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ORIGINAL ARTICLE

Effect of Treatment of Subclinical Thyroid Dysfunction on Pregnancy Outcome in Patients with 1st Trimester Recurrent Miscarriages

AMBAR RIAZ[1], MARYAM RANA[2], ASMA MUSHTAQ[3], UMAIR RIAZ AHMAD[4], SHAYAN RASHID KHAWAJA[5], AWAIS RASHEED[6]
[1]*S.R. Obstetrics & Gynaecology, Amna Inayat Medical College, Lahore*
[2]*Assistant Professor obstetrics & Gynaecology, K. E. Medical University/Lady Willingdon Hospital, Lahore*
[3,6]*Medical Officer, Saira Mairaj Memorial Hospital, Lahore*
[4]*Assistant Professor Radiology, University of Lahore*
[5]*Senior Registrar Radiology, Amna Inayat Medical College, Lahore*
Correspondence to: Umair Riaz Ahmad, Email: riazumair@hotmail.com, Cell: 0300-9445224

ABSTRACT

Introduction: Thyroid dysfunction and thyroid autoimmunity are prevalent among women of reproductive age and are associated with adverse outcomes including miscarriage and preterm delivery. Preconception or early pregnancy screening for thyroid dysfunction has been proposed but is not widely accepted

Objective: To determine the effect of treatment of subclinical thyroid dysfunction on pregnancy outcome(pregnancy going beyond 24 weeks ;period of viability in developing world/ miscarriage in first trimester) in patients with recurrent 1st trimester miscarriages.

Material and Mathod:

Study Design: Randomized controlled trial

Settings: Department of Obstetric and Gynaecology, Lady Wallingdon Hospital, Lahore

Duration: One year after submission of synopsis.

Data Collection: The data was collected from the patients admitted in gynae unit 2 through outpatient department with history, examination and investigation which was included according to the inclusion criteria mentioned above. All the patients were assessed with thyroid hormone level. TSH and free T4 was sent to in pathology lab, the result was interpreted by the pathologist to evaluate for the presence of subclinical thyroid dysfunction according to operational definitions. The women with subclinical thyroid dysfunction was categorized as subclinical hypothyroidism and subclinical hyperthyroidism according to results. These women were further evaluated by endocrinologist to allocate them between treatment and control groups. The data collection procedure will be explained to each patient and informed written consent was taken . Each woman was ensured that confidentiality of each subject is kept. It is the matter of controversary in subject of gynecology whether to treat the subclinical thyroid dysfunction or not during pregnancy on the basis of which control group was selected. However if during research study convincing evidence comes in favour of giving treatment to control group then treatment was offered to those patient as well. Single blinding was maintained in control group by giving placebo therapy. Eligible women were allocated in 1:1 in treatment and control groups. The thyroxin (dose 0.5mg/kg body weight) was given to women with subclinical hypothyroidism in treatment group and propylthiouracil (0.3mg/kg body weight) was given to women with subclinical hyperthyroidism in treatment group to maintain TSH (0.45 to4.5IU) and the free t4 level between (14-20umol/l).woman thyroid function test was carried out on biweekly basis in follow up and dose adjustment accordingly. In non-treatment group no treatment given for subclinical thyroid dysfunction and outcomes was assessed and compared in both groups in current pregnancy in respect of miscarriage in first trimester or continuation of pregnancy beyond period of viability.

Results: Frequency of miscarriage in treatment group and in control group was 60.2% and 78.5%. However frequency of miscarriage was significantly higher in control group as that of treatment group. There were 37(39.85) women in treatment group and 20(21.5%) women in control group in which continuation of pregnancy was seen beyond 24 weeks. However women in treatment group had high pregnancy continuation rate as that of control group. i.e. p-value=0.007

Conclusion: Results of this study showed that treatment of subclinical thyroid dysfunction during pregnancy in women with 1st trimester recurrent miscarriages has better pregnancy outcomes. Treatment of thyroid insufficiency during pregnancy is important in avoiding hostile not only maternal as well as fetal outcome

Keywords: Treatment, Subclinical thyroid dysfunction, Pregnancy outcome, Recurrent, 1st trimester miscarriages

