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International Journal of Current Research
Vol. 10, Issue, 07, pp.71109-71115, July, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

PREVALENCE OF HYPOTHYROIDISM IN A HOSPITAL BASED SAMPLE OF PREGNANT KASHMIRI WOMEN WITH RECURRENT ABORTIONS AND PREGNANCY OUTCOME

***Prof. Shahnaz Taing and Dr. Shazia Nisar**

Postgraduate Department of Obstetrics and Gynaecology, Government Medical College, Srinagar

ARTICLE INFO

Article History:
Received 27th April, 2018
Received in revised form
16th May, 2018
Accepted 19th June, 2018
Published online 30th July, 2018

Key words:
Hypothyroidism,
Thyroid autoimmunity,
IUGR.

ABSTRACT

Background: Pregnancy has a profound effect on the thyroid gland and its function. Hypothyroidism complicates 0.3-0.7% of all pregnancies. Most common cause of hypothyroidism in pregnancy is Hashimoto's thyroiditis. Women with thyroid autoimmunity are twice as likely to experience spontaneous miscarriages. Hence, there is a need to screen for subclinical hypothyroidism and thyroid autoimmunity in pregnancy, especially in women with a history of miscarriages. **Objectives:**(a) To assess prevalence of hypothyroidism in a hospital based sample of Kashmiri women with recurrent abortions and perinatal outcome after receiving treatment. (b) Is universal screening needed or not? **Methodology:** It was a prospective hospital based multiple unit study. Two groups were formulated, one group comprising of 100 pregnant women with a history of two or more recurrent abortions were labelled as case group while as another group comprising of 100 pregnant patients with one successful pregnancy were labelled as controls. Prevalence of subclinical hypothyroidism, thyroid auto immunity and maternal and fetal complications were analysed in the groups with appropriate statistical methods. **Results:** In our study the prevalence of subclinical hypothyroidism in case group with recurrent miscarriage was 27%. Thyroid autoimmunity was present in 31% of cases while as in controls it was 18 %, p-value statistically significant (0.033). Also mean TSH of cases and control groups were not significant (0.893). Complications between cases and controls were statistically not significant after receiving treatment. However postdatism was statistically significant (p value 0.024). Another subgroup was created within case group labelled TPO positive and TPO negative groups, TPO positive were 31 in number, while 61 were TPO negative. Statistical comparison was drawn between these two groups. The mean TSH in TPO positive group and TPO negative group was statistically significant (p value 0.001). With respect to complications between TPO positive and TPO negative groups, there was no statistical significance. However, IUGR was statistically significant with p value of 0.002. Hypothyroidism was statistically significant with 27 in TPO positive and none in TPO negative, p value 0.001. **Conclusion:** The prevalence of subclinical hypothyroidism and thyroid autoimmunity was higher in pregnant women with a history of recurrent abortion compared with a healthy pregnant control population. Following L-T4 treatment, there was no difference in the prevalence of miscarriage between hypothyroid and euthyroid individuals in TPO positive women. All euthyroid women with thyroid autoimmunity should be treated with LT4 to achieve a favourable maternal and perinatal outcome.

Citation: Prof. Shahnaz Taing and Dr. Shazia Nisar. 2018. "Prevalence of hypothyroidism in a hospital based sample of pregnant kashmiri women with recurrent abortions and pregnancy outcome", *International Journal of Current Research*, 10, (07), 71109-71115.

INTRODUCTION

Pregnancy has a profound effect on the thyroid gland and its function. In iodine-replete countries, the gland size has been found to increase by 10% during pregnancy, and in areas of iodine deficiency, the gland size increases by 20%-40%. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3–0.5% for overt hypothyroidism and 2–3% for subclinical hypothyroidism.

