

DOI: <http://dx.doi.org/10.18203/2319-2003.ijbcp20200709>

Original Research Article

A prospective study on evaluation of maternal and foetal outcomes of hypothyroidism with levothyroxine and prevalence of hypothyroidism in pregnancy in a tertiary care teaching hospital in Kerala

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Received: 02 February 2020

Revised: 17 February 2020

Accepted: 18 February 2020

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ABSTRACT

Background: Pregnancy influences a profound alteration in thyroid function and hypothyroidism has a massive impact on adverse pregnancy outcomes. An appropriate treatment with appropriate dose of levothyroxine is much essential during pregnancy. The present study evaluates the effect of levothyroxine dose in preventing maternal and foetal outcomes and the prevalence of hypothyroidism among pregnant women.

Methods: 1500 antenatal women with singleton gestation attending outpatient of Obstetrics and Gynaecology Department, were analysed. Apart from routine obstetrical investigations, thyroid stimulating hormone (TSH) tests were done at the first antenatal visit. Patients were followed up till delivery after levothyroxine treatment. Their obstetrical and perinatal outcomes were noted. TSH estimation was done 3 days after delivery in new-borns to screen for neonatal thyroid disorders.

Results: The prevalence of hypothyroidism was 10.54%. The common adverse maternal and foetal complications were preeclampsia (15.19%) and low birth weight babies (17.72%) respectively. The mean age of pregnant women was 26.66 years. As age advances there is an increased risk of developing hypothyroidism in pregnancy. Levothyroxine 25 µg daily was highly prescribed in 63.92% hypothyroid patients.

Conclusions: Overall, the prevalence of hypothyroidism was high. Since maternal and foetal complications were higher in patients with hypothyroidism, levothyroxine treatment had decreased the risk of maternal and foetal outcome. Pre-pregnancy screening should be implemented at least in patients with high risk factors for thyroid dysfunction. Universal screening for new-borns is also recommended to detect hypothyroidism. Expert decisions and cost-effectiveness studies will promulgate the impact of universal screening.

Keywords: Hypothyroidism, Prevalence, Levothyroxine

INTRODUCTION

Thyroid disorders are the commonest endocrine disorders affecting women of reproductive age group.¹ Hypothyroidism is the second most common endocrinopathies found in pregnancy, first being

diabetes.² Pregnancy is a stressful condition to the maternal thyroid gland and is associated with intense changes in the regulation of thyroid function. There is 30% to 100% increase in total triiodothyronine and thyroxine concentrations, two to threefold increase in thyroxine-binding globulin concentration, increased

serum thyroglobulin, and increased renal iodide clearance.³ Furthermore, human chorionic gonadotropin hormone (beta-HCG), during pregnancy has mild thyroid stimulating activity as it has structural similarities with thyroid stimulating hormone (TSH).⁴

Thyroid hormone is critical for normal foetal brain development, neuronal multiplication, migration and structural organization, thus on future intellectual development. During early pregnancy, the foetus is totally dependent on maternal thyroid hormone supply. Foetal thyroid gland starts producing hormones from 8-10 weeks of gestation and significant amounts after mid-gestation.⁵ Maternal thyroid hormone excess or deficiency can influence the outcome of mother and foetus at all stages of pregnancy. The most frequent thyroid disorder in pregnancy is maternal hypothyroidism.

According to the western literature the prevalence of hypothyroidism in pregnancy is around 2.5%.⁶ According to few Indian studies the prevalence of hypothyroidism in pregnancy is ranging from 4.8% to 14.3%.⁷⁻¹⁰

In pregnancy, physiological changes like fatigue, sluggishness, constipation, oedema may simulate hypothyroidism. Thyroid dysfunction in pregnancy may lead to abortion, placental abruption, pre-eclampsia, preterm delivery, low birth weight babies, foetal growth restriction, neonatal hyperbilirubinemia and reduced intellectual function in the offspring.⁵

