Determinants of medication adherence to Levothyroxine in pregnant women with Hypothyroidism

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Abstract

Objectives: Pregnant women with hypothyroidism require hormone replacement therapy with thyroxine. It is prudent to initiate prompt treatment of hypothyroidism to prevent adverse outcomes in both mother and the neonate. Non-adherence to medication is synonymous with treatment failure, it increases health care costs and may lead to poor quality of life. The aim of this study was to determine the factors contributing to non-adherence to levothyroxine in pregnant women.

Methods: This was a cross-sectional interventional study. Pregnant women >18 years of age, with hypothyroidism on levothyroxine for minimum 3 months were eligible for inclusion. Women with sub-clinical hypothyroidism and those on drugs likely to interfere with thyroxine were excluded.

Results: The study enrolled 75 patients with a mean age of 27.2±4.3 years. The mean duration of illness (hypothyroidism) was 26±30.6 (range, 2-120 months). The mean TSH levels were 3±1.4 (range, 1.1-5.7 milli-international/L). The mean dose of levothyroxine was 64.5±34.8 (range, 12.5-125 mcg). Fifty-three (70.7%) women were taking folic acid supplements and fifteen (20%) women were on alternative and complimentary medications. Morisky, Green and Levine (MGL) medication adherence scale was administered to eligible participants. The study revealed that 54.7% pregnant women with hypothyroidism have low to medium adherence to levothyroxine therapy. Multiple regression analysis revealed that patient's age, education level and disease insight, gestational age, folic acid supplementation and cost of medication significantly (P<0.05) influenced adherence to levothyroxine in this cohort.

Conclusion; Patient's age, educational status and disease insight, andmedication costs significantly influence adherence to medication in pregnancy women with hypothyroidism.

Keywords: Pregnancy; hypothyroidism; Levothyroxine; medication adherence.

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1. Introduction

Iodine is an essential micronutrient required for normal thyroid function, growth, and development. Pregnancy is known to affect the normal functioning of thyroid gland; there is a physiologic increase in the demand for iodine and thyroid hormones during pregnancy, leading to an increase in size of thyroid gland. This impact may significantly higher in the goitre belt (a goitre endemic area of about 2400 km, in northern part of the subcontinent). Low iodine concentrations or compromised thyroid gland status during pregnancy may lead to clinical hypothyroidism. [1,2] The prevalence of hypothyroidism in pregnancy in western countries is about 2.5%. However, in India, the prevalence ranges between 4.8% to 11%. [3-6]

Hypothyroidism during pregnancy adversely affects both mother and the child. A meta-analysis of 18 cohort studies have found that pregnant women with untreated hypothyroidism are at increased risk for loss of pregnancy, placental abruption, premature rupture of membranes, and neonatal death as compared to those with normal thyroid function.[7]

Patients with hypothyroidism may require hormone replacement therapy with thyroxine for life. However, a good clinical outcome with long term therapy is challenging in more than one way; non-adherence to medication, drug interactions and comorbid conditions may lead to failure of treatment, higher mortality rates and poor quality of life. Having said this, a high medication adherence rate may help reduce healthcare costs by reducing the number of hospitalizations and emergency room visits. [8]

Although ample evidence exists to substantiate the importance of adherence with medication in influencing treatment outcome, there is a relative paucity of studies on whether pregnant women do or do not adhere to their medication. More specifically, there are only a few studies in literature on patterns of adherence and factors associated with adherence to levothyroxine in pregnant women with hypothyroidism. Medline search for keywords 'hypothyroidism,' 'pregnancy,' and 'drug adherence,' did not reveal any study evaluating adherence to levothyroxine in pregnant women. The rationale behind the current cross-sectional study was to explore the factors related to low adherence to levothyroxine in pregnant women in order to achieve better clinical outcomes and improve quality of life in women and their off springs. Thus, the present study aimed to identify patient's nonadherence to levothyroxine and study the clinical factors contributing to drug adherence in these patients.

