

## PREVALENCE OF HYPOTHYROIDISM IN UNEXPLAINED RECURRENT MISCARRIAGES

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### HOW TO CITE THIS ARTICLE:

Deepa Masand, Jaya Patel. "Prevalence of Hypothyroidism in Unexplained Recurrent Miscarriages". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 03, January 20; Page: 767-774, DOI:10.14260/jemds/2014/1900

**ABSTRACT: AIM AND OBJECTIVES:** To establish the prevalence and association of hypothyroidism in women affected with unexplained recurrent miscarriages. **MATERIAL AND METHODS:** This is an Observational case control study conducted in Obstetrics and Gynecology Department of NIMS Medical College and Hospital, Jaipur (Rajasthan); between July 2011 to June 2012. One hundred non-pregnant women with history of recurrent pregnancy losses were included in study group and one hundred non-pregnant women of similar age group with at least one successful pregnancy outcome were taken as control. All women who had known Thyroid disorder, diabetes, collagen and heart disease, were excluded from study. Detailed history, thorough physical examination was done and subjected to the quantitative estimation of triiodothyronine {T3}, Thyroxine {T4} and TSH hormone by CLIA method. **RESULT:** In the study 63% women experienced two or more pregnancy loss while 37% presented with three or more pregnancy losses. Total 7 patients were reported to have hypothyroidism out of which 3 were observed with subclinical hypothyroidism while 4 were detected overt hypothyroidism. In Control group 2 patient of subclinical hypothyroidism were detected. **CONCLUSION:** Prevalence of Hypothyroidism was 7 % and it has a statistically significant relationship with recurrent pregnancy losses in <20 weeks of gestation. Screening for thyroid dysfunction should be done early in pregnancy. Looking at the high percentage of abnormal TSH in pregnancies; universal screening should be considered as impaired thyroid function may predispose to miscarriage.

**KEYWORDS:** Hypothyroidism, tri-iodothyronine{T3}, Thyroxine{T4} and TSH hormone, recurrent pregnancy losses.

**INTRODUCTION:** Thyroid disorders are among the common endocrine disorders in pregnant women. It is now well established that not only overt hypothyroidism but also subclinical thyroid dysfunction can have adverse effects on fetal and maternal outcome. Maternal hypothyroidism during pregnancy raises serious concern about long-lasting psycho-neurologic consequences for the progeny, due to the risk of insufficient placental transfer of maternal thyroid hormones to the developing fetus during the first half of gestation.<sup>1</sup> The risk for miscarriage increased by 15% for each 1mIU/l elevation of the TSH level on the basis of logistic regression analysis.<sup>2</sup> During the last decade there has been an increasing appreciation of the incidence of thyroid dysfunction during pregnancy as well as the resultant adverse maternal and fetal effects.<sup>3,4,5</sup> In the hope that many of these adverse effects could be prevented or ameliorated by early detection and appropriate treatment the proposal to implement screening for thyroid function during pregnancy deserves consideration. To validate the need of antenatal screening for maternal thyroid dysfunction this study was undertaken to the prevalence of thyroid dysfunction among pregnant women in India. Recurrent pregnancy loss (RPL) is defined as three or more consecutive spontaneous pregnancy

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losses before 20 weeks of gestation. Pregnancy loss in the first trimester is the most common complication affecting approximately 15-20% of clinically recognized pregnancies.<sup>6, 7</sup> Hypothyroidism is linked to recurrent pregnancy loss.<sup>8, 9</sup>

**MATERIAL AND METHODS:** This is an Observational Case Control study, conducted in the Department of Obstetrics and Gynecology, NIMS Medical College and Hospital, Shobha Nagar, Jaipur, Rajasthan from July 2011-July 2012.

100 Non pregnant women of reproductive age group (18 to 40 years) with previous history of unexplained recurrent miscarriages were taken as cases.

100 Non pregnant women of reproductive age group with previous history of At least one successful pregnancy outcome were taken as control.

All the women selected for this study were non-pregnant and non-diabetic with normal uterine anatomy, no known thyroid disorder or Collagen disease or Heart disease, normal peripheral blood karyotype and anticardiolipin antibody negative and negative for TORCH infections and their spouses were non-diabetic with normal karyotype, normal sperm count and normal sperm morphology. Detailed history was taken and full clinical examination is performed in all the cases with special regard to patient's age, parity, gestational age, prior obstetric, medical and surgical history and clinical features suggestive of thyroid dysfunction. Informed consent of participation in the study was taken. Blood samples were collected and sent for investigation to central laboratory. Serum TSH and Free T4 was measured by CLIA (Chemiluminescence Immunoassay) in all the cases as initial hormonal investigations.

