“ANTI THYROID PEROXIDASE POSITIVITY IN RECURRENT MISCARRIAGES AND ASSOCIATED OBSTETRIC COMPLICATIONS”

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CHENNAI

MAY 2019

CERTIFICATE

This is to certify that the dissertation entitled **"ANTI THYROID PEROXIDASE POSITIVITY IN RECURRENT MISCARRIAGES AND ASSOCIATED OBSTETRIC COMPLICATIONS."** is a bonafide record of work done by **Dr. K.MANJULA**in Madras Medical college, Chennaiduring the period March 2017 to March 2018 under the guidance of **Dr.K.KANMANI, M.D., D.G.O.,** Professor of Obstetrics and Gynaecology, Institute of Social Obstetrics, Madras Medical College in partial fulfilment of requirement of M.S Degree in Obstetrics and Gynaecology degree examination of The Tamilnadu Dr. M.G.R Medical University to be held in May 2019.

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DECLARATION

I **Dr. K.MANJULA,** Post graduate, Department of Obstetrics and Gynaecology, Madras Medical College, solemnly declare that this dissertation entitled **"ANTI THYROID PEROXIDASE POSITIVITY IN RECURRENT MISCARRIAGES AND ASSOCIATED OBSTETRIC COMPLICATIONS"** was done by me at Madras Medical College during 2016-2019 under the guidance and supervision of **Prof.Dr.K.KANMANI M.D.,D.G.O.,** Professor of Obstetrics and Gynaecology, Institute of Social Obstetrics, Madras Medical College. This dissertationis submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.S. Degree in Obstetrics and Gynaecology (Branch-II).

Place: Chennai-3

Date: **Dr.K.MANJULA**

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Guide,
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Madras Medical College,
Chennai

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I thank all my patients for their cooperation and hence for the success of study.

I thank my family and friends for their inspiration and support given to me.

CONTENTS

INTRODUCTION

Any pregnancy ending spontaneously prior the fetus can survive is defined as miscarriage. Recurrent miscarriage, defined as loss of 3 or more consecutive pregnancies affects 1% of couples trying to conceive.

The important causes for recurrent spontaneous miscarriage includes epidemiological factors such as maternal age and numberof previous miscarriages, anti-phospholipids syndrome, genetic factors, anatomical factors, endocrine factors, immune factors; inherited thrombophilic defects etc.,

Autoimmune thyroid disease (AITD) is the most frequent cause of Hypothyroidism in women of reproductive age. Thyroid disorders have been suspected to cause early pregnancy loss and other adversepregnancy outcomes. Although the worst overthypothyroidism is infrequent in pregnancy, subclinical hypothyroidism has an incidence of 2-3%.

Thyroid dysfunction and autoimmunity are relatively common in women of reproductive age group and has been associated with various adverse pregnancy outcomes such as recurrent miscarriage, preeclampsia and preterm labour. The main objective of this study was to find out association between anti-Thyroid peroxidase antibody and recurrent miscarriages and to evaluate obstetric complications such as preeclampsia and preterm labour in them.

Maternal age and number of previous miscarriages are two independent risk factors for a further miscarriage. Advancing maternal age is associated with a decline in both the number and quality of the remaining oocytes.

A large prospective register linkage study reported the age-related risk of miscarriage in recognised pregnancies to be: 12–19 years, 13%; 20–24 years, 11%; 25–29 years, 12%; 30–34 years, 15%; 35–39 years, 25%; 40–44 years, 51%; and ≥45 years, 93%.

Advanced paternal age has also been identified as a risk factor for miscarriage. The risk of miscarriage is highest among couples where the woman is ≥35 years of age and the man ≥40 years of age.

Previous reproductive history is an independent predictor of future pregnancy outcome. The risk of a further miscarriage increases after each successive pregnancy loss, reaching approximately 40% after three consecutive pregnancy losses, and the prognosis worsens with increasing maternal age. A previous live birth does not preclude a woman developing recurrent miscarriage.

The evidence on the effect of environmental risk factors is based mainly on data studying women with sporadic rather than recurrent miscarriage. The results are conflicting and biased by difficulties in controlling for confounding factors and the inaccuracy of data on exposure and the measurement of toxin dose.

Maternal cigarette smoking and caffeine consumption have been associated with an increased risk of spontaneous miscarriage in a dose-dependent manner. However, current evidence is insufficient to confirm this association.

Recent retrospective studies have reported that obesity increases the risk of both sporadic and recurrent miscarriage

Definition of Miscarriage and Recurrent Pregnancy Loss

The term miscarriage (or abortion) is used to describe a pregnancy that fails to progress, resulting in death and expulsion of the embryo or fetus. The generally accepted definition stipulates that the fetus or embryo should weigh 500 g or less, a stage that corresponds to a gestational age of up to 20 weeks (World Health Organization).

Unfortunately, this definition is not used consistently, and pregnancy losses at higher gestational ages are also, in some studies, classified as miscarriage instead of stillbirth or preterm neonatal death. Thus, from a definition perspective, it is important to characterize the population being studied so that comparisons across therapeutic trials can be made more appropriately and reliably.

Recurrent miscarriage should, according to the aforementioned definition of miscarriage, be defined as at least three consecutive miscarriages, whereas recurrent pregnancy loss (RPL) could also include

pregnancy losses up to gestational week 28; however, unfortunately there is no consensus on the definition of recurrent miscarriage or RPL.Pregnancy losses after week 20 are rare, so defining recurrent miscarriage and RPL as above will result in almost identical populations.