***Corresponding author:** Prof. Shahnaz Taing
Postgraduate Department of Obstetrics and Gynaecology, Government Medical College, Srinagar

DOI: https://doi.org/10.24941/ijcr.30797.07.2018

Worldwide, iodine deficiency remains one of the leading causes of both overt and subclinical hypothyroidism. However, there are many other causes of hypothyroidism during pregnancy, including autoimmune thyroiditis, the most common organic pathology (Klein, 1991). Other causes include the following: thyroid radioiodine ablation (to treat hyperthyroidism or thyroid cancer), hypoplasia and/or agenesis of the thyroid gland, surgery (for thyroid tumors) and rarely, central hypothyroidism, including lymphocytic hypophysitis or ectopic thyroid) and some drugs, such as rifampicin and phenytoin, which can alter thyroid metabolism (Say, 2012). Given that maternal iodine supplementation has a positive impact on the developmental quotient of children living in

areas of iodine deficiency, the current WHO guidelines suggest that iodized salt provides sufficient iodine intake for pregnant women (WHO, 2007). In particular, iodine supplementation is recommended beginning in early pregnancy to ensure adequate foetal brain development. A useful test to verify sufficient iodine intake is the assessment of urinary iodine concentration. Thresholds for median urinary iodine sufficiency have been identified for populations but not for individuals, given the significant day-to-day variation of iodine intake (Vejbjerg, 2009). The cut-off for iodine sufficiency is a median urinary iodine concentration of 100–199 µg/L in adults and of 150–249 µg/L in pregnant women (UNICEF, 2007). Some studies analyzing mildly iodine-deficient pregnant European women revealed that iodine supplementation is stopped before or at the moment of delivery (Zimmermann, 2004). In these patients, iodine supplementation was observed to increase maternal urinary iodine excretion and reduce thyroid volume. Additionally, no alterations in newborn thyroid volumes and no increased thyroglobulin maternal serum levels were present. However, these studies only demonstrate that iodine supplementation affects infant growth and development. Several studies (Berbel, 2009; Velasco, 2009; Murcia, 2011). have attempted to analyze the relationship between iodine supplementation and foetal effects, but no significant effects on mental or motor development in the offspring were observed (Melse-Boonstra, 2012). Thyroid function may be altered by serum thyroid antibodies, including serum anti-thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb), particularly inolder women (Gough, 2002).Several studies (Aghini-Lombardi, 1999; Hollowel, 1988; Kasag, 2009; Spencer, 2007; Lucas, 2010; Knudsen, 1999; Pedersen, 2003 and Hoogendoorn, 2006), indicate that elevated levels of anti-thyroid antibodies are present in women three times more often than in men. This discordant predominance in thyroid auto immunity could be associated with the X chromosome, which preserves some sex and immune-related genes responsible for immune tolerance (McCombe, 2009). Hypothyroidism occurs in approximately 2.5% of all pregnancies in United states of America (Allan, 2000 and Allan, 2011). Overt hypothyroidism is defined as having a low free thyroxin level and an elevated thyroid stimulating hormone, subclinical hypothyroidism is defined as having a normal free thyroxin level but an elevated thyroid stimulating hormone leve (Mandel. 2005). In early pregnancy the maternal thyroid gland is challenged with an increasing demand for thyroid hormone secretion mainly due to three different factors; increase in thyroxin binding globulin (TBG) due to the effect of estrogen in the liver (Mestman, 2002), stimulatory effect of human chorionic gonadotrophin (HCG) on thyroid stimulating hormone (TSH) receptor (Mandel, 2005) and decrease supply of iodine available to gland. The normal gland is able to compensate for these demands by increasing secretion of thyroid hormones and maintaining serum levels of free hormones within normal limits. However, if there is pathologic abnormality of the thyroid gland, normal increase in production of the thyroid hormones is not met leading to development of hypothyroidism (Mestman, 2002). Hypothyroidism complicates 0.3-0.7% of all pregnancies. Women with overt hypothyroidism are at increased risk for complications such as early pregnancy failure, preeclampsia, placental abruption, low birth weight and stillbirths (Velasco, 2009). Most common cause of hypothyroidism in pregnancy is Hashimoto's thyroditis (Murcia, 2011), symptoms of hypothyroidism include excessive fatigue, dry skin, cold intolerance, constipation, bradycardia and irritability (Semba, 2001).