2. Methods

2.1 Trial population

This study was a cross-sectional study conducted at a tertiary care teaching hospital. Ninety-two pregnant women were diagnosed with hypothyroidism from January 2018 to February 2019 at our referral center. Out of these, 86 (93.5%) met none of the exclusion criteria and were asked to come for eligibility confirmation visit. Of the 86 patients who returned for the eligibility confirmation visit, 75 (87.2.1%) were eligible for inclusion in the trial. The institutional review boards and the local ethics committee approved the trial. Written informed consent was obtained from all patients willing to participate in the study based on the tenets of the declaration of Helsinki.

2.1 Thyroid Function tests

Thyroid function test was performed by analysing patients' serum and plasma on ChemiluminescenceImmuno Assay.

2.3 Eligibility criteria

Pregnant women above 18 years of age with hypothyroidism on levothyroxine for minimum 3 months were enrolled in the study.

2.4 Exclusion criteria

Hypothyroid women (subclinical hypothyroidism) not on levothyroxine therapy, comorbid conditions affecting thyroid function and those on drugs likely to interfere with thyroxine were excluded.

2.5 Medication Adherence

All eligible participants were administered the Morisky, Green and Levine (MGL) medication adherence scale, a validated, structured self-reporting medication adherence measure, to identify patients with regard to adherence to prescribed medications.[9-10] The MGL scale is a four-item scale; the higher the score, the more likely are the respondent's adherent to their treatment. Typically, the patient was considered adherent when his/her score was at least 3 points.

2.6 Sample size calculation

To estimate the sample size in pregnant women with hypothyroidism to determine adherence to medication, prevalence (P) of hypothyroidism was found to be approximately 5% (based on previously published studies, worldwide). The standard normal variate (Z) was 1.96 and precision error (d) of 5% and type I error of 5%, the estimated sample size was calculated to be 73. (<https://www.stat.ubc.ca/~rollin/stats/ssize/>).

2.7 Statistical Analysis

Statistical analysis was performed using IBM, SPSS Statistics version 25 (IBM Corp., New York, NY). The test values of continuous variables were expressed as mean ± SD (standard deviation). A P-value < 0.05 was considered statistically significant. Dichotomous variables and proportions were compared with Chi-square tests. The impact of independent variables like age, religion, medication costs, education level, past medical history, history of abortion, duration of illness, gestational age on adherence to medication (dependent variable, MGL score) in these subjects was estimated using multiple regression analysis. The assumptions for performing regression analysis were met. The aim was to determine the overall fit (variance explained) of the model and the relative contribution of each of the predictors to the total variance.

3. Results

The number of valid cases was 75. The mean age of patients was 27.2±4.3 (range, 20-37 years). The mean gestational age was 26.2±10.9 (range, 3-37 months). The mean duration of illness (hypothyroidism) was 26±30.6 (range, 2-120 months). The mean TSH levels were 3±1.4 (range, 1.1-5.7 milli-international/L). The mean dose of levothyroxine was 64.5±34.8 (range, 12.5-125 mcg).

Fifty-three (70.7%) women were taking folic acid supplements and 58 (77.3%) were taking additional supplements. Fifteen (20%) women were on alternative and complimentary medications. Sixty-five (86.7%) women were Hindu and 10(13.3%) were Muslims, respectively. A past history of abortion was seen in 24(32%) women.

Adherence was low in 11(14.7%) of medicated women, while it was intermediate and high in 34(45.2%) and 30(40.1%), respectively.

The adherence score did not significantly differ (Chi square test, P=0.382) across religions (Hindu and Muslims). The adherence was significantly (Chi-square test, P<0.05) lower in uneducated patients (13.3%) and school dropouts (41.3%).

Younger age was associated with a significantly low adherence to medication (Chi-square test, P<0.05) and vice versa. Adherence was significantly (Chi-square tests, P<0.05) lower at higher age of gestation. Patients with a past medical history had lower adherence to medication. Adherence to medication was significantly lower (Chi-square test, P<0.05) when duration of illness was more and overall cost of medication higher.