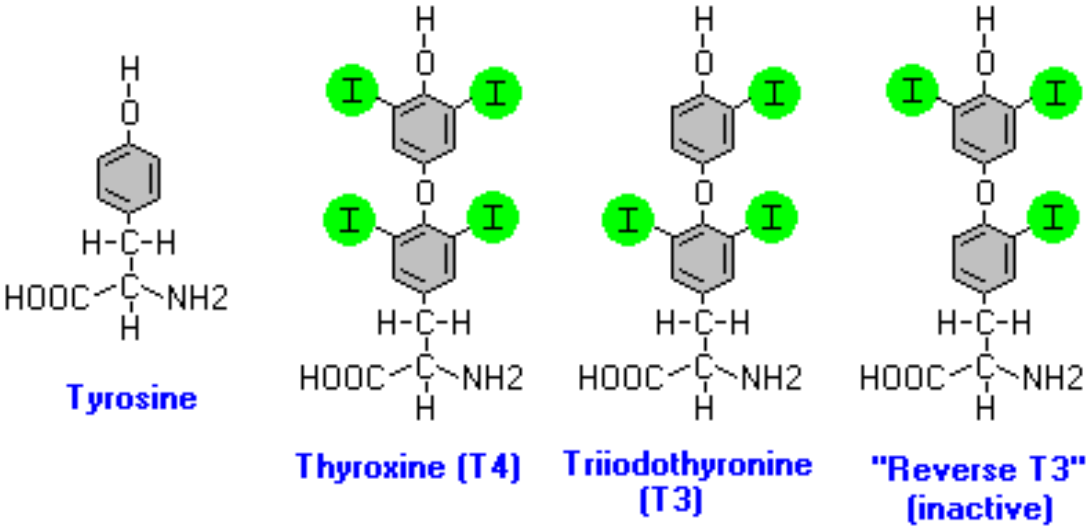
In some countries and according to some national guidelines only two miscarriages are required for diagnosis of RPL. More and more published studies of RPL therefore include women with only two previous miscarriages, which from an epidemiological point of view is very problematic.

Chemistry of Thyroid Hormones

Thyroid hormones are derivatives of the the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are:

- **thyroxine** (also known as T4 or L-3,5,3',5'-tetraiodothyronine)
- **triiodothyronine** (T3 or L-3,5,3'-triiodothyronine)

As shown in the following diagram, the thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or four positions on the aromatic rings. The number and position of the iodines is important. Several other iodinated molecules are generated that have little or no biological activity; so called "reverse T3" (3,3',5'-T3) is such an example



A large majority of the thyroid hormone secreted from the thyroid gland is T4, but T3 is the considerably more active hormone. Although some T3 is also secreted, the bulk of the T3 is derived by deiodination of T4 in peripheral tissues, especially liver and kidney. Deiodination of T4 also yields reverse T3, a molecule with no known metabolic activity.

Thyroid hormones are poorly soluble in water, and more than 99% of the T3 and T4 circulating in blood is bound to carrier proteins. The principle carrier of thyroid hormones is *thyroxine-binding globulin*, a glycoprotein synthesized in the liver. Two other carriers of import are transthyrein and albumin. Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells.

THYROID BIOSYNTHESIS:

Thyroid hormones are synthesized by mechanisms fundamentally different from what is seen in other endocrine systems. Thyroid follicles serve as both factory and warehouse for production of thyroid hormones.

Constructing Thyroid Hormones

The entire synthetic process occurs in three major steps:

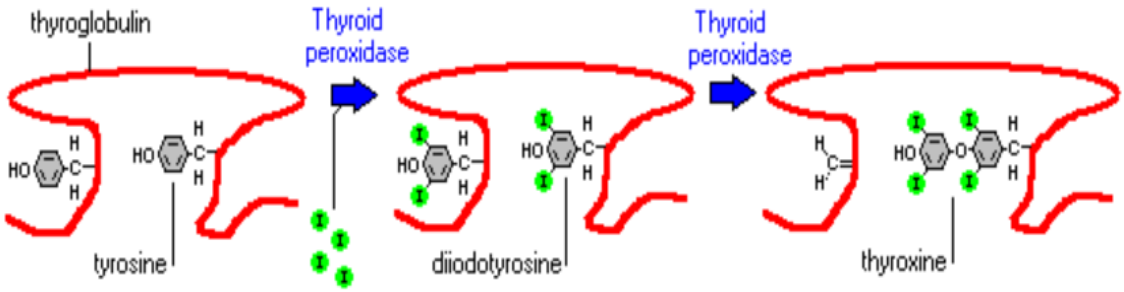
- Production and accumulation of the raw materials
- Fabrication or synthesis of the hormones on a backbone or scaffold of precursor
- Release of the free hormones from the scaffold and secretion into blood

The recipe for making thyroid hormones calls for two principle raw materials:

- *Tyrosines* are provided from a large glycoprotein scaffold called *thyroglobulin*, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle - colloid is essentially a pool of thyroglobulin. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3.
- *Iodine*, or more accurately iodide (I^-), is avidly taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane a sodium-iodide symporter or "*iodine trap*". Once inside the cell, iodide is transported into the lumen of the follicle along with thyroglobulin.

Fabrication of thyroid hormones is conducted by the enzyme *thyroid peroxidase*, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

1. Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").
2. Synthesis of thyroxine or triiodothyronine from two iodotyrosines.

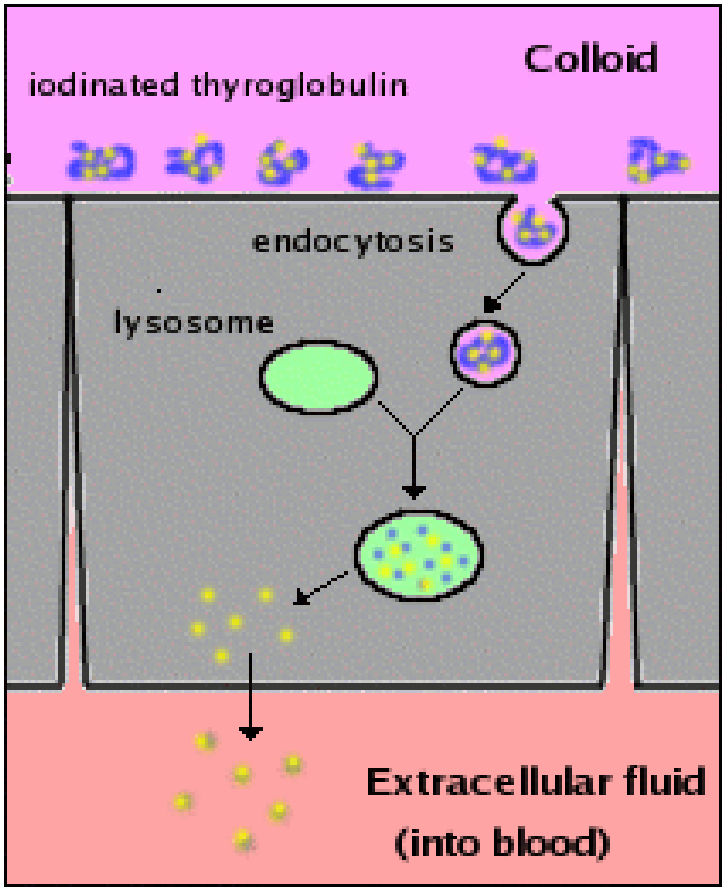


Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells. Remember that hormone is still tied up in molecules of thyroglobulin - the task remaining is to liberate it from the scaffold and secrete free hormone into blood.