When the women diagnosed to be hypothyroid during pregnancy were treated overall pregnancy complication rate was 4.8% in those who became euthyroid by 20th weeks of gestation, compared to 19% who were euthyroid after 20th weeks. Those who never achieved euthyroid had pregnancy complications of 31.5%. Recurrent abortion is classically defined as three or more consecutive pregnancy losses at 20 weeks or less or foetal weight less than 500gms. Although the definition includes three or more abortions, many agree that evaluation should at least be considered following two consecutive losses[29]. First trimester losses account for 75% of recurrent abortions and remaining 25% occur in second trimester. Causes of recurrent abortions may have genetic, immunological, anatomical, infective, endocrine, environmental origin but in many cases no cause is found (Balen, 2008). The thyroid hormones have an impact on oocyte at the level of granulosa and luteal cells that interfere with normal ovulation. Low thyroxine levels have a positive feedback on thyrotropin releasing hormone (TRH), elevation in thyrotropin releasing hormone has been associated with prolactin elevation which alters the pulsatility of gonadotrophin releasing hormone (GNRH) and interferes with normal ovulation. Therefore severe forms of hypothyroidism rarely complicate pregnancy, because they are usually associated with anovulation and infertility. However in mild hypothyroidism, pregnancies can occur but are associated with higher rates of pregnancy loss and maternal complications. One postulated explanation for this relationship is that luteal phase defects have been linked to thyroid hypofunction (Luisi, 2007). Since Kashmir is an iodine deficiency belt and plus scarcity of literature on prevalence of hypothyroidism in Kashmiri women suffering from recurrent abortions prompted us to take up study in the Department of Gynaecology and Obstetrics, Government LallaDed hospital of Government Medical College, Srinagar.

