

STUDY OF THYROID PROFILE IN PATIENTS OF RECURRENT ABORTIONS

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ABSTRACT: INTRODUCTION: Recurrent spontaneous abortion of unknown etiology provided fundamental insight into process of embryogenesis, and implantation. It is also a frustrating and emotionally charged clinical problem. Hormonal imbalances are important cause of recurrent pregnancy loss, in the 1st trimester as well as in 2nd trimester. Thyroid diseases are the commonest disorders affecting women of reproductive age group. They constitute the commonest endocrine disorder complicating pregnancy. In women incidence of hypothyroidism diagnosed before pregnancy is 1%. Maternal and fetal complications have been found to be higher in this population. In women incidence of hypothyroidism diagnosed before pregnancy is 1%. Maternal and fetal complications have been found to be higher in this population. **OBJECTIVE:** We studied the Thyroid profile in patients of recurrent abortion. **MATERIALS AND METHODS:** 60 non pregnant healthy women with complaints of vaginal bleeding, pelvic pain, tissue discharge up to 8, 16, and 22 weeks with 20 subjects in each group. Details of history, physical findings, laboratory evaluation and medication were noted from their case records and verified. 60 healthy, pregnant women who were at same gestational age and then reached the term and had successful pregnancy outcome, were selected as controls. The controls were not under any regimen and were free from any chronic illness. Elisa method was used for estimation of thyroid hormones. **RESULTS:** We studied 60 non pregnant healthy women (27±2.6 years) with established diagnosis of recurrent spontaneous abortion. Serum TT3, fT3, TT4, fT4 was found to be significantly low in cases as compared to controls. 21 women out of 60 i.e. 35 % showed overt hypothyroidism. Majority of these cases were showing recurrent pregnancy lost in between 8-16 weeks of gestation when their history was traced. **CONCLUSION:** Hypothyroidism is frequent cause in recurrent pregnancy loss. Severe maternal hypothyroidism early in gestation is strongly associated with fetal distress and abortion. We suggest evaluation of maternal TSH as a routine test for screening hypothyroidism to potentially improve the pregnancy outcome and maternal well being.

KEYWORDS: Recurrent spontaneous abortion, Hypothyroidism, TSH, Total Thyroxine (TT4), Total Tri-Iodothyronine (TT3), Free Tri-Iodothyronine (fT3), Free Thyroxine (fT4) Subclinical Hypothyroidism (SCH).

INTRODUCTION: There are few subjects of such clinical importance as recurrent abortions so bedeviled by inconsistency, imprecision and unwarranted assumption. This applies to the fundamental question of etiology in which physicians all too frequently confuse "association" with "cause".

Spontaneous abortion is one of the least understood pathological processes. In 50% or more couples with recurrent spontaneous abortion an evaluation including parental karyotype, hysteroscopy, hormonal evaluation, and antibody testing will be negative. Therefore majority of the couples with recurrent spontaneous abortion will have no certain diagnosis.

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It has been estimated that fetal viability is achieved only in 30% of all human conceptions, 50% of which are lost prior to first menses.¹ In a study of Reagan et al. (1989) and Wilcox et al (1988) clinically recognized intrauterine pregnancy loss occurs in 12 -14 %of all pregnancies, and can be attributed to random factors such as chromosomal abnormalities, hormonal imbalance.^{2,3}

Recurrent pregnancy loss is the spontaneous loss of 2 or more consecutive pregnancies before 20 weeks of gestation, which takes into consideration that woman over 35 years is at greater risk for pregnancy loss than 25 years old woman.⁴ Hormonal imbalances are important cause of recurrent pregnancy loss; in the 1st trimester as well as in 2nd trimester.⁵ Thyroid diseases are the commonest disorders affecting women of reproductive age group. They constitute the commonest endocrine disorder complicating pregnancy. In women incidence of hypothyroidism diagnosed before pregnancy is 1%. Maternal and fetal complications have been found to be higher in this population.^{6,7,8} Hypothyroidism during pregnancy occurs in 1/1600- 1/2000 (0.06-0.05) deliveries. Probably the rarity of hypothyroidism in pregnancy is due to the fact that hypothyroid women have higher prevalence of anovulatory cycles and in case of conception they have higher rate of fetal loss in first trimester.^{9,10}