Thyroid hormones are excised from their thyroglobulin scaffold by digestion in lysosomes of thyroid epithelial cells. This final act in thyroid hormone synthesis proceeds in the following steps:

- Thyroid epithelial cells ingest colloid by endocytosis from their apical borders - that colloid contains thyroglobulin decorated with thyroid hormone.

- Colloid-laden endosomes fuse with lysosomes, which contain hydrolytic enzymes that digest thyroglobluin, thereby liberating free thyroid hormones.
- Finally, free thyroid hormones apparently diffuse out of lysosomes, through the basal plasma membrane of the cell, and into blood where they quickly bind to carrier proteins for transport to target cells



Control of Thyroid Hormone Synthesis and Secretion

The chief stimulator of thyroid hormone synthesis is thyroid-stimulating hormone from the anterior pituitary. Binding of TSH to receptors on thyroid epithelial cells seems`` Q to enhance all of the processes necessary for synthesis of thyroid hormones, including synthesis of the iodide transporter, thyroid peroxidase and thyroglobulin.

The magnitude of the TSH signal also sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.

The thyroid gland is part of the hypothalamic-pituitary-thyroid axis, and control of thyroid hormone secretion is exerted by classical negative feedback, as depicted in the diagram. Thyroid-releasing hormone (TRH) from the hypothalamus stimulates TSH from the pituitary, which stimulates thyroid hormone release. As blood concentrations of thyroid hormones increase, they inhibit both TSH and TRH, leading to "shutdown" of thyroid epithelial cells. Later, when blood levels of thyroid hormone have decayed, the negative feedback signal fades, and the system wakes up again.

A number of other factors have been shown to influence thyroid hormone secretion. In rodents and young children, exposure to a cold environment triggers TRH secretion, leading to enhanced thyroid hormone release. This makes sense considering the known ability of thyroid hormones to spark body heat production

MATERNAL THYROID FUNCTION DURING PREGNANCY

Normal pregnancy entails substantial changes in thyroid function in all animals. These phenomena have been studied most extensively in humans, but probably are similar in all mammals. Major alterations in the thyroid system during pregnancy include:

- *Increased blood concentrations of T4-binding globulin*: TBG is one of several proteins that transport thyroid hormones in blood, and has the highest affinity for T4 (thyroxine) of the group. Estrogens stimulate expression of TBG in liver, and the normal rise in estrogen during pregnancy induces roughly a doubling in serum TBG concentrations.
- *Increased levels of TBG lead to lowered free T4 concentrations*, which results in elevated TSH secretion by the pituitary and, consequently, enhanced production and secretion of thyroid hormones. The net effect of elevated TBG synthesis is to force a new equilibrium between free and bound thyroid hormones and thus a significant increase in total T4 and T3 levels. The increased demand for thyroid hormones is reached by about 20 weeks of gestation and persists until term.
- *Increased demand for iodine*: This results from a significant pregnancy-associated increase in iodide clearance by the kidney (due to increased glomerular filtration rate), and siphoning of maternal iodide by the fetus. The World Health Organization recommends increasing iodine intake from the standard 100 to 150 ug/day to at least 200 ug/day during pregnancy.
- *Thyroid stimulation by chorionic gonadotropin:* The placenta of humans and other primates secrete huge amounts of a hormone called chorionic gonadotropin (in the case of humans, human chorionic gonadotropin or hCG) which is very closely related to luteinizing hormone. TSH and hCG are similar enough that hCG can bind and transduce signalling from the

TSH receptor on thyroid epithelial cells. Toward the end of the first trimester of pregnancy in humans, when hCG levels are highest, a significant fraction of the thyroid-stimulating activity is from hCG. During this time, blood levels of TSH often are suppressed, as depicted in the figure to the right. The thyroid-stimulating activity of hCG actually causes some women to develop transient hyperthyroidism.

The net effect of pregnancy is an increased demand on the thyroid gland. In the normal individuals, this does not appear to represent much of a load to the thyroid gland, but in females with subclinical hypothyroidism, the extra demands of pregnancy can precipitate clinicial disease.

Thyroid Hormones and Fetal Brain Development

In 1888 the Clinical Society of London issued a report underlining the importance of normal thyroid function on development of the brain. Since that time, numerous studies with rats, sheep and humans have reinforced this concept, usually by study of the effects of fetal and/or maternal thyroid deficiency. Thyroid hormones appear to have their most profound effects on the terminal stages of brain differentiation, including synaptogenesis, growth of dendrites and axons, myelination and neuronal migration.

Thyroid hormones act by binding to nuclear receptors and modulating transcription of responsive genes. Thyroid hormone receptors are widely

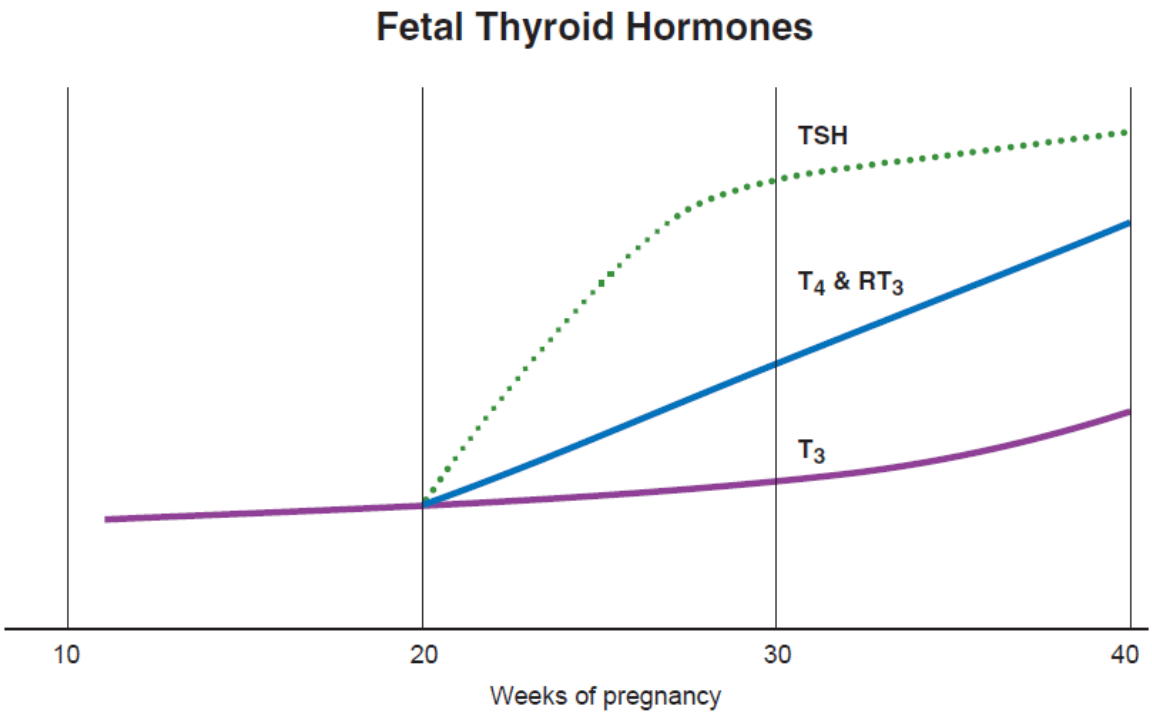
distributed in the fetal brain, and present prior to the time the fetus is able to synthesize thyroid hormones.