The adherence to medication did not differ significantly between women taking folic acid supplements and those without (Chi-square test, P=0.09).

In order to predict adherence to medication (MGL Score) from age, cost of medication, educational status, duration of illness, gestational age, history of abortion, past medical history and alternative medicine, a multiple regression model was constructed. There was linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.650. The assumption of normality was met, as assessed by a Q-Q Plot. The multiple regression model statistically significantly predicted adherence to medication, $F_{(9,65)} = 24.01$, $P < 0.05$, adjusted $R^2 = 0.737$. The variables that added statistically significantly to the prediction ($p < .05$) were, age, education level, disease insight, gestational age, folic acid supplementation and cost of medication. Regression coefficients and standard errors can be found in Table 2. The regression plots are shown in Figure 1.
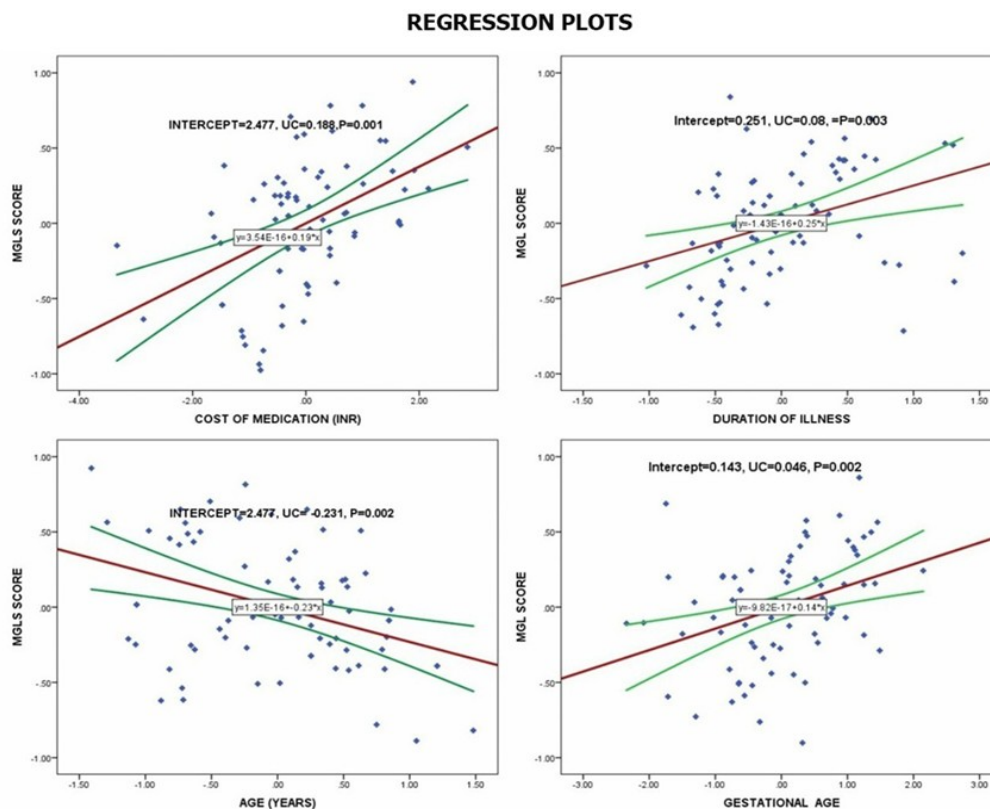

Figure 1: Regression plots showing unstandardized regression coefficients and significance levels.

Table 1: Regression Coefficients and standard error

Variable	B	SE	Significance
Intercept	1.670	0.512	0.002
Duration of illness	0.251	0.080	0.003
Cost of medication	0.166	0.036	0.001
Education and disease insight	-0.038	0.028	0.184
Age	-0.242	0.063	0.001
Folic Acid supplements	0.259	0.097	0.010
Abortion	-0.049	0.109	0.657
Medical History	-0.234	0.154	0.134
Alternative Medicine	-0.050	0.113	0.661
Gestational age	0.143	0.046	0.002

B (unstandardized regression), SE (Standard error), Significance (P value)

4. Discussion

Beyond doubt, advances in drug therapies have led to efficacious treatments being available for many medical conditions; however, it is well recognized that "medicines will not work in those patients who do not take them regularly."