The importance of thyroid hormones for normal fetal development is very well established. Thyroid hormones have been found to be crucial in brain development, maturation, and normal function. Maternal hypothyroidism has been associated with increased fetal and neonatal losses and mental retardation with living euthyroid offsprings.¹¹⁻¹³ Sub clinical hypothyroidism is defined as isolated elevation of serum TSH level in setting of normal serum T4 level, in presence or absence of symptoms.¹⁴ The world wide prevalence of subclinical hypothyroidism ranges from 1-10%. Since these patients can develop overt hypothyroidism at rate of 5% per year it is important to identify these patients at risk. When SCH occurs in pregnancy, there is increased risk for miscarriage in both first and second trimester.

Hence hypothyroidism is definitely fitted into condition, warranting a routine screening during pregnancy. Abnormalities of thyroid are reversible and possibility of thyroid dysfunction must always be considered during the investigations of recurrent pregnancy loss.

Thus the present study was carried out with purpose to evaluate the thyroid profile in patients of recurrent abortion, and to decide whether universal screening of pregnant women for hypothyroidism is required.

MATERIALS AND METHODS: The present case-control study was carried out in department of biochemistry, Government medical college & Hospital, from July 2007 to June 2009.

Cases include 60 non pregnant healthy women who presented to the OPD at gynecology and obstetrics department Government medical college & Hospital, Nagpur.

A woman was considered to be eligible for inclusion in the present study only when the following criteria were being fulfilled.

1. The subject was willing to enter the study.
2. Known subjects with complaints of vaginal bleeding, pelvic pain, tissue discharge, diagnosed with spontaneous abortion up to 8, 16, 22, weeks with 20 subjects in each group.
3. Patients with absent gestational pouch and absent fetal cardiac activity on trans-vaginal ultrasonography.
4. Patients with spouses having normal karyotype, normal sperm count and morphology.

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The patients excluded from study were as follows:-

1. The patients with history of metabolic and endocrinological disorders.
2. The patients with diseases that may affect the placental circulation such as one with the multiple pregnancies, genital organ anomaly, advanced malnourishment, diabetes, infections (TORCH).
3. The patients having history of chronic diseases.

60 healthy, pregnant women who were at same gestational age and then reached the term and had successful pregnancy outcome, were selected as controls. The controls were not under any regimen and were free from any chronic illness.

After obtaining the written and informed consent, all the women were thoroughly examined clinically at the institute. Particulars pertaining to their age, place, health status, menstrual history, consanguinity, previous medical and reproductive data, were recorded in the prescribed case sheets.

In study and control groups, 5 ml of blood was collected from each woman. Serum was separated and stored at (- 20°) Celsius in aliquots for thyroid hormones investigation.

Serum total T3 (TT3), total T4 (TT4), TSH, free T3 (fT3), free T4 (fT4) were estimated in the both groups by using commercially available competitive immunoassay kits (ACCUBIND, USA) on microplate reader.

RESULTS: 60 cases were selected according to the inclusion criteria. The mean age group in our study was 27.16 ± 2.6 years for both cases and controls. The commonest age group in our study was between 26-28 years. They amounted 51.67% (31) cases of RSA. Next to follow was the age group of 29-31 years, and they amounted 28.33% (17) cases. Rest of them i.e.10% (6) cases belonged to age group of 20-22 years and 23-25 years. In our study maximum cases i.e. 45% (27) had attained menarche at 12-14 years of age, while 30% (18) cases had attained menarche at age of 15 -17 years. Rest of them i.e. 25% (15) cases attained menarche at age before 12 years. The mean age of menarche was 13.27 ± 2.22 years in cases, while in control group it was 13.52 ± 2.25 years. The mean value of TT3 in abortus group and control group was 2.15 ± 1.52 ng/ml and 2.656 ± 0.909 ng/ml respectively. The mean value of TT4 in abortus and control group was 4.88 ± 1.53 µg/dl and 5.80 ± 1.041 µg/dl respectively. Thus we found that mean value of TT3 at lower range in cases as compared to controls, and difference is statistically significant ($P < 0.05$). We also found that mean value of TT4 at lower range in cases as compared to controls, and difference is statistically significant ($P < 0.001$). The mean value of fT3 in abortus group was 4.25 ± 1.87 pmol/l, and in control group it was 5.116 ± 1.705 pmol/l. Thus fT3 was significantly lower in abortus group as compared to control group. Decrease in fT3 level was found to be statistically highly significant ($P < 0.05$).