INTRODUCTION

1st trimester recurrent miscarriages are defined as when there are three or > three losses of pregnancy before 13 weeks of pregnancy. Causes of recurrent miscarriages are chromosomal, anatomical, immunological ,ovarian causes and endocine.[1]

Thyroid dysfunctions are one of common endocrine dysfunctions in women during pregnancy. Both overt and subclinical thyroid dysfunctions have adverse impact on pregnancy like fetal loss.[2] The second common endocrine disorders are thyroid disorders during pregnancy after diabetes mellitus.[3]

A fetus needs thyroid hormones for its metabolism and growth .In early pregnancy fetus fulfills its need of thyroid hormones from its mother. So if the mother reserves are not sufficient for fetus thyroid hormones need,she is at increase risk of miscarriage.[4] Thyroid disorders during pregnancy may cause recurrent miscaraiges.[5, 6]

A previous subclinical thyroid dysfunction may worsens during pregnancy as demand of thyroid hormones increases . Concentration of thyroid hormones increases in blood during pregnancy , because of high estrogen concentration and weak thyroid stimulating effect of HCG, which act like TSH.T4(thyroxin) level increases from 6 to 12 weeks of gestation and reaches its peak by midgestation, the situation is reverse for TSH.[7]

About 633 pregnant women were screened in second trimester by Sahu,Meenakshi,Titoria in 2010. Their TSH level were estimated. The results showed that ,in the study ,prevalence of dysfunctions of thyroid was high .The prevalence of subclinical thyroid disorder like hypothyroidism was 6.47% and clinical hypothyroidism was 4.58% . The women with clinical hypothyroidism were more at risk of intra uterine death (P ; 0.0004) as compared to control. [8]In an Indian study, Sahasrabuddhe A, et al, the frequency of overt hypothyroidism was 10.96%.[9]

Subclinical thyroid dysfunction is one of the cause of bad obstetrical outcome. Subclinical hypothyroidism is there when thyroid stimulating hormone level is high and thyroxin level is in range of normal levels but usually low normal limits. The prevalence of subclinical thyroid dysfunction (hypothyroidism)is 5% in females during reproductive age.[4] Recurrent miscarriages, preeclampsia, abruption placenta, preterm birth, IUGR, cretinism, low IQ are the complications of subclinical hypothyroidism.[1, 10] The treatment of hypothyroidism in pregnancy is L Thyroxin. Thyroid function should be within normal range prior to conception

in women with previous thyroid dysfunction. Once the pregnancy is diagnosed the dose should be adjusted according to thyroid function test (TSH, free T4);start to patient at 6 to 8weeks of gestation and monitored 4 to 6 weekly until euthyroid state achieved. There may be no bad impact in treating the subclinical hypothyroidism. The Association of American Clinical Endocrinologists ,Endocrine Society and the Association of American Thyroid Association gave the joint view on treatment of subclinical disorders of thyroid and believe that treatment of patients with raised serum TSH with thyroxin is beneficial.[4]

The incidence of subclinical hyperthyroidism is reported as 0.2 to 0.4 %. Recurrent pregnancy losses, preeclampsia, Intrauterine growth retardation fetal and neonatal hyperthyroidism are the complications of hyperthyroidism. Methimazole and propylthiouracil are effective drugs in pregnancy. The rate of miscarriage is increased in successive pregnancies in a woman with past history of miscarriage.The cause of miscarriage remains unclear in majority of patients . The prognosis cannot be improved as long as the causes of recurrent miscarriages are unknown. Worse maternal and fetal outcome may also be present in women with recurrent miscarriages ,as these are also associated with subclinical lthyroid dysfuntions. Previously, no such study had been done to determine the effect of treatment on pregnancy outcome among patients with recurrent miscariages due to subclinical thyroid dysfunction. This research is conducted to find the effect of treatment of subclinical thyroid disoder on pregnancy outcomes in 1st trimester recurrent miscarriages. It will improve the management of subclinical thyroid dysfunction.