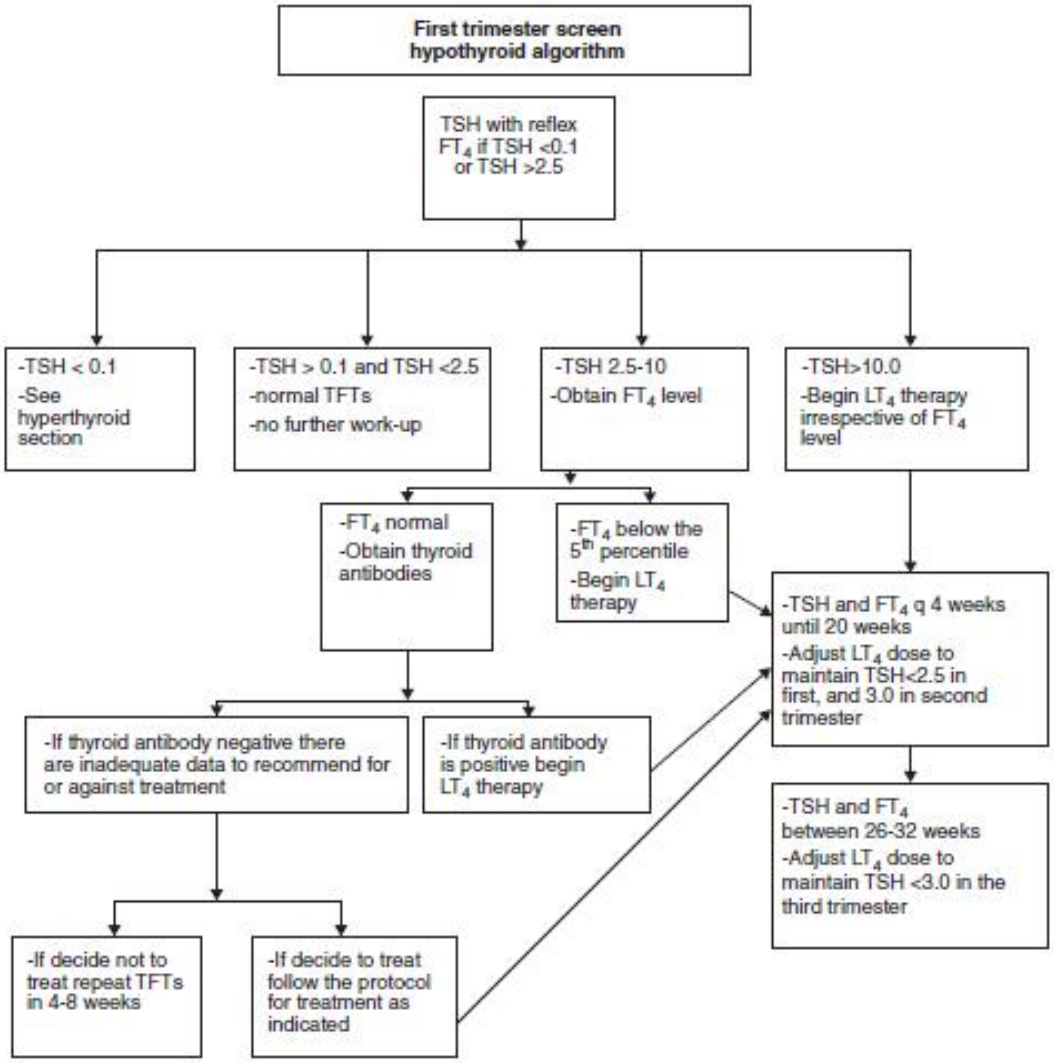
Objectives

- To assess prevalence of hypothyroidism in a hospital based sample of Kashmiri women with recurrent abortions.
- Abortion rate within case group as against previous abortions after receiving treatment.
- Pregnancy outcome in case and control groups with respect to:
  - Preterm delivery
  - Low birth weight
  - Intrauterine growth retardation
  - Foetal death
- Is universal screening needed or not?

MATERIAL AND METHODS

This study "prevalence of hypothyroidism in a hospital based sample of pregnant Kashmiri women suffering from recurrent abortions and pregnancy outcome" was conducted over a period of 18 months. It was a comparative prospective cross-sectional hospital based multiple unit study (various units of LallaDed Gynaecology and Obstetrics Hospital). The study design include 200 women divided into two equal groups viz-a-viz.

- Case group – consisting of 100 women with recurrent early abortions.



- Control group – consisting of 100 women with at least one successful pregnancy.

Inclusion Criteria

- Age: patients should be in the reproductive age group (17-40 years).
- Suffering from at least two recurrent early abortions.

Exclusion Criteria

- Patients with known thyroid disorders already on treatment
- Patients with uterine anomalies e.g. septate uterus.
- Patients with antiphospholipid syndrome and thrombophilia and hyperprolactinemia.
- Diabetic patients.

Institutional ethics committee permission was obtained and subjects were recruited for the study after obtaining written informed consent, all patients were subjected to the following:

- Full history taking, general abdominal and pelvic examination with careful examination of thyroid gland.
- Screening for thyroid function by serum thyroid stimulating hormone levels (serum TSH), by enzyme linked immunosorbent assay (ELISA) was done also free t3, free t4 and thyroid peroxidase antibody screening was done
- Lupus anticoagulant IgG and IgM.
- AnticardiolipinIgG and IgM.
- Oral glucose tolerance test.
- Serum prolactin.
- Transvaginalsonography
- Cases were treated according to the "November 2011 guidelines of the American Thyroid Association for the diagnosis and management of thyroid diseases during pregnancy" as shown in algorithm.

Cases were followed till end and pregnancy outcome was compared with respect to control group taking following into consideration:

- Preterm delivery
- Low birth weight
- Intrauterine growth retardation
- Foetal death

METHODS

Blood Sample Collection

- 5ml of venous blood was obtained from all women by vein puncture and left to clot at room temperature for 30 minutes. Clotted blood was centrifuged at 1000-

2000rpm for 10 minutes. Serum was separated and stored at -20^0 until collecting all blood samples.