It has proven surprisingly difficult to identify the molecular targets for thyroid hormone action in the developing brain, but some progress has been made. For example, the promoter of the myelin basic protein gene is directly responsive to thyroid hormones and contains the expected hormone response element. This fits with the observation that induced hypothyroidism in rats leads to diminished synthesis of mRNAs for several myelin-associated proteins.

It seems clear that there is a great deal more to learn about the molecular mechanisms by which thyroid hormones support normal development of the brain.

Thyroid Deficiency in the Fetus and Neonate

The fetus has two potential sources of thyroid hormones - it's own thyroid and the thyroid of it's mother. Human fetuses acquire the ability to synthesize thyroid hormones at roughly 12 weeks of gestation, and fetuses from other species at developmentally similar times. Current evidence from several species indicates that there is substantial transfer of maternal thyroid hormones across the placenta. Additionally, the placenta contains deiodinases that can convert T4 to T3.



The major thyroid hormone secreted by the fetus is T4. However, total T3 and free T3 levels are low throughout gestation, and levels of RT3 are elevated, paralleling the rise in T4. Like T3, this compound is derived predominantly from conversion of T4 in peripheral tissues.

The increased production of T4 in fetal life is compensated by rapid conversion to the inactive RT3, allowing the fetus to conserve its fuel resources. However, there is some evidence that RT3, as well as T4, through nongenomic actions, regulate fetal brain development.

The fetus is iodine deficient when a mother's iodine intake is low. Supplying the mother adequate iodine is an important problem in many parts of the world. A fetalgoiter is occasionally detected by ultrasonography at a size that could impede normal delivery. The fetus can be treated, with

regression of the goiter, by the administration of levothyroxine into the amniotic fluid.

However, the fetus is usually protected by the transplacental transfer of maternal T4, and, therefore, fetal treatment of hypothyroidism can usually be postponed until delivery.

There are three types or combinations of thyroid deficiency states known to impact fetal development:

Isolated maternal hypothyroidism:

Overt maternal hypothyroidism typically is not a significant cause of fetal disease because it usually is associated with infertility. When pregnancy does occur, there is increased risk of intrauterine fetal death and gestational hypertension. Subclincial hypothyroidism is increasingly being recognized as a cause of developmental disease - this is a rather scary situation.

Several investigators have found that mild maternal hypothyroidism, diagnosed only retrospectively from banked serum, may adversely affect the fetus, leading in children to such effects as slightly lower performance on IQ tests and difficulties with schoolwork. The most common cause of subclinical hypothyroidism is autoimmune disease, and it is known that anti-thyroid antibodies cross the human placenta. Thus, the cause of this disorder may be a passive immune attack on the fetal thyroid gland.

Isolated fetal hypothyroidism:

This condition is also known as sporadic congenital hypothyroidism. It is due to failure of the fetal thyroid gland to produce adequate amounts of thyroid hormone. Most children with this disorder are normal at birth, because maternal thyroid hormones are transported across the placenta during gestation. What is absolutely critical is to identify and treat this condition very shortly after birth. If treatment is not instituted quickly, the child will become permanently mentally and growth retarded - a disorder called cretinism. This problem has largely due to large scale screening programs to detect hypothyroid infants.

Iodine deficiency - Combined maternal and fetal hypothyroidism: Iodine deficiency is, by a large margin, the most common preventable cause of mental retardation in the world. Without adequate maternal iodine intake, both the fetus and mother are hypothyroid, and if supplemental iodine is not provided, the child may well develop cretinism, with mental retardation, deaf-mutism and spasticity.

The World Health Organization estimated in 1990 that 20 million people had some degree of brain damage due to iodine deficiency experienced in fetal life. Endemic iodine deficiency remains a substantial public health problem in many parts of the world, including many areas in Europe, Asia, Africa and South America.

In areas of severe deficiency, a large fraction of the adult population may show goiters. In such settings, overt cretinism may occur in 5 to 10

percent of offspring, and perhaps five times that many children will have mild mental retardation. This is a serious, tragic and, most importantly, a preventable problem.

The effects of mild maternal hypothyroidism on cognitive function of children has been evaluated in several studies, including some in which mothers will low levels of T4 or high levels of TSH were treated prophylactically with thyroid supplementation. The results of these studies are somewhat divergent, and the benefit of routinely testing pregnant women and treating those with suspected thyroid deficiency remains unsettled.

The fetus of an iodine-deficient mother can be successfully treated if iodine supplementation is given during the first or second trimester. Treatment during the third trimester or after birth will not prevent the mental defects.

Iodine deficiency can also be a sigificant problem in animal populations. The most common manifestation in sheep, cattle, pigs and horses is a high incidence of stillbirths and birth of small, weak offspring.

Hyperthyroidism in Pregnancy

Gestational hyperthyroidism is associated with increased risk of several adverse outcomes, including preeclampisa, premature labor, fetal or perinatal death and low birth weight. In humans, hyperthyroidism usually is

the result of Grave's disease, which involves development of autoantibodies against the TSH receptor that stimulate the thyroid gland.