Chemiluminescence Immunoassay (CLIA) detection using Microplate luminometers provides a sensitive, high output, and economical alternative to conventional colorimetric methodologies. The chemiluminescent immunoassay has been shown to be more sensitive than the conventional colorimetric method(s) and does not require long incubations or the addition of stopping reagents, as is the case in some colorimetric assays. Among various enzyme assays that employ light-emitting reactions, one of the most successful assays is the enhanced chemiluminescent immunoassay involving a horseradish peroxidase (HRP) labeled antibody or antigen and a mixture of chemiluminescent substrate, hydrogen peroxide, and enhancers.<sup>10</sup> The CLIA Kits are designed to detect glow-based chemiluminescent reactions. The kits provide a broader dynamic assay range, superior low-end sensitivity, and a faster protocol than the conventional colorimetric methods. Furthermore, with the methodological advantages, Chemiluminescent immunoassay will play an important part in the Diagnostic and Research areas that ELISAs cannot do.

HISTORY	PHYSICAL EXAMINATION	LAB INVESTIGATION
Name	Height	CBC
Age	Weight	TSH, T3, T4
Parity	Pedal edema	Serum Na, K
Previous illness	Neck swelling	Urine(routine and microscopic)
Cold intolerance	Brittle nails	HDL, VLDL, LDL
Weight gain	Coarse facial feature	USG(Whole abdomen and pelvis)
Fatigue	Dry and pale skin	TORCH
Constipation	Cool on touch	VDRL

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Radiotherapy	Thin and brittle hairs	
Heavy menses	PV-cervical incompetence	
Addiction		
Vaginal bleeding		

## OBSERVATIONS:

	Average age in years	Average Height	Average Weight in Kg	Average Hb in gm. %
CASE	24.37±3.02	5'1"±1.9	45.6± 2.3	9.6
CONTROL	24.37±3.02	5'1.5"±1.8	47.2 ±2.6	9.5

Table: 1 Comparison of case and control groups according to average age, height, weight and Hb.

Table 2: Test group

Pregnancy losses in test group	No of women
2 Miscarriages	63
>3 Miscarriages	37

Table 2(a): Distribution of pregnancy losses according to no. of miscarriages

Pregnancy losses in test group	No of women
<12 weeks	73
12 to 20 weeks	27

Table 2(b): Distribution of pregnancy losses according to period of gestation

HYPOTHYROIDISM	TEST GROUP	CONTROL GROUP
SUBCLINICAL	3	2
OVERT	4	0
TOTAL	7	2

Table 3: Distribution of hypothyroidism in test and control groups

HYPOTHYROIDISM	TEST GROUP	CONTROL GROUP
SUBCLINICAL	6.1 ± 0.32mgm/dL	7.2 ± 0.26mgm/dL
OVERT	2.5 ± 0.67mgm/dL	NIL

Table 4: Comparison of T4 levels in test and control groups

HYPOTHYROIDISM	TEST GROUP	CONTROL GROUP
SUBCLINICAL	7.3 ± 0.2μIU/ml	6.3 ± 8.9μIU/ml
OVERT	12.79 ± 1.21μIU/ml	-

Table: 5 COMPARISION OF TSH LEVELS

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### RESULTS:

- TSH Levels among the sub clinical Cases and control group is higher than the normal value but the difference is found to be statistically insignificant ( $p>.05$ ).
- TSH Levels in subclinical hypothyroidism cases is significantly lower than the overt hypothyroidism cases. Difference is found to be statistically significant ( $p<.05$ ).
- T4 level among cases of overt hypothyroidism was significantly lower than the cases of subclinical hypothyroidism ( $p<.05$ ).
- However T4 level among subclinical control group was higher than the subclinical case group, but the difference is not significant ( $p>.05$ ).
- In present study we found hypothyroidism in 7% women having recurrent miscarriages