- TSH level and Free T3, Free T4 level measurement by using ELISA technique was done: The assay system utilizes a unique monoclonal antibody detected against antigenic determinant on the intact TSH molecule.
- Antithyroidperoidase antibody measurement was done by electro-chemiluminescence assay.
- The reference range for above were as follows.TSH, R; 0.27-2.5miu / L [1st trimester], 0.27-3.0miu / L [2nd trimester], 0.27 - 3.0miu / L [3rd trimester] FT3, RR; 1.7-4.2ng/ml FT4, RR; O.7-1.8ng/ml TPOAb RR ;<34u/ml
- All patients with thyroid peroxidase antibody were treated with 25micrograms of levothyroxine and titrated according to TSH at the time of recruitment into the study as shown in above algrothim. All patients were followed in the antenatal peroid every 4 weekly until their gestational outcome. Ultrasonograpy was done at 8 weeks for confirmation of viability and a repeat scan was done around 18 weeks of gestation to find any foetal anomaly. After 28 weeks they were followed fortnightly until their gestational outcome .All patients were monitored for any signs and symptoms of; IUGR, preterm labour, gestational hypertension, intahepaticcholestatasis, premature rupture of membranes, foetal death. After 37 weeks subjects were followed weekly and were delivered according to their obstetrical outcome. Details of the mode of delivery and any intra partial and postpartal complications were noted.

Statistical Analysis: Data was expressed as mean±SD or number (%) of cases.

Comparison of proposition and means were made by using □2 test and paired 't' test, non-parametric data was analyzed using Mann Whitney test.

Analysis was performed by using statistical package for social sciences (SPSS Version 15). Justification of sample size was guided by:

- Power of test by significance = 80%
- Confidence level (true difference) = 95%
- Accepted Error (□-error) = 5%

Total sample sizes was 200 women divided into two equal groups, 100 women with recurrent early abortions and 100 with at least one successful pregnancy.

RESULTS

The study "of hypothyroidism in hospital based sample of pregnant Kashmiri women with recurrent abortions and pregnancy outcome" was carried in Govt. LallaDedDed hospital over a period of 18 months.It was a comparative, prospective, cross-sectional multi-unit study.Sample size in our study was 200.100 were allocated as case with the history of recurrent abortions and 100 were allocated as control group with at least one successful pregnancy. Another subgroup was created within case group 31 as TPO +ve and 69 as TPO -ve.The mean age of case and controls was 28.17±1.50and 27.24±2.52 respectively. P value 0.002 (significant).Within case group out of 100, 34 were in urban areas and 66 in rural areas, while in control group 33 were residing in urban areas and 67 in rural areas. P value 0.881(not significant). Mean TSH of case and control was 2.7miu/l and 1.5miu/l respectively. P value < 0.05 (significant).Mean free T3 of case and control group was 2.52±0.74ng/ml and 2.74±0.29ng/ml respectively. (p value 0.76) not significant.

Mean free T4 for case and control was 1.49±0.58ng/ml and 1.15±0.11ng/ml. p value 0.86 (not significant).TPO+ve individuals in case group was 31 while in control it was 18. P value 0.031 (significant) Prevalence of hypothyroidism in case group in our study was 27%.With respect to pregnancy outcome after receiving treatment there was no statistical significance between case and control in terms of missed abortion (2 in case and zero in control with p value of 0.155 not significant), intrauterine growth retardation, preterm labour, premature rupture of membranes, foetal death. Only postdatism was significant. P value was 0.024. Mean gestational age in case and control was 38.36±3.36 and 38.41±1.79. p value was 0.898 (not significant). As per mode of delivery no statistical significance was found with 82 normal vaginal delivery, 14 Lower segment caesarean section, 4 operative vaginal delivery in case group and 72 normal vaginal delivery, 22 lower segment caesarean, 6 operative vaginal delivery in control.