MATERNAL AND FETAL THYROID LEVELS :

In response to the metabolic demands of pregnancy, there is an increase in the basal metabolic rate (which is mainly due to fetal metabolism), iodine uptake, and the size of the thyroid gland caused by hyperplasia and increased vascularity. However, despite this increase in thyroid activity, a pregnant woman is euthyroid with levels of TSH, free T4, and free T3 remaining within the normal range; thyroid nodules and goiter require evaluation.

During pregnancy, iodide clearance by the kidney increases. For this reason (plus the iodide losses to the fetus), the prevalence of goiter is increased in areas of iodine deficiency. In many parts of the world, iodine is not sufficiently available in the environment, and pregnancy increases the risk of iodine deficiency.

The increase in thyroid activity in pregnancy is accompanied by a marked increase in the circulating levels of TBG in response to estrogen; therefore, a new equilibrium is reached with an increase in the bound portion of the thyroid hormone. The mechanism for the estrogen effect on TBG is an increase in hepatic synthesis and an increase in glycosylation of the TBG molecule that leads to decreased clearance.

The increase in thyroid activity is attributed to the thyrotropic substances secreted by the placenta: a chorionic thyrotropin and the thyrotropic activity in human chorionic gonadotropin (hCG).

It has been calculated that hCG contains approximately 1/4,000th of the thyrotropic activity of human TSH. In conditions with very elevated HCG levels, the thyrotropic activity can be sufficient to produce hyperthyroidism (gestational hyperthyroidism), and this can even be encountered in normal pregnancy TBG levels reach a peak (twice nonpregnant levels) at about 15 weeks, which is maintained throughout the rest of pregnancy.

T4 undergoes a small increase in the first trimester, but T3 increases more markedly. Because of the increase in TBG, free T4 and T3 levels then decrease, although they remain within the normal range. There is an inverse relationship between maternal circulation levels of TSH and hCG.60 TSH reaches a nadir atthe same time that hCG reaches a peak at 10 weeks of pregnancy. TSH levels then increase as hCG levels drop to their stable levels throughout the rest of pregnancy.

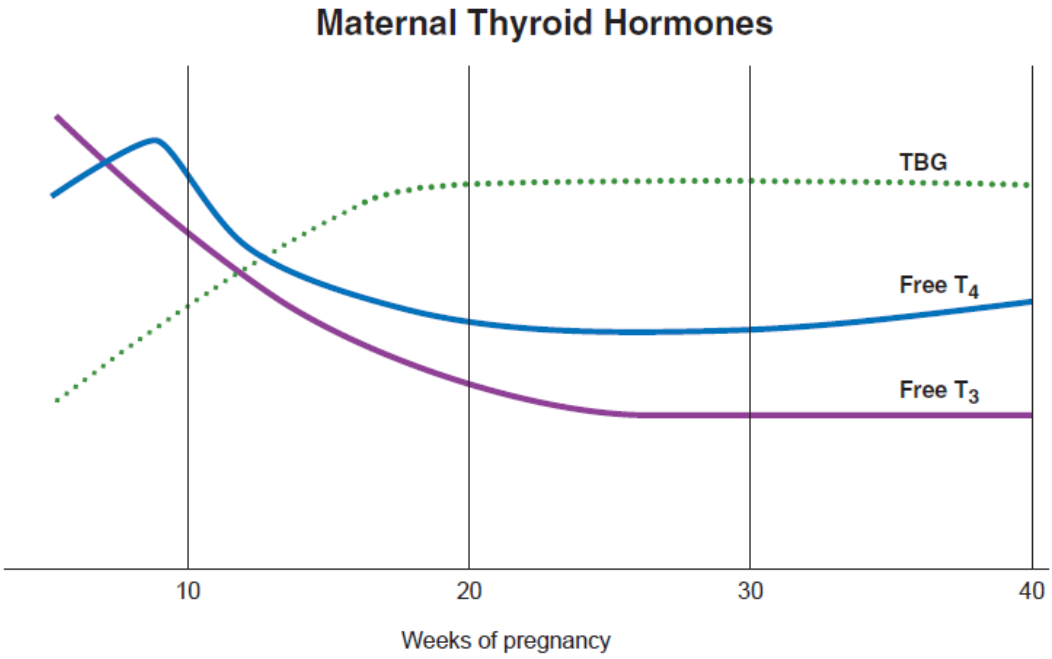
Thus, the range of normal for TSH levels change with each trimester. The lower limit of TSH in the first and second trimesters is 0.03 and 0.13 mU/L in the third trimester. The upper limit of normal in the first trimester is 2.3 and 3.5 mU/L in the second and third trimesters.

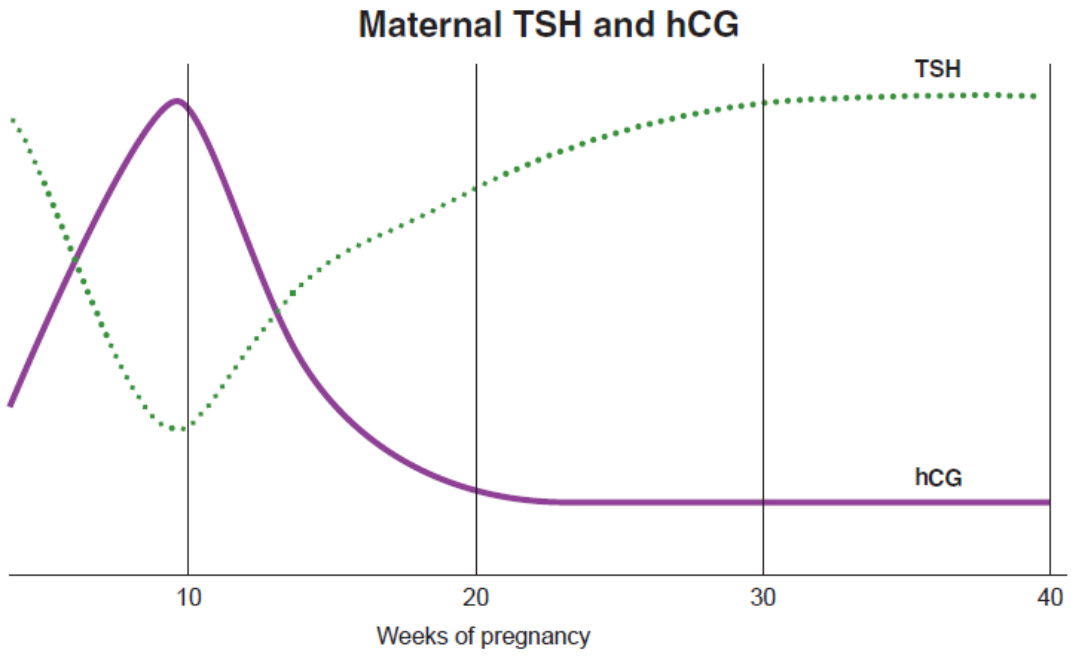
These changes support a role for hCG stimulation of the maternal thyroid gland, especially during early pregnancy, providing a small but important increase in maternal thyroid hormones for the fetus until fetal thyroid function is sufficient to serve fetal needs.