MATERIALS AND METHODS

Study Design: Randomized controlled trial

Setting: Department of Obstetric and Gynaecology, Lady Wallingdon Hospital, Lahore

Sample Size: Sample size of 186 patients will be taken (93 in each group) by using 95% confidence level, 80% power of test with expected miscarriage rate in control and in treatment group as 13.7 % and 3.5% respectively[11].

$$n = \frac{\left\{ z_{1-\alpha}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{(P_1-P_2)^2}$$

Adopted from: [Sample size determination in health studies]
Percentage of miscarriage of Control Group= P1 = 13.7%
Percentage of miscarriage of Treatment Group==P2 = 3.5%
P= (P1+P2)
Level of Significance= Z1-α/2=5%
Power of Test= Z1-β=80%

Duration of Study: The study was conducted from March 2019 to April 2020.

Sampling Technique: Non probability purposive sampling

Inclusion Criteria:

The following patients were included:

- Singleton pregnancy on ultrasonography.
- Age: 20 – 30 years (by date of birth)
- All the women with 1st trimester recurrent miscarriages (as per operational definition) with subclinical thyroid dysfunction

Exlusion Criteria:

The following patients were excluded:

- Patients with previous thyroid surgery (by history)
- Women who are known patients of any thyroid disorder and on treatment already.(by history)
- Women with history of recurrent miscarriages due to reason other than thyroid dysfunction as by following investigations.
- Personnel and family history of congenital malformation in couple
- BSR (>140 mg/dl)[12]
- HbAIC (>6%)[12]
- Lupus Anticoagulant (Prolonged a PTT >50sec) [10,13]
- Anticardiolipin Antibodies (Igm/IgG +ve)[10]
- Pelvic scan – (genital tract abnormilities)
- Patients with twin pregnancy on ultrasonography.

Data Collection: The data was collected from the patients admitted in gynae unit 2 through outpatient department with history, examination and investigation which was included according to the inclusion criteria mentioned above. All the patients were assessed with thyroid hormone level. TSH and free T4 was sent to in pathology lab, the result was interpreted by the pathologist to evaluate for the presence of subclinical thyroid dysfunction according to operational definitions. The women with subclinical thyroid dysfunction was categorized as subclinical hypothyroidism and subclinical hyperthyroidism according to results. These women were further evaluated by endocrinologist to allocate them between treatment and control groups. The data collection procedure will be explained to each patient and informed written consent was taken . Each woman was ensured that confidentiality of each subject is kept. It is the matter of controversary in subject of gynecology whether to treat the subclinical thyroid dysfunction or not during pregnancy on the basis of which control group was selected. However if during research study convincing evidence comes in favour of giving treatment to control group then treatment was offered to those patient as well. Single blinding was maintained in control group by giving placebo therapy. Eligible women were allocated in 1:1 in treatment and control groups. The thyroxin (dose 0.5mg/kg body weight) was given to women with subclinical hypothyroidism in treatment group and propylthiouracil (0.3mg/kg body weight) was given to women with subclinical hyperthyroidism in treatment group to maintain TSH (0.45 to4.5IU) and the free t4 level between (14-20umol/l).woman thyroid function test was carried out on biweekly basis in follow up and dose adjustment accordingly. In non-treatment group no treatment given for subclinical thyroid dysfunction and outcomes was assessed and compared in both groups in current pregnancy in respect of miscarriage in first trimester or continuation of pregnancy beyond period of viability. A comprehensively designed proforma recorded all data.

Data Analysis: Data was tabulated and analyzed by SPSS version 17.The quantitative data was presented in form of mean±S.D and qualitative data was given in frequency%. Chi-square test was used to see the association in qualitative attribute. A p-value less than 5% was taken as significant.

RESULTS

- Mean age of women in treatment and in control group was 27.18±2.68 and 27.38±2.00 years. In Treatment group minimum age and maximum age of women was 20 and 30 while in control group it was 21 and 30 years.(Table-1)
- In treatment group mean TSH level at base line and at 2 weeks post treatment was 3.55±3.61 and 3.11±2.84. While in control group at base line mean TSH level was 4.66±3.01 and at 2 weeks time interval it was 4.61±2.98. (Table-2)
- In treatment group mean T3 level at base line and at 2 weeks post treatment was 1.65±0.65 and 1.70±0.57. While in control group at base line mean T3 level was 1.74±0.25 and at 2 weeks time interval it was 1.75±0.26. (Table-3)
- In treatment group mean T4 level at base line and at 2 weeks post treatment was 16.30±5.13 and 16.10±3.27. While in control group at base line mean T4 level was 13.77±4.65 and at 2 weeks time interval it was 13.98±4.55. (Table-4)
- Frequency of miscarriage in treatment group and in control group was 60.2% and 78.5%. However frequency of miscarriage was significantly higher in control group as that of treatment group. i.e. (p-value=0.007) (Table-5)
- There were 37(39.85) women in treatment group and 20(21.5%) women in control group in which continuation of pregnancy was seen beyond 24 weeks. However women in

treatment group had high pregnancy continuation rate as that of control group. i.e. p-value=0.007(Table-6)