The mean fT4 value in abortus and control group was 14.77 ± 6.19 pmol/l and 17.099 ± 5.028 pmol/l respectively. Thus fT4 was significantly lower in cases as compared to control group. This decrease in fT4 level was found to be statistically highly significant ($P < 0.05$).

Mean TSH value in abortus group was 10.024 ± 4.13 µIU/L and in control group it was 7.658 ± 3.114 µIU/L. Thus mean TSH value was significantly higher in abortus as compared to control group with ($P < 0.001$).

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In our study incidence of thyroid dysfunction in form of hypothyroidism was found to be 35% i.e. 21 out of 60 cases of recurrent spontaneous abortions. All of these 21 cases showed the overt clinical hypothyroidism.

Age group in years	Cases (n=60)		Controls (n=60)	
	No.of. subjects	Percentage	No.of. subjects	Percentage
20-22	6	10 %	6	10 %
23-25	6	10 %	6	10 %
26-28	31	51.67 %	31	51.67 %
29-31	17	28.33 %	17	28.33 %
Total	60	100 %	60	100 %

AGE INCIDENCE

Age at menarche	Cases (n=60)		Controls (n=60)	
	No.of. Subjects	Percentage	No.of. Subjects	Percentage
<12	15	25 %	12	20 %
12-14	27	45 %	28	46.67 %
15-17	18	30 %	20	33.33 %
Total	60	100 %	60	100 %

Table 2: Distribution of study subjects according to age at menarche

Thyroid functions tests	Cases (n=60)	Controls (n=60)	P value
TT3 (ng/ml)	2.15±1.52	2.656±0.909	0.003*
TT4 (µg/dl)	4.88±1.53	5.801±1.041	0.000*
fT3 (p mol/l)	4.25±1.87	5.116±1.705	0.009*
fT4 (p mol/l)	14.77±6.19	17.99±5.028	0.002*
TSH (µIU/l)	10.024±4.13	7.568±3.114	0.000*

Table 3: Thyroid functions test in cases (n=60)

Gestational age	Hypothyroid patients	percentage
8 weeks	7	11.67%
8 - 16 weeks	10	16.67%
16- 22 weeks	4	6.67%
Total	21	35%

Table 4: Distribution of hypothyroid patients having recurrent pregnancy loss according to gestational age

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DISCUSSION: Spontaneous abortion is most common complication of pregnancy with majority of loss occurring prior to first missed menses. There are various etiologies of RSA, of which thyroid disorders constitute the important one. Thyroid disorders are the commonest endocrine disorders affecting the women of reproductive age group hence constitute, commonest endocrine disorders complicating pregnancy. In women incidence of hypothyroidism diagnosed before pregnancy is 1%. Hypothyroidism is linked to the recurrent pregnancy loss.^{15,16} It is of prime importance to diagnose correctly and to assess accurately the underlying biochemical abnormality. The commonest age group in our study was between 26-28 years. They amounted 51.67% (31) cases of RSA. Next to follow was the age group of 29-31 years, and they amounted 28.33% (17) cases. Rest of them i.e.10% (6) cases belonged to age group of 20-22 years and 23-25 years. The mean age group in our study was 27.16±2.6 years for both cases and controls.