**DISCUSSION:** Hypothyroidism is defined by inadequate thyroid hormone production. Hypothyroidism is often caused by factors associated with the thyroid itself (primary hypothyroidism). Only 5% of hypothyroidism are the result of central hypothyroidism, i.e. due to lack of TSH or its effect.<sup>11</sup> Endemic iodine deficiency accounts for most hypothyroidism in pregnant women worldwide while chronic autoimmune thyroiditis is the most common cause of hypothyroidism in iodine sufficient parts of the world.<sup>12</sup> The presentation of hypothyroidism in pregnancy is not always classical and may sometimes be difficult to distinguish from the symptoms of normal pregnancy.<sup>13</sup> Subclinical Hypothyroidism characterized by an elevated thyrotropin (TSH) concentration but a normal serum free thyroxine level.<sup>14, 15, 16</sup> Overt Hypothyroidism an abnormally high serum thyrotropin level is accompanied by an abnormally low thyroxine level.<sup>17</sup> The thyroid gland increases 10% in size during pregnancy in iodine-replete countries and by 20%–40% in areas of iodine deficiency. Production of Thyroxine (T4) and Triiodothyronine (T3) increases by 50%, along with a 50% increase in the daily iodine requirement. Overt hypothyroidism is estimated to occur in 0.3-0.5% of pregnancies. Subclinical hypothyroidism appears to occur in 2-3%, and hyperthyroidism is present in 0.1-0.4%<sup>18</sup>. The symptoms of subclinical hypothyroidism are vague and nonspecific. The diagnosis is based on a normal level of free thyroxine (FT4) and an elevated TSH level. Clinically apparent maternal hypothyroidism during pregnancy has long been known to be associated with both maternal and fetal complication. The importance of maternal thyroid hormones for fetal central nervous system development is well established. Maternal thyroxine is particularly critical early in pregnancy because the fetal thyroid gland cannot synthesize iodothyronines until after 10 weeks of gestation. From this time onward, maternal as well as fetal thyroid hormones seem to be necessary for normal neurodevelopment.<sup>19</sup> Women with subclinical hypothyroidism (high free thyroxine (FT4) levels accompanied with normal or slightly elevated TSH levels) have a higher rate of miscarriage<sup>21</sup>. In contrast to hyperthyroidism, hypothyroidism is quite common in pregnancy<sup>22</sup>. Severe hypothyroidism with pregnancy is uncommon, probably because it is often associated with infertility and increased miscarriage rates. HCG levels are used as markers for miscarriage; women with low hCG levels are at much higher risk of child loss. La Marca et al. (1998), however, showed in a case-control study that TSH levels are positively associated with miscarriage; this effect was not due to hCG levels since there was no correlation between TSH and hCG levels.<sup>23, 24</sup> Development of fetal brain (with neuronal multiplication, migration and architectural organization) during the second trimester corresponds to a phase during which the supply of thyroid hormones to the growing fetus is almost exclusively of maternal origin. During later phases of fetal development (with glial cell multiplication, migration,

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and myelination) from the third trimester onward, the supply of thyroid hormone to the fetus is essentially of fetal origin.<sup>25, 26</sup> The euthyroid status is important during the first and second trimesters of pregnancy for optimal fetal neuronal development. Suboptimal maternal thyroid functioning indicated by high levels of TSH may have detrimental effects on the fetal brain development and IQ. Thyroid disease has multiple deleterious impacts on pregnancy, postpartum, and the developing fetus. Complications include miscarriage.<sup>27-31</sup> The risk of miscarriage is increased in autoimmune thyroid disease.<sup>32</sup> Benhadi, et al in year 2009 concluded that Pregnant women with high TSH levels without overt thyroid dysfunction and previous preterm delivery are independent factors that increase the risk of miscarriage; however, maternal Free T4 concentrations are not associated with fetal loss.<sup>33</sup> BijayVaidya, et al in year 2006, in their study concluded that targeted thyroid function testing of only high-risk pregnant women would miss nearly one third of women with overt/subclinical hypothyroidism during early pregnancy.<sup>34</sup>

**CONCLUSIONS:** Since the majority of women are not sure that they are pregnant until four to six weeks after the last menstrual period, they don't go in to see doctors and test their thyroid function until the first trimester is more than half over. The study demonstrates that hypothyroidism has a statistically significant relationship with recurrent pregnancy. This in depth study on the basis of its findings conclude that screening for thyroid dysfunction should be done in all the pregnant and non-pregnant women who had recurrent pregnancy losses necessarily during first trimester itself soon after the confirmation of pregnancy, so that thyroid management is initiated at the earliest stage to control thyroid dysfunction of the mother and thereby to prevent consequential harm effects on the growing fetus.

**LIMITATIONS:** After grouping the population according to levels of TSH and T4, some of the rendered study groups were small which may decrease the power to detect all significant difference. Although several confounding factors were evaluated, some might still have had an effect on the outcome results. Small number of cases in some groups has limited the use of adjustable variable. Another limitation is the loss to follow up. The study being academic could not be further broad based with higher study group due to limitation of time and cost.

The findings emerging from the present study needs to be further strengthened and validated by multilocal and higher sample sized research studies.

**RECOMMENDATIONS:** Universal screening for detection of thyroid dysfunction among Indian women (had history of recurrent miscarriages / pregnant) attending clinic (Obst & Gynae Dept.) to be done compulsorily and also she should be appraised of associated maternal and fetal complications to bring home the indispensability of thyroid screening. The treatment of thyroid dysfunction be started as early as possible after the diagnosis of thyroid dysfunction to reduce thyroid manifestations in maternal complications such as: Recurrent pregnancy losses, pre-eclampsia, gestational hypertension, gestational diabetes, abruption placentae and also improves pregnancy outcome such as: lowers the incidence of miscarriage, intrauterine death and neonatal death.

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**FURTHER SCOPE:** The role of anti-thyroid antibody in pregnancy is controversial. Rushworth et al and Esplin et al found no association between antithyroid antibodies and recurrent pregnancy loss whereas Abramson and Green and others found an association between the two. As these studies could not emphasize that auto antibodies are responsible for fetal loss, we evaluated only the thyroid hormones in our study.

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Date of Submission: 27/12/2013.  
Date of Peer Review: 28/12/2013.  
Date of Acceptance: 03/01/2014.  
Date of Publishing: 18/01/2014