSH, fT4, and fT3 levels are not significantly different between the two groups. At the second and third visits, the levels of TSH in the two groups were different, and the difference was statistically significant. In addition, only in group A did TSH levels decrease noticeably.

While, in the study of[11] the TSH and thyroid antibody levels of 8530 pregnant women in Southern Italy were checked throughout the first trimester of their pregnancies. Group A included levothyroxine-treated group of 198 women with euthyroid thyroid antibodies; untreated group of 195 women with euthyroid thyroid antibodies; untreated group of 197 women with negative thyroid antibodies. Based on thyroid antibody status.

In the study of[12] Compared to the placebo group, those who took levothyroxine saw decreases in serum thyrotropin and increases in free T4 across the board, indicating a physiologic effect. Similar percentages of women in the levothyroxine and placebo groups discontinued the trial drug due to aberrant results on thyroid function testing (9.8 % and 9.6 %, respectively). Adherence was excellent, ranging from 81 % to 94 % at all time points among women for whom data was available.

Furthermore[1] revealed that both the mean body mass index and the mean serum thyroid stimulating hormone level were larger in group A than in group B (29 7.7 kg/m2 vs. 27 6.6 kg/m2; $P = 0.04$ and 4.9 ± 1.4 mIU/l vs. 3.5 ± 0.9 mIU/l, respectively; $P < 0.0001$, respectively). TSH testing was performed between 6.3 and 10 weeks of pregnancy in both groups, with a median of 7.1 weeks (interquartile range [IQR]: 6.3–9.1) for group A and 7.6 weeks (IQR: 6.3–10 weeks) for group B.

Table 6. Neonatal outcome distribution between the two studied groups.

	Group A ($N = 70$) N (%)	Group B ($N = 70$) N (%)	χ^2	P
Low birth weight	1 (1.4 %)	8 (11.4 %)	5.82	0.016
Low Apgar score	0 (–)	6 (8.6 %)	6.27	0.012
Stillbirth	0 (–)	2 (2.9 %)	2.03	0.154
IUGR	1 (1.4 %)	2 (2.9 %)	0.341	0.560
NICU admission	2 (2.9 %)	3 (4.3 %)	0.207	0.649
Preterm	4 (5.7 %)	8 (11.4 %)	1.46	0.228
Congenital malformations	0 (–)	1 (1.4 %)	1.01	0.318
Fetal death	0 (–)	1 (1.4 %)	1.01	0.318

According to the findings of this research, outcomes and complications for mothers were slightly higher in group B than in group A, however, there was no discernible difference.

Morover[5] corroborated our findings, reporting statistically negligible in the occurrence of poor pregnancy and neonatal outcomes among the two trials. In both trials, Levothyroxine and placebo groups had similar mean gestational ages at birth (subclinical hypothyroidism trial: 39.1 ± 2.5 weeks and 38.9 ± 3.1 weeks, respectively; $P = 0.57$; and hypothyroxinemia trial: 39.0 ± 2.4 weeks and 38.8 ± 3.1 weeks, respectively; $P = 0.46$). Overall, adverse events were low in both studies, and serious adverse events were not significantly varied across groups.

Similarly[12] demonstrated that the occurrence of pregnancy-related problems was not significantly different.

Also[1] revealed that 30 pregnancies were lost in the cohort (24 miscarriages and 6 stillborn). In group A ($n = 5$; 6.1 %) there were fewer miscarriages than in group B (n = 25; 8.8 %), but the results showed no statistically significant change ($P = 0.12$).

Our results showed that low birth weight and in group B, low Apgar values were significantly more prevalent than in group A. However, the rest neonatal outcome/complications were slightly higher in group B compared to group A but without statistically significant difference.

While, in the study of[9] group B had the highest rate of preterm births, while groups A and C had the lowest (RR = 0.30, 95 % CI: 0.1–0.85, $P = 0.0229$) and (RR = 0.23, 95 % CI: 0.14–0.40, $P < 0.001$) respectively. There was no significant difference in the rates of preterm labor between groups A and C (RR = 0.79, 95 % CI: 0.30–2.09, $P = 0.64$). The number needed to treat (NNT) for the preterm birth was 5.9 (95 % CI: 3.33–25.16).

4.1. Conclusion

This investigation concluded that levothyroxine intervention has an effect on the incidence of low birth weight and low Apgar score.

Conflicts of interest

None.

Acknowledgements

None.

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