It is well recognized that patients who have conditions associated with very high levels of hCG (trophoblastic disease, hCG-secreting cancers) can develop hyperthyroidism. The thyroid stimulating activity of hCG is explained by the molecular homology between hCG and TSH, and between their receptors.

In normal pregnancies, placental transfer of TSH, T4, and T3 is limited in both directions. Slight, but significant, transfer of T4 and T3 does occur, however, when maternal levels are very high or when fetal levels are substantially lower than the maternal levels.

Therefore, in the early weeks of pregnancy, before the fetal thyroid gland becomes active, the fetal brain is dependent on the placental transport of maternal T4. Both overt and subclinical maternal hypothyroidism are associated with increased risks of miscarriage, preeclampsia, low birth weight, premature delivery, and a decrease in intelligence in the children.


Maternal Thyroid Hormones
TBG
Free T_4
Free T_3
10
20
30
40
Weeks of pregnancy


Maternal TSH and hCG
TSH
hCG
10
20
30
40
Weeks of pregnancy

Epidemiological Parameters Relevant for Recurrent Pregnancy Loss Occurrence

Using the traditional definition, the incidence of RPL is the number of new women each year (or in another defined period) suffering their third consecutive pregnancy loss, and the prevalence of RPL is the number of women in a population who, at a specific time point, have had three or more consecutive pregnancy losses. The incidence/prevalence is often expressed as a rate of those individuals being at risk for the disorder.

The number in the denominator could be all women in the population, women of fertile age or women who had attempted pregnancy at least two or three times. Indeed, the estimateof the incidence/prevalence of RPL is very uncertain since in most countries there is no nationwide registration of miscarriages or RPL, and many early miscarriages will not be treated in hospitals and are thus not registered.

There is no valid estimate of the incidence of RPL whereas there are a few estimates of the prevalence rate of RPL. One of the most informative studies of the prevalence rate of RPL was performed by Alberman,who asked female doctors to report retrospectively about the outcome of their previous pregnancies.

Nine out of 742 + 355 women (0.8%) who had had three or four previous pregnancies reported three or more consecutive pregnancy losses.

This study must still be considered the best estimate of the prevalence of RPL since the cohort was restricted to women who had attempted pregnancy at least three times, and because it consisted of doctors it is expected that misclassification of delayed menstruations, induced abortions, and ectopic pregnancies as miscarriages will be small.

However, since the study is from before 1980 many early miscarriages may not have been registered due to lack of highly sensitive human chorionic gonadotropin tests and ultrasound examinations at that time. Furthermore, female doctors may not reflect the background population: on one side they may be healthier than other women, which may lower the miscarriage risk, but on the other side, due to their long education they are older than average when attempting pregnancy, which increases the miscarriage risk.

Other estimates of the population prevalence of RPL are roughly in accordance with that of Alberman. An RPL prevalence of 2.3% was found in 432 randomly identified women in a multicenter study.4 In a group of 5901 Norwegian women with at least two pregnancies screened for toxoplasma antibodies, 1.4% had experienced RPL.5 Data from a Danish questionnaire-based study6 found, in a random sample of 493 women with at least two intrauterine pregnancies, that 0.6% had had at least three consecutive miscarriages, 0.8% at least three consecutive pregnancy losses during all trimesters, and 1.8% had had at least three, not necessarily

consecutive, losses some time during pregnancy. Overall, these studies thus find the prevalence of RPL to be between 0.6% and 2.3%.

Number of Previous Miscarriages

Almost all prospective studies of RPL patients show remarkable consistency in finding an increasing risk of miscarriage as the number of previous miscarriages increases. The chance of subsequent live birth in untreated RPL patients with three, four, and five or more miscarriages has been found to be 42–86%, 41–72%, and 23–51%, respectively.The significant variability in the estimate of the subsequent risk of miscarriage in RPL patients can probably be attributed to the time of ascertainment of the pregnancies since the average age of the patients and the duration of follow-up in the various studies were not different.

Thyroid Abnormalities and Pregnancy Loss

Hyperthyroidism

Hyperthyroidism occurs in approximately 0.1–0.4% of pregnancies.It seems that excess production of thyroid hormone usually is not correlated with infertility or RPL. Women with subclinical or mild hyperthyroidism have evidence of ovulation when endometrial sampling is performed. Pregnant women with untreated overt hyperthyroidism are at increased risk for spontaneous miscarriage, congestive heart failure, thyroid storm,

preterm birth, pre-eclampsia, fetal growth restriction, and increased perinatal morbidity and mortality.

Treatment of overt Graves' hyperthyroidism in pregnancy to achieve adequate metabolic control has been associated with improved pregnancy outcomes.However, hyperthyroidism has not been reported commonly as an independent cause of RPL. Only a recent retrospective study has suggested that excess exogenous thyroid hormone is associated with an elevated rate of fetal loss.

A study by Nakayama et al.study was performed in a unique population of patients with a genotype (Arg243-Gln mutation in the TH receptor β gene) showing resistance to thyroid hormone, and a high serum concentration of free thyroxine (FT4) and tri-iodothyronine without suppressed thyrotropin. These women maintain a euthyroid state despite high thyroid hormone levels. Patients were analyzed in three different groups: affected mothers (n = 9), affected fathers (n = 9), and unaffected relatives (n = 18).

The mean miscarriage rates were 22.9, 2.0, and 4.4%, respectively ($\chi 2 = 8.66$; $p = 0.01$). Affected mothers had an increased rate of miscarriage ($z = 3.10$; $p = 0.002$, by Wilcoxon rank-sum test).

Hypothyroidism

The most common cause of hypothyroidism in pregnant women, affecting approximately 0.5% of patients is chronic autoimmune thyroiditis (Hashimoto's thyroiditis).Other causes of hypothyroidism include endemic iodine deficiency (ID), prior radioactive iodine therapy and thyroidectomy. There seems to be no doubt that hypothyroidism is associated with infertility.