Comparison was drawn then between TPO+ve 31 in number and TPO-ve 69 in number within case group.Prevalence of thyroid autoimmunity in our study was 24% (31% in case and 18% in control) P value was 0.03 significant.Mean age of TPO+ve and TPO-ve was 28.33 and 28.1 respectively. P value was 0.490 (not significant).Mean gestational age in TPO+ve group was 37.65 and in TPO-ve group it was 38.67. P value was 0.160 (not significant).Mean TSH of TPO+ve and TPO-ve group was 3.65±0.94 and 1.84±0.45 respectively (p value < 0.001) significantMean TPO titre in TPO+ve and TPO-ve group was 83.03 and 17.81 respectively with p value 0.001 (significant). No statistical difference with respect to missed abortions (1 in TPO+ve and 1 in TPO-ve) preterm labour, premature rupture of membranes, foetal death was found in TPO+ve and TPO-ve group after receiving treatment. However intrauterine growth retardation was significant with P value 0.002(significant). With respect to mode of delivery there was no statistical significance between TPO+ve and TPO-ve group with 25 normal vaginal deliveries, 3 lower segment caesarean section and 3 operative vaginal deliveries in TPO+ve group and 57 normal vaginal deliveries,11 lower segment caesarean section,1operative vaginal delivery in TPO-ve group. P value not significant.

Comparison of Age (years) Between Case and Control Group

Age	N	Mean	SD	Range	P-value	Remarks
Case	100	28.17	1.50	23.0-30.4	0.002	Significant
Control	100	27.24	2.52	20.6-33.9		

Prevalence of hypothyroidism in case and control group

Hypothyroid	Cases		Controls	
	No.	%age	No.	%age
Yes	27	27%	10	10%
No	73	73%	90	90%
Total	100	100%	100	100%

P value = < 0.05 (significant)

Comparison of TPO positivity in case and control group				
TPO +	Cases		Controls	
	No.	%age	No.	%age
Yes	31	31%	18	18%
No	69	69%	82	82%
Total	100	100%	100	100%

P value = 0.031 (Significant)

DISCUSSION

This study was conducted over a period of 18 months. It was a comparative, prospective, cross sectional hospital based multiple unit study, two groups were formulated 100 each viz case and control .Case group comprising of pregnant women with a history of two or more recurrent abortions with 57 having primary cause, while as control group comprises of pregnant patients with one successful pregnancy, another sub group was formulated in case group 31 subjects as TPO positive and 69 as TPO negative. Prevalence of sub clinical hypothyroidism, thyroid auto immunity and pregnancy outcome was analysed and compared with literature following were the salient observations of our study. In our study the case and control groups were comparable, the mean age of our study in case and control groups were 28.17±1.50 years and 27.24 ±2.52 years respectively, it was statistically significant [p value 0.002], because in case group, subjects have already aborted two or more times so age was statistically significant than control who had one successful pregnancy. In case group 34% of people were residing in urban region while as 66 %people in rural region while as in control group 33%were residing in urban region and 67% people in rural region ,it was statistically not significant [p value .881] .

The mean TSH of the case group was 2.7miu/L while as in control it was 1.5miu/L, it was statistically significant[p value <0.05].The mean free T3 Of Case group was 2.52 ±0.74ng/ml while as in control group it was2.74±0.29 ng/ml it was statistically not significant [p value .76].The mean free T4 in our study for cases was 1.49±0.58ng/ml,while in control it was 1.15±0.11ng/ml, it was statistically not significant [p value 0.86]. In case group 31 were TPO positive while as 18 were TPO positive in control group it was statistically significant [p value 0.031]. The prevalence of hypothyroidism in our case group was 27% such a high prevalence could be due to selection bias, lack of iodine status in our patients, different assay methods and different cutoff levels of TSH used to define subclinical hypothyroidism in previous studies. No statistical significance with respect to missed abortion [p value 0.155], 2 in case group and zero in control group. Mean age of gestation in case group was 38.36±3.36 weeks while as in control it was 38.41±1.79, statistically not significant [p value 0.898]. There was no statistical significance with respect to mode of delivery, 82 were normal vaginal delivery, 14 LSCS and 4 operative vaginal delivery in case group while as with respect to control 72 were normal vaginal delivery, 22 LSCS and 6 operative vaginal delivery. There was no statistical significance with respect to complications that is preterm labour, intrauterine growth retardation (IUGR), gestational hypertension, premature rupture of membranes (PROM), intrahepatic cholestasis (IHC) and foetal death, only post datism was statistical significant.