Table 1: Descriptive statistics for age of women

	Treatment Group	Control Group
N	93	93
Mean	27.18	27.38
SD	2.68	2.00
Min	20.00	21.00
Max	30.00	30.00

Table 2: Descriptive statistics for TSH level at Base line and at 2nd week

	Base Line		2nd Week	
	Treatment Group	Control Group	Treatment Group	Control Group
n	93	93	93	93
Mean	3.55	4.66	3.11	4.61
SD	3.61	3.01	2.84	2.98
Min	0.18	0.03	0.30	0.03
Max	10.00	10.00	8.50	10.00

Table 3: Descriptive statistics for T3 level at Base line and at 2nd week

	Base Line		2nd Week	
	Treatment Group	Control Group	Treatment Group	Control Group
n	93	93	93	93
Mean	1.65	1.74	1.70	1.75
SD	0.65	0.25	0.57	0.26
Min	1.00	1.20	.30	1.20
Max	3.00	2.00	3.00	2.00

Table 4: Descriptive statistics for T4 level at Base line and at 2nd week

	Base Line		2nd Week	
	Treatment Group	Control Group	Treatment Group	Control Group
n	93	93	93	93
Mean	16.30	13.77	16.10	13.98
SD	5.13	4.65	3.27	4.55
Min	10.00	8.00	10.00	8.00
Max	22.00	22.00	21.00	22.00

Table 5: Miscarriage in first Trimester

Miscarriage	Treatment Group	Control Group	Total
Yes	56(60.2%)	73(78.5%)	129
No	37(39.8%)	20(21.5%)	57
Total	93	93	186

Chi-Square test= 7.310
p-value= 0.007

Table 6: Continuation of Pregnancy

Pregnancy Continue	Treatment Group	Control Group	Total
Yes	37(39.8%)	20(21.5%)	57
No	56(60.2%)	73(78.5%)	129
Total	93	93	186

Chi-Square test= 7.310
p-value= 0.007

DISCUSSION

Autoimmune thyroid disease (AITD) is by far the most frequent cause of hypothyroidism in women of reproductive age. The prevalence of hypothyroidism in the general population of reproductive age is w2–3%.[14] Overthypothyroidism is commonly associated with infertility, as thyroid hormones have a direct effect on granulosacells, luteal cells and oocyte maturation. Euthyroid women with thyroid autoimmunity are twice as likely to experience spontaneous miscarriages. This probably represents a generalised activation of the immune system, or an increased risk of progression to subclinical hypothyroidism,or it could be due to the transplacental transfer of thyroid receptor blocking antibodies.[15]

Hence, there is a need to screen for subclinical hypothyroidismand thyroid autoimmunity in pregnancy, especially in women with a history of miscarriages. However, the management of women with recurrent miscarriage who have thyroid autoimmunity remains controversial. Some investigators recommend the use of empirical thyroxine (T4) therapy in women with thyroid per oxidase antibody positive (TPOAbC) autoimmunity, although there was no evidence of hypothyroidism. A few studies showed that empirical T4 therapy in patients with TPOAbC did not improve the obstetrical outcome.[16,17]

There is evidence that thyroid autoimmunity is associated with pregnancy loss, because maternal thyroid hormones (TH) play a critical role in the development of both fetus and placenta. Pregnancy loss in women with positive thyroid autoantibodies occurs within the first trimester of gestation, when the fetus is dependent on maternal thyroid hormones.[18] Following implantation, the preservation of the pregnancy is reliant on a mass of immunological events that will assistance in the successful growth and development of the fetus.[19]

A women with hypothyroidism when conceives faces problems like spontaneous abortions, premature birth, placental abruption and irreversible damage to the fetus like failure of differentiation of nerves, inadequate central nervous system development and increased risk of perinatal death due to ovulatory dysfunction. These serious complications can be positively influenced by timely detection and prescription of thyroxine.[20'21]