In a study conducted by V. Ramachandra, A.Lakshmi et al (2008) mean age of women with RSA was found to be 25.19±4.01 years for cases, whereas in study conducted by Melahat Donmez, Tolga Sisli, Aleve Atis et al (2005) mean age was 28±3.34 years in abortus group and 24.14±4.66 years in control group.^{17,18}

The mean value of TT3 in abortus group and control group was 2.15±1.52 ng/ml and 2.656±0.909 ng/ml respectively. The mean value of TT4 in abortus and control group was 4.88±1.53 µg/dl and 5.80±1.041 µg/dl respectively. Thus we found that mean value of TT3 at lower range in cases as compared to controls, and difference is statistically significant (P<0.05). We also found that mean value of TT4 at lower range in cases as compared to controls, and difference is statistically significant (P<0.001).

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In our study incidence of thyroid dysfunction in form of hypothyroidism was found to be 35% i.e. 21 out of 60 cases of recurrent spontaneous abortions. All of these 21 cases showed the overt clinical hypothyroidism.

Sharma Partha, Mukhopadhyaya Partha, Mukhopadhyaya Amitabha, et al (2007)¹⁹ found that the incidence of hypothyroidism during pregnancy was 1.15%.

They also found spontaneous abortion in 14.63% of cases as compared to 4.96% of controls. They also observed that there were no significant differences in pregnancy outcome when hypothyroid pregnant women on thyroxine therapy were compared with the euthyroid pregnant women.

V. Ramachandra, A.Lakshmi et al (2008) observed the hypothyroidism in 4.29% cases as cause of recurrent pregnancy loss. Thus they concluded that hypothyroidism had statistically significant relation-ship with recurrent pregnancy loss in first trimester and diagnosis of hypothyroidism could help couples with recurrent pregnancy loss to have a successful outcome in subsequent pregnancies.

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Our study co-relates well with the Poonam G, A Radotra, Devi K, et al (2005).²⁰ They found hypothyroidism in 33.33% cases as cause bad obstetric history. Out of those 33.33% cases 20% had recurrent spontaneous abortions and 13.3% had an unexplained still birth.

In our study we found that all the patients of recurrent pregnancy loss were having overt hypothyroidism. Whereas Matsua et al (2002) & Melahat Donmez, Tolga Sisli, Aleve Atis et al (2005) observed the increased frequency of subclinical hypothyroidism in pregnancy and its association with spontaneous abortion.²¹

In our study we found that 7 hypothyroid patients (11.67%) had spontaneous abortion up to 8 weeks of gestational age, 10 hypothyroid patients (16.67%) had spontaneous abortion in between 8-16 weeks of gestational age, and 4 hypothyroid patients (6.67%) had spontaneous abortion in between 16-22 weeks of gestational age. Our study proved that hypothyroidism is common problem in recurrent pregnancy loss.

Severe maternal hypothyroidism early in gestation is strongly associated with fetal distress in labour. Also early adequate replacement therapy is especially prudent in women presenting with severe hypothyroidism to have successful pregnancy outcome.

CONCLUSION: Our study proved that hypothyroidism is common problem in recurrent pregnancy loss. Severe maternal hypothyroidism early in gestation is strongly associated with fetal distress in labour. Also early adequate replacement therapy is especially prudent in women presenting with severe hypothyroidism to have successful pregnancy outcome.

The relative high occurrence of hypothyroidism in women with pregnancy, the possible role of thyroid functional disorders in etiology of at least some part of recurrent spontaneous abortions, and based on our results association. between spontaneous abortion and overt hypothyroidism, had emphasized the importance of thyroid functions tests screening as routine in all pregnancies.

We propose the inclusion of serum TSH as screening test for hypothyroidism during pregnancy. There should be a high index of suspicion for hypothyroidism in patients with recurrent pregnancy loss. Careful monitoring & control of hypothyroidism during pregnancy & intrapartum period is necessary, since these patients are at increased risk of developing fetal distress during labour. Hence routine TSH should be evaluated as a way to potentially improve pregnancy outcome & maternal well being.

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