It is best to screen women early in the pregnancy for thyroid dysfunction. They are common, treatable, and to some extent preventable conditions which produce morbidity and pose special risks for pregnancy and the developing foetus. Screening for thyroid dysfunction in a woman who is pregnant is important because thyroid hormone status is directly related to foetal brain development. Reference ranges of TSH obtained from non-pregnant populations do not reflect normal values in pregnant women because of their physiologic changes in thyroid function.¹¹ As per the American thyroid society and Indian thyroid society recommendations, the following reference ranges are recommended during pregnancy. 1st trimester was 0.1 to 2.5 mIU/l, 2nd trimester was 0.2 to 3.0 mIU/l, 3rd trimester was 0.3 to 3.0 mIU/l.^{12,13} Notably, the lower reference limit of TSH concentrations is also decreased in pregnant women, so euthyroid women can be diagnosed as hyperthyroid if non-pregnant reference ranges are used.¹⁴

The objective of this study was to evaluate the benefit of levothyroxine at different doses in preventing maternal and foetal outcomes and to analyse the prevalence of hypothyroidism among the pregnant women with an ultimate aim of creating awareness on pre-conceptional screening for all antenatal women.

Ethical approval

This study was approved by the Institutional Ethics Committee of PVS Hospital (P) Ltd, [PVS/EC/02/13-14], (dated 12th October 2013).

METHODS

This is a prospective analytical study which was carried out in a total of 1500 antenatal women attending OPD of first and second units in the Department of Obstetrics and Gynaecology, PVS Hospital, Calicut, which is a 310 bedded multi-specialty hospital with a full-fledged obstetrics and gynaecology department with up to 1700 deliveries per year. Of the 1500 pregnant women, 1407 women had their first visit during first trimester and 93 women had their first visit during second trimester. The duration of study was for two year i.e., from October 2013 to October 2015.

All women with singleton gestation attending OBG outpatient department, PVS hospital, Calicut, were included irrespective of their gravida status and the period of gestation. Women with documented history of hypothyroidism and on treatment, multiple pregnancies, gestational trophoblastic diseases, pregestational diabetes and past history of thyroid disorders were excluded from analysis.

After obtaining informed consent from the patient, detailed history was taken in a prescribed proforma. Physical examination was done to look for thyroid enlargement and to ascertain the pregnancy. Apart from recommended routine antenatal investigations, TSH estimation during their first visit was also done. The reference ranges of the test values used in this study were as per the guidelines of American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum.¹² As per ATA Guidelines, if trimester-specific ranges for TSH are not available in the laboratory, the following upper normal reference ranges are recommended: 1st trimester was 0.1 to 2.5 mIU/l, 2nd trimester was 0.2 to 3.0 mIU/l, 3rd trimester was 0.3 to 3.0 mIU/l.

Women with hypothyroidism were treated with levothyroxine and monitored by repeat tests every trimester and the doses of the levothyroxine were adjusted to keep serum TSH within normal limit ≤ 2.5 mIU/l in first trimester and ≤ 3.0 mIU/l in second and third trimester. All pregnant women were followed throughout the pregnancy and allowed to continue till 40 weeks of gestation, unless termination was indicated for maternal or foetal indications. Adverse pregnancy outcomes like preeclampsia, abruption, preterm delivery, abortions, intrauterine growth restriction (IUGR), foetal distress, low birth weight were analysed. TSH estimation was done 3 days after delivery in new-borns to screen for neonatal thyroid disorders. The reference range used for neonatal TSH was <40 uIU/ml at 72 hours of life.

The collected data was analysed statistically using SPSS version 16 software package. Data was analysed by Pearson's chi square test. A p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

In this study, a total of 1500 antenatal women attending outpatient Department of Obstetrics and Gynaecology were included. Of the total population analysed, 158 (10.54%) were found to have hypothyroidism in pregnancy and 1342 (89.46%) women were euthyroid (Table 1).

Table 1: Distribution of the population according to thyroid status.

	Number	Percentage (%)
Euthyroid	1342	89.46
Hypothyroid	158	10.54

With regard to the age wise distribution of screened population for euthyroid and antenatal women with hypothyroidism. As the age advances there is an increased risk of developing hypothyroidism in pregnancy. This observation is statistically significant ($p=0.019$) (Table 2).

Table 2: Age wise distribution of screened population.

Age (in years)	Euthyroid (n=1342)		Hypothyroid (n=158)		P value
	Number	%	Number	%	
≤20	91	83.49	18	16.51	0.019
21-25	520	92.53	42	7.47	
26-30	491	89.11	60	10.89	
31-35	184	89.76	21	10.24	
≥36	56	76.71	17	23.29	

Table 3: Association of hypothyroid and maternal complication.