The results of the present cross-sectional study revealed that 59.9% pregnant women with hypothyroidism have low to medium adherence to levothyroxine prescription. It was observed that patient's education level, medication costs, age, history of recurrent abortions and gestational age significantly correlated with the level of adherence. Although, folic acid consumption did not significantly influence drug adherence as an independent variable, it did so in the multiple regression model.

In Denmark [11], a survey on 2041 pregnant women found that the overall compliance rate with prescription drugs was about 43%. An Australian study [12] found that 59.1% pregnant women suffering from another chronic condition were non-adherent to medication. The main reason for not taking medications in these women was fear of harming the unborn child. There may be a wide variability in reasons for poor adherence in developing countries. Although, the non-compliance rate in the present study (59.9%) was comparable to Australian women, lack of education and cost of medication was the main reasons for poor drug adherence in the sub-continent.

A Mediterranean cross-sectional study [13] involving 337 patients found that 54.9% hypothyroid patients had low adherence to levothyroxine. Alcohol consumption, water-pipe smoking, presence of comorbidities and last-minute cancellation of physician's appointment were significantly associated with low adherence in a logistic regression model.

A study from Nepal [14] in 113 patients with hypothyroidism, out of which 85.8% were females of 31-40 years age group, found that 48.7% had poor adherence to levothyroxine. Illiteracy, longer treatment duration and missed appointment with endocrinologist were factors significantly associated with poor adherence. The first two observations in this study were in agreement with the present study.

In a cross-sectional study conducted across 18 countries, 61% pregnant women had low or moderate adherence to levothyroxine. Younger age of mother and not using folic acid supplements were factors significantly associated with low adherence. Younger maternal age and folic acid supplementation added significantly to the prediction in the regression model constructed in the present study.[15]

In an observational cross-sectional study, conducted in 289 hypothyroid patients in Pakistan, [16] the study population had 27.3% low adherers (compared to 14.7% in our study), 40.5% medium adherers (compared to 40.5% in ours), and 32.2% high adherers (as opposed to 45.3% in this study). In this study, patient's level of education, affordability and assistance in taking medication significantly influenced drug adherence.

In chronic diseases like hypothyroidism, poor medication adherence is the main cause of low efficacy of pharmacological therapy. Scavone *et al*[17] observed that at a 5-year follow up, 21.5% patients on levothyroxine therapy had serum TSH levels greater than 5mU/L due to poor drug adherence. We also observed a significant difference (Chi-square test, $P<0.05$) in adherence in the present study with increasing treatment duration.

The formulation of levothyroxine (tablet versus liquid form) may play a crucial role in medication adherence for lifetime treatment. A study on 320 patients in Italy found that patients consuming tablets more frequently forgot to take their medication and had difficulty in complying to their treatment plan ($p < 0.001$) than those on liquid treatment.[18]

In conclusion, a significant number of hypothyroid women have low adherence to thyroid medication during pregnancy. The high percentage of patients reporting poor compliance with a simple and safe regimen of treatment for common conditions like hypothyroidism is worrisome. Non-adherence to medication during pregnancy may be observed in both developed and developing countries. However, the reasons for non-adherence may differ. In developing countries, lack of education, insight into the disease and consequences of not taking medicines, and affordability of medicines significantly influenced adherence to medication. Undoubtedly, women who take their thyroid hormone regularly and keep their TSH values in the normal range will have less problems during pregnancy and their babies will have improved developmental outcomes. Educating patients about the disease and its consequences during pregnancy may improve adherence and treatment outcomes.

Disclosure of interest statement:

The authors report no conflict of interest.

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