In this study frequency of miscarriage in treatment group and in control group was 60.2% and 78.5%. However frequency of miscarriage was significantly higher in control group as that of treatment group. i.e. (p-value=0.007) and there were 37(39.85) women in treatment group and 20(21.5%) women in control group in which continuation of pregnancy was seen beyond 24 weeks. However women in treatment group had high pregnancy continuation rate as that of control group. i.e. p-value=0.007

Kusum Lata from India in her study reported no difference in prevalence of miscarriage between hypothyroid and euthyroid individuals in TPOAb+ women. The prevalence of miscarriage was independent of thyroid status.22 Similar results were also found with $TPOAb^-$ women, when adjusted for age, weight, TFT, TPOAb titre, period of gestation and haemoglobin level. The miscarriage rate reported by Kusum Lata in her study was 4%, which is comparable to a healthy control population.[22] Kusum Lata study results are contradicting to the results of this study as she has reported equal miscarriage rate in cases and controls however in this study miscarriage rate was higher in controls when compared with cases.

The issue of TPO positivity and the risk of miscarriage in future pregnancies was reported by Pratt et al.[23] A study by Alexander et al and Shrestha A showed that treatment with thyroid supplements are known to improve the pregnancy outcomes. So, it is necessary to find out the abnormal thyroid function and auto-antibodies in those with recurrent pregnancy loss as early treatment helps in improving the viability of pregnancy.[24'25]

Alexander et al and Shrestha A both results are consistent with the results of this study that treating subclinical thyroid dysfunction can effectively produce good pregnancy outcome in terms of pregnancy continuation in women with 1st trimester recurrent miscarriages.

Shrestha A, Chawla from Nepal in his study reported that ladies with diagnosis of hypothyroidism underwent treatment and 17 (44.73%) out of 38 had conceived.24 Shrestha A, Chawla is line with the results of this study showing that treating sub clinical thyroid dysfunction may give significant results in terms of pregnancy continuation in women and minimizing the chances of miscarriages in women who had 1st trimester recurrent miscarriage.

E. Gianetti in his study reported that in all groups of investigated patients, the rate of spontaneous abortion was not higher as compared to that of the general population (12–15 %).26 In particular, a miscarriage occurred in 9/89 pregnancies (10 %) in group 1, 3/35 (8, 6 %) in group 2, 4/32 (12, 5 %) in group 3, 0/20 in group 4 and 11/203 (5, 4 %) in group 5. One voluntary termination was recorded in each group no. 1, 2, 3 and 5.27

Although multiple studies had demonstrated a risk of miscarriage in patients with AITD, the cause has yet to be established.[19] TPOAb+ is one of the markers of recurrent miscarriage. However, more evidence is needed before dismissing antibody positivity as a cause of adverse pregnancy outcome28. The association of thyroid autoimmunity and miscarriage could be due to heightened autoimmune imbalance that in turn leads to a greater rejection rate of the foetal graft, and TPOAb+ women would tend to become pregnant at an older age(3–4 years older, on average), and older women are more prone to pregnancy loss.[29]

Recently, Twig et al. described the pathogenesis that underlies infertility and increased pregnancy loss among women with AITD (Autoimmune thyroid disease). Thyroid autoantibodies exert their effect in both a TSH-dependent and TSH-independent manner. The latter involves quantitative and qualitative changes in the profile of endometrial T cells, which results in the reduced secretion of IL4 and IL10together with the hyper secretion of interferon-g. Polyclonal B-cell activation is two to three times more frequent in thyroid autoimmunity. The hyperactivity and increased migration of cytotoxic natural killer cells which alter the immune and hormonal response of the uterus is up to 40% more common in women with thyroid autoimmunity. Vitamin D deficiency is also linked to infertility and pregnancy loss, suggesting a potential interplay with thyroid autoimmunity in the context of infertility.[15]

CONCLUSION

Results of this study showed that treatment of subclinical thyroid dysfunction during pregnancy in women with 1st trimester recurrent miscarriages has better pregnancy outcomes. Treatment of thyroid insufficiency during pregnancy is important in avoiding hostile not only maternal as well as fetal outcome

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