Antenatal complications	Euthyroid (n=1342)		Hypothyroid (n=158)		P value
	Number	%	Number	%	
No complication	1012	75.41	104	65.82	
Preeclampsia	125	9.31	24	15.19	0.01
Preterm labour	143	10.65	19	12.02	0.453
Abortion	47	3.5	10	6.33	0.13
Abruption	15	1.12	1	0.63	0.5

Table 4: Association of hypothyroid and foetal complications.

Foetal Complications	Euthyroid (n=1342)		Hypothyroid (n=158)		P value
	Number	%	Number	%	
No complications	742	55.32	67	42.41	
LBW	227	16.91	28	17.72	0.7
Foetal distress	100	7.45	23	14.56	0.02
Preterm birth	143	10.66	19	12.02	0.453
IUGR	80	5.96	10	6.33	0.264
Abortion	47	3.51	10	6.33	0.13
IUD	3	0.22	1	0.63	0.3

Among the association of hypothyroid with the maternal complication, 15.19% of hypothyroid patients had preeclampsia while it is only 9.31% in euthyroid patients. This observation was found to be statistically significant ($p=0.01$). 12.02% of hypothyroid patients and 10.65% of euthyroid population were found to have preterm delivery. The incidence of preterm delivery was more in hypothyroid population but had not shown a statistically significant difference between them. Abortion was noted in 6.33% of patients with hypothyroidism, while it was 3.5% in euthyroid patients. The incidence of abortion was more in hypothyroid patients but had not shown a statistically significant difference between them.

Abruption was noted in 0.63% of hypothyroid patients while it was 1.12% in euthyroid patients and this observation was found to be statistically not significant ($p=0.5$) (Table 3).

With respect to the association of hypothyroid and foetal complications, the lower birth weight babies are higher with 17.72% of patients when compared to other foetal complications in hypothyroidism and its 16.91% in euthyroid women. The result is statistically insignificant. The foetal distress was noted in 14.56% of patients with hypothyroidism whereas it was 7.45% in euthyroid population. This observation was found to be statistically

significant ($p=0.02$). Here, preterm birth was noted in 12.02% followed by Foetal distress in hypothyroid patients, whereas its 10.66% in euthyroid pregnant mother. Among hypothyroid patients 6.33% had IUGR while it was 5.96% in euthyroid population. This observation was not found to be statistically significant. Also, 17.72% of hypothyroid patients and 16.91% of euthyroid population were found to have delivered babies of weight ≤ 2.5 kg. IUD was noted in 0.63% of hypothyroid patients and 0.22% of euthyroid patients. Abortion was noted in 6.33% of patients with hypothyroidism while it was 3.5% in euthyroid patients (Table 4).

Table 5: Distribution of hypothyroid population according to treatment.

Treatment	Number	Percentage (%)
L-thyroxine 25 μg	101	63.92
L-thyroxine 50 μg	44	27.85
L-thyroxine 75 μg	7	4.43
L-thyroxine 100 μg	6	3.80

Table 5 shows the distribution of hypothyroid population on treatment, of which 63.92% of hypothyroid patients required L-thyroxine 25 μg on daily basis, whereas 27.85% required levothyroxine 50 μg daily, a less percentage of 4.43% required levothyroxine 75 μg daily and a higher dose of levothyroxine 100 μg daily was needed for 3.80% of antenatal population.

DISCUSSION

This clinical study was conducted to assess the maternal and fetal outcomes with levothyroxine and to analyze the prevalence of hypothyroidism in pregnancy outpatients of Obstetrics and Gynaecology Department. Out of 1500 antenatal women, 158 (10.54%) were found to have hypothyroidism and 1342 (89.46%) were euthyroid. All the patients with hypothyroidism were treated with levothyroxine and followed up in euthyroid state till delivery. Also, the fetal and maternal outcomes were compared to that of the euthyroid group.