Untreated hypothyroidism in pregnancy has consistently been shown to be associated with an increased risk for adverse pregnancy complications, as well as detrimental effects on fetal neurocognitive development.30 Specific adverse outcomes associated with maternal overt hypothyroidism include increased risks for premature birth, low birth weight, and miscarriage

Thyroid hormones have an impact on oocytes at the level of the granulosa and luteal cells that interfere with normal ovulation.Low thyroxine levels have a positive feedback on thyroid-releasinghormone (TRH). Elevations in TRH have been associated with PRL elevation.It is believed that elevated PRL alters the pulsatility of gonadotropin-releasing hormone (GnRH) and interferes with normal ovulation.

Therefore, severe forms of hypothyroidism rarely complicate pregnancy because they are associated with anovulation and infertility.

Even if an association exists between low thyroid function and pregnancy loss, direct evidence for a causal role is missing.One postulated explanation for this relationship is that LPD has been linked to thyroid hypofunction.

A study of thyroid function and pregnancy outcome in 2009 demonstrated a positive linear relationship between fetal loss and maternal thyroid-stimulating hormone (TSH) levels assayed in healthy women, without overt thyroid dysfunction.Surprisingly, in this study any association was found between FT4 levels and subsequent risk of child loss in these women.

We believe it is prudent to screen for thyroid disease and normalize thyroid function prior to conception when function is found to be abnormal. Even if there is no clear cause–effect relationship between hypothyroidism and RPL, there is some evidence that subclinical hypothyroidism is correlated with poor maternal outcome as well as prematurity and reduced intelligence quotient in the offspring.

There is disagreement as to the suitable upper limit of normal serum TSH in order to make the diagnosis of subclinical hypothyroidism. There is a trend with the new TSH assays to decrease the upper limit of normal TSH (range, 4.5 to 5.0 mU/L) to 2.5 mU/L. This upper limit is recommended by the National Academy of Clinical Biochemistry guideline, and based on the fact that 2.5 mU/L represents more than 2 standard deviations above meticulously screened euthyroid volunteers.Clearly, this new upper limit

will significantly increase the number of patients diagnosed with subclinical hypothyroidism, and its clinical benefit remains questionable.

Thyroid peroxidase antibody

Thyroid peroxidase is a poorly glycosylated membrane-bound enzyme, responsible for iodine oxidation and iodination of thyrosyl residues of the Tg molecule ` It had been termed microsomal antigen based on its intracellular localization. Antibodies react against conformational epitopes at the surface of the molecules and against linear epitopes . Polyclonal antibodies from healthy individuals and patients are directed against the same epitopes.

Anti-TPO antibodies from healthy subjects did not block TPO activity or interfere with the blocking activity of anti-TPO antibodies from AITD patients , while anti-TPO antibodies from AITD patients can fix complement, destroy thyrocytes, and act as competitive inhibitors of enzymatic activity . These antibodies can be of any class of IgG, although some studies indicated a higher prevalence of IgG1 (70%) and IgG4 (66.1%) compared to IgG2 (35.1%) and IgG3 (19.6%).

Low levels of IgA antibodies have also been reported . Anti-TPO antibodies are more common than anti-Tg antibodies and more indicative for thyroid disease. Anti-TPO antibodies are inductors of oxidative stress evidenced by decreased antioxidant potential, advanced glycosylation

products and oxygen metabolites in blood . However, their contribution to thyroid damage compared to T cell and cytokine-mediated apoptosis is minor . Anti-TPO antibodies are detected in 90–95% of AITD patients, 80% of GD, and 10–15% of non-AITD patients.

While anti-TPO antibodies may act cytotoxic on thyrocytes in HT they do not have an established role in GD. Anti-TPO antibodies are able to cross the placenta barrier to variable extent, but the effect on the neonate is unclear. Concerns on a potential negative effect on cognitive development of the offspring have not been confirmed so far.

Symptoms can be mild, and patients might not seek medical advice. Even when treatment has been initiated, titers of anti-TPO antibodies decrease only slowly (e.g., over 5 years) upon treatment with levothyroxine, and anti-TPO antibody titers remain in the pathological range. Normal anti-thyroid antibody titers are lower for anti-TSHR antibodies than for anti-TPO and anti-Tg antibodies.

Thyroid Autoimmunity and Pregnancy Loss

Autoimmune thyroid disease is the most common endocrine disorder in women of reproductive age with an overall prevalence in women of 10 to 15%38 and among pregnant women, autoimmune thyroid disease has a prevalence of 5 to 20%.39 In recent years many studies have found an association between thyroid autoimmunity (TA) and recurrent abortions;

moreover it has been suggested that thyroid autoantibodies may be employed as a marker for at-risk pregnancies.

Many studies have linked TA with recurrent miscarriages, although the mechanism involved is unclear. Despite this, three mechanisms have been postulated to explain the possible association between TA and early pregnancy loss:

(1) the presence of thyroid autoantibodies reflects a generalized activation of the immune system and a generally heightened autoimmune reactivity against the feto-placental unit

(2) The presence of thyroid autoantibodies may act as an infertility factor and may delay conception. Thus, when women with thyroid autoantibodies do become pregnant, they are older and have a higher risk of miscarriage

(3) The presence of thyroid autoantibodies in euthyroid women may be linked with a mild deficiency in thyroid hormone concentrations or a lower capacity of the thyroid gland to adapt to the demands of the pregnancy state.

Indeed, the mean serum TSH values, while being within normal range, were significantly higher in thyroid autoantibody positive women compared to women with negative thyroid autoantibodies. This may reflect lower thyroidal reserve during pregnancy when a greater amount of thyroid hormones is demanded.However, the various hypotheses mentioned above are not contradictory to each other, so it is possible that the mechanisms explained act in concert.

Thyroxine administration seems to be effective in reducing the number of miscarriages when given during the early stages of pregnancy, because miscarriages with maternal thyroid autoimmunity generally occur within the first trimester.Poppe et al. have proposed that serum TSH, free FT4 and thyroid autoantibodies should be measured in early gestation. When serum TSH is elevated or free FT4 is below normal, levothyroxine (LT4) should be administered during pregnancy.