Amirtabriz Pour *et al*[32] while describing thyroid autoimmunity and recurrent abortions had mean age 30.6±6.4years while as in control it was 30.05±6.6years. Thyroid antibodies were present 24.5% in case group while as 12.6% in control group [p value <0.001]. In cases 40% were where residing in urban region while as 60% in rural. In controls 43% were urban while as 57% rural [p >0.05]. Mean TSH, Free T3 and Free T4 were statistically significant between case and controls. Thyroid autoimmunity was significantly associated with recurrent abortions independent of impact of age with an odds ratio of 2.24[95% confidence interval]. Rao VR *et al*[33] while describing prevalence of hypothyroidism in recurrent abortions had mean age of cases 29.8 years while as in control 27.2 years, statistically significant, prevalence of hypothyroidism was4.12% .The difference in levels of T3, T4 and TSH between case and control was statistically significant. In cases T3, T4 and TSH values were 3.0, 2.0 and 1.49 respectively while as in control it was 1.9, 2.7 and 1.22 respectively. Another subgroup was created within case group labelled TPO positive and TPO negative groups, TPO positive were 31 in number, while 69 were TPO negative. Comparison was drawn between these two groups statistically, and compared with literature. No foetal death was reported in case or control group. Vimal Nambiar*et al*[34] while describing prevalence and thyroid disorders on maternal outcome in Asian Indian pregnant women derive similarity with our results.

Kusum etal[35] also derived same analogy of results as ours while describing thyroid autoimmunity and obstetrical outcome in Women with recurrent miscarriages; a case control study. The prevalence of thyroid autoimmunity in our study was 24% (31%in pregnant women with recurrent abortion) while it was significantly lower (18%) in the healthy group (31 vs 18%, P value 0.03). The prevalence in the general population described in the literature is 10-15%. A meta-analysis by Prummel*et al*[36] showed that TPOAb was associated with a twofold increased risk of miscarriage as shown in this study. In both the groups, the outcome of current pregnancy was not influenced by TPO positivity or by TSH values. This could be because all cases of either isolated TPOAb positivity or of elevated TSH were treated during the course of pregnancy. Similar results were found by Negro *et al*[37]., who found the miscarriage rate in the TPOAb+ group supplemented with levothyroxine was comparable to healthy controls (3.5 vs. 2.4%). However, unlike our study population, these patients had no history of recurrent miscarriage. None of our patients had isolated hypothyroxinaemia. However, the odds of having the miscarriage were increased with decreasing FT4 values. As expected, the mean TSH in the TPOAb+ve group was higher (3.65±0.94) compared with those in the TPOAb-ve group (1.84±0.45, p<0.001). A possible explanation for high TSH in the TPOAb+ve group is a reduced functional thyroid reserve associated with chronic autoimmune thyroiditis.

Conclusion

Prevalence of subclinical hypothyroidism and thyroid autoimmunity was higher in pregnant women with recurrent abortions. Following levothyroxine treatment there was no difference in prevalence of miscarriage between case and control group and between TPO+ve and TPO-ve within the case group. We thus advise screening for subclinical hypothyroidism and thyroid autoimmunity in pregnant women with history of recurrent abortions attending the outpatient department of LallaDed Hospital and also such women should then be treated with levothyroxine to achieve favourable pregnancy outcome.

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