Association of hypothyroidism in pregnancy with age and parity

The mean age of pregnant women in this study was 26.66 years (SD=4.00), which was lower compared to western studies by Vaidya et al.¹⁵ This reflects early marriage and early conception prevalent in our area. In this study, the occurrence of thyroid dysfunction in pregnancy has showed an increasing trend as the maternal age advances (10.24% vs 23.29%, $p=0.019$). A study by Ajmani et al, has also shown an increased occurrence of thyroid dysfunction with advancing maternal age.⁷ Increased incidence of hypothyroidism was noted in multigravida; however, it is statistically not significant. This was comparable with the study by Ajmani et al.⁷

Association of hypothyroidism in pregnancy and preeclampsia

The incidence of preeclampsia was 15.19% in patients having hypothyroidism and 9.31% in euthyroid patients. This finding is statistically significant 15.19% vs 9.31%, ($p=0.01$). The incidence of preeclampsia in hypothyroidism in the present study is compared with other studies below.

Ajmani et al reported incidence of preeclampsia (38.9%) in hypothyroidism and (7.8%) in euthyroid status, where the hypothyroidism incidence is less in our study but the euthyroid incidence is almost similar to the previous study.⁷ Similarly, in western studies by Leung et al and Davis et al the findings were comparable to our study.^{16,17}

Association of hypothyroidism in pregnancy and preterm labor

In this study 12.02% of patients with hypothyroidism had preterm delivery while it was 10.65% in euthyroid. The incidence of preterm labor is compared with various studies below. In a study by Ajmani et al, the incidence of preterm labor was 39.1% and 25% in hypothyroidism and euthyroid respectively which was high and not consistent with our study.⁷ In our study, the low incidence can be attributed to the early detection and better control of thyroid dysfunction in the study group. Stagnaro, reported that women with high TSH levels has threefold increase in risk of preterm delivery.¹⁸

Association of hypothyroidism in pregnancy and abortion

In this study, 6.33% abortions were noted in hypothyroidism patients and 3.51% in euthyroid patients. In a study by Ajmani et al, incidence of abortion was 8.3% in pregnant women with hypothyroidism which was higher when compared to our study.⁷ Abalovich et al, reported that untreated hypothyroidism at the time of conception is associated with miscarriage rate of 31.4% compared with 4% in euthyroid subjects.¹⁹ Similar to our study out of 10 abortions, 4 (40%) miscarriages in hypothyroidism were untreated as these patients had their first visit and TSH measurement was done after 9 weeks of gestation which is also, in parallel to a study by negro et al.²⁰

In a study by Goldman et al, miscarriage rates were almost the same in hypothyroid patients and euthyroid group, where the cut off for hypothyroidism was TSH >4.29 mU/l.²¹ Lower incidence of abortion in our study could probably be the result of early detection and good control of thyroid dysfunction with medications.

Association of hypothyroidism in pregnancy and abruption

In this study, incidence of abruption was 0.63% in hypothyroidism patients and 1.12% in euthyroid patients.

This association was found to be statistically not significant (0.63% vs 1.12%) ($p=0.5$). Ajmani et al reported an incidence of 16.6% in hypothyroidism which is higher than our study.⁷ Our study had 1 (0.63%) case of abruption in hypothyroid patients (10%), which is very less compared to studies by Abalovich et al and Davis et al.^{17,19}

Association of hypothyroidism in pregnancy and low birth weight

The incidence of low birth weight (birth weight <2.5 kg) was 17.72% in patients having hypothyroidism and 16.91% in euthyroid group. The incidence of low birth weight babies in hypothyroidism in the present study is compared with other studies below. When compared to our study, the low birth weight babies in hypothyroidism were very high in studies conducted by Leung et al, Ajmani et al and Davis et al.^{7,16,17}

Association of hypothyroidism in pregnancy and fetal distress

Fetal distress in our study was noted in 14.56% of patients having hypothyroidism whereas it was 7.45% in euthyroid population. There was an increased incidence of fetal distress in population having thyroid dysfunction. This observation was found to be statistically significant (14.56% vs 7.45%, $p=0.02$). This was lower when compared to a study by Goel et al who reported a higher incidence of fetal distress (20%) in pregnancies complicated by maternal hypothyroidism.²² Fetal distress in labor could be due to increased incidence of hypothyroidism exerting irreversible effects on the fetus and placenta in early pregnancy. These irreversible effects impaired their subsequent ability to tolerate stress, thereby increasing the incidence of fetal distress in labor.