In women with thyroid autoantibodies and serum TSH <2 mU/L, LT4 treatment is not warranted; however, serum TSH and free FT4 should be measured later in gestation, preferably at the end of the second trimester. For women with thyroid autoantibodies and TSH between 2 and 4 mU/L in early gestation, treatment with LT4 should be considered. It is important to consider that serum TSH is downregulated during the first half of gestation by hCG.47 However, further studies are required to understand if all women with positive thyroid autoantibodies should be started on LT4 therapy during their pregnancies to decrease miscarriage rate.

AIM OF THE STUDY

The aim of the study was to find out the association between Anti-TPO antibody and recurrent miscarriages

To evaluate obstetric complications such as Pre Eclampsia and Preterm labour in them

REVIEW OF LITERATURE

1. L. Mehran,1 M. Tohidi, F. Sarvghadi, H. Delshad, A. Amouzegar,O. P. Soldin, and F. Azizi in a study of Management of Thyroid Peroxidase Antibody Euthyroid Women in Pregnancy: Comparison of the American Thyroid Association and the Endocrine Society Guidelines concluded that The current available data regarding associations between thyroid autoantibodies and spontaneous or recurrent pregnancy loss and preterm delivery is convincing. However, the reduction of these complications by treatment with LT4 supplementation is less robust. The evidence is not conclusive enough to recommend screening for thyroid autoantibodies or for the treatment of euthyroid women who are positive for thyroid autoantibodies during pregnancy. Both sets of guidelines discussed here are of high quality, and there does not seem to be contradiction or disagreement between the recommendations of the American Thyroid Association (2011) and of the Endocrine Society (2012) on the screening and management of women with thyroid autoantibodies in pregnancy. They suggested that either one of the two guidelines may be used by clinicians for appropriate and up-to-date management of thyroid autoimmunity during pregnancy.

2. Alex Stagnaro-Green, MD; Sheila H. Roman, MD; Rhoda H. Cobin, MD; et al in a study of Detection of At-Risk Pregnancy by Means of Highly Sensitive Assays for Thyroid Autoantibodies screened 552 women who

presented to their obstetrician in the first trimester of pregnancy using highly sensitive enzyme-linked immunosorbent assays for the presence of thyroglobulin and thyroidperoxidase autoantibodies and found an incidence of positivity of 19.6%. The tendency to secrete detectable levels of thyroid autoantibodies was significantly correlated with an increased rate of miscarriage. Thyroid autoantibody—positive women miscarried at a rate of 17%, compared with 8.4% for the autoantibody-negative women. Individual levels of thyroglobulin and thyroidperoxidase autoantibodies were similarly related to this increased miscarriage rate, with no evidence of autoantibody specificity in the relationship. Furthermore, the increase in miscarriages could not be explained by differences in thyroid hormone levels, the presence of cardiolipin autoantibodies, maternal age, gestational age at the time of maternal entry into the study, or previous obstetric history and concluded that thyroid autoantibodies are an independent marker of "at-risk" pregnancy.

3. MF Prummel and WM Wiersinga in a study of Thyroid autoimmunity and miscarriage in European Journal of Endocrinology with aim to ascertain the strength of the association between thyroid autoimmunity and miscarriage, performed a meta-analysis of both case-control and longitudinal studies performed since 1990 when this association was first described. A clear association between the presence of thyroid antibodies

and miscarriage was found with an odds ratio (OR) of 2.73 (95 % confidence interval (CI), 2.20-3.40) in eight case-control and ten longitudinal (OR, 2.30; 95 % CI, 1.80-2.95) studies. This association may be explained by a heightened autoimmune state affecting the fetal allograft, of which thyroid antibodies are just a marker. Alternatively, the association can be partly explained by the slightly higher age of women with antibodies compared with those without (mean+/-S.D. age difference, 0.7+/-1.0 years; P<0.001). A third possibility is mild thyroid failure, as thyroid-stimulating hormone (TSH) levels in antibody-positive but euthyroid women are higher than in antibody-negative women: difference 0.81+/-0.58 mU/l (P=0.005). Randomized clinical trials with l-thyroxine (aiming at TSH values between 0.4 and 2.0 mU/l) and with selenium (to decrease antibodies against thyroid peroxidase) are clearly needed to elucidate further the nature of this association.

4. Thyroid autoimmunity and the risk of miscarriage Alex Stagnaro-Green, Daniel Glinoer in a study Thyroid autoimmunity and the risk of miscarriage concluded that in approximately one-third of all pregnancies end in miscarriage. The etiology of recurrent abortion remains unknown in approximately 50% of all women. In the early 1990s it was discovered that unselected euthyroid women who present with thyroid antibodies (thyroid peroxidase and thyroglobulin) in the first trimester of pregnancy have a two–four-fold increase in their miscarriage rates. Although the etiology of

miscarriage in thyroid antibody women remains unknown, recent data have revealed a potential direct effect of thyroglobulin antibodies on pregnancy loss in a murine model. Uncontrolled studies assessing the effect of levothyroxine on decreasing the miscarriage rate in euthyroid antibody positive women, have demonstrated a decreased miscarriage rate.

5. Kris Poppe, Brigitte Velkeniers& Daniel Glinoer in a study of The role of thyroid autoimmunity in fertility and pregnancy found that Hypothyroidism influences ovarian function by decreasing levels of sex-hormone-binding globulin and increasing the secretion of prolactin. In women of reproductive age, hypothyroidism can be reversed by thyroxine therapy to improve fertility and avoid the need for use of assisted reproduction technologies. For infertile women, preparation for medically assisted pregnancy comprises controlled ovarian hyperstimulation that substantially increase circulating estrogen concentrations, which in turn can severely impair thyroid function. In women without thyroid autoimmunity these changes are transient, but in those with thyroid autoimmunity estrogen stimulation might lead to abnormal thyroid function throughout the remaining pregnancy period. Prevalence of thyroid autoimmunity is significantly higher among infertile women than among fertile women, especially among those whose infertility is caused by endometriosis or ovarian dysfunction. Presence of thyroid autoimmunity does not interfere with normal embryo implantation, but the risk of early miscarriage is substantially raised. Subclinical and overt

forms of hypothyroidism are associated with increased risk of pregnancy-related morbidity, for which thyroxine therapy can be beneficial. Systematic screening for thyroid disorders in pregnant women remains controversial but might be advantageous in women at high risk, particularly infertile women.

6. Roberto Negro, Gianni Formoso, TizianaMangieri, Antonio Pezzarossa, DavideDazzi, Haslinda Hassan in