Association of hypothyroidism in pregnancy and IUGR

In this study 6.33% of patients with thyroid dysfunction had IUGR while it was 5.96% in euthyroid patients. This finding is comparable to a study by Sahu et al where the incidence of IUGR in hypothyroidism was 8.1% which stands very similar to our present study.⁸

Association of hypothyroidism in pregnancy and levothyroxine treatment

Levothyroxine (T4) is the major hormone produced by the thyroid gland. In our study, starting with low dose of levothyroxine 25 µg on daily basis was required for 63.92% of antenatal women which was sufficient to maintain an euthyroid state in pregnant hypothyroid women and also higher dose of levothyroxine 100 µg daily was required very less (3.80%), which remains inconsistent with Kashi et al where 84% of the pregnant hypothyroid women studied, needed an increase in their levothyroxine dose.²³ These results also agree with other studies that suggested the levothyroxine dose should be

increased during pregnancy.²⁴⁻²⁸ But in our present study, escalated dose of levothyroxine was not required. There are few explanations possible for this increased requirement for levothyroxine during pregnancy like the increased level of TBG, increase in plasma volume and the influence of the mass of the foetal-placental unit are the reasons.^{24,29} Thyroxine metabolism by the foetal placental unit can be a possible cause of an incremented requirement for levothyroxine in the later phases of gestation and a reduce in the need after parturition.³⁰ To maintain adequate concentrations of thyroid hormone during pregnancy, T4 and triiodothyronine (T3) production are increased physiologically by the thyroid gland throughout a normal pregnancy which is unseen in hypothyroid women.

Prevalence of hypothyroidism

The prevalence of hypothyroidism constituted 10.54% in our study. Sahu et al has reported prevalence of hypothyroidism to be 11.05%, which is in line with our prevalence study.⁸ Dhanwal et al from Delhi, reported a prevalence of hypothyroidism as 14.3%, with a cut off of 4.5 mIU/l as upper limit of normal.⁹ In another study from Delhi, Ajmani et al reported a prevalence of 13.25% amongst 400 pregnant women in 2nd trimester at a cut off of 3.0 mIU/l.⁷

The maternal and foetal complications were considerably less in patients with thyroid dysfunction after detection and treatment with levothyroxine, but still there is not much significant improvement in maternal and foetal outcome grossly. Hence pre-conceptional counselling and correction of thyroid dysfunction at the earliest when pregnancy is confirmed is essential. Pregnancy in euthyroid state will have the optimum results.

CONCLUSION

The prevalence of hypothyroidism was high in this study. The maternal and fetal complications were higher in patients with hypothyroidism. Hence all pregnant women should have screening for thyroid function status as early as the pregnancy is confirmed. This is to prevent central nervous system developmental delay in the new-borns, as the foetus depends on maternal thyroxine till 10 weeks of pregnancy. Foetal and maternal outcome will be optimum if the person conceives at the euthyroid state. Patients diagnosed with hypothyroidism should be treated with levothyroxine. Increases in levothyroxine dosage administered in pregnancy appear to be indispensable in the majority of patients with well-controlled hypothyroidism, especially in the first trimester. However, this change was not universal and levothyroxine dosage decreased in a few cases and remained unchanged in others too. We suggest individualization of LT4 therapy for every pregnant woman. Levothyroxine use was associated with a decreased risk of pregnancy loss in this study. Hence it is ideal to have pre-conceptional screening to detect and

manage thyroid dysfunction before conception. Pre-pregnancy screening should be implemented at least in patients with high risk factors for thyroid dysfunction. Hypothyroidism in pregnancy should be diagnosed with reference to the lower levels of TSH values in each trimester compared to the non-pregnant levels. Universal screening for new-borns is also recommended to detect hypothyroidism.

ACKNOWLEDGEMENTS

Our heartfelt thanks to all the staff of Department of Obstetrics and Gynecology, PVS Hospital, Calicut, Kerala, for their constant support throughout the study without which this study would not be possible.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of PVS Hospital (P) Ltd

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Cite this article as: Justin SA, Johnson MS. A prospective study on evaluation of maternal and foetal outcomes of hypothyroidism with levothyroxine and prevalence of hypothyroidism in pregnancy in a tertiary care teaching hospital in Kerala. *Int J Basic Clin Pharmacol* 2020;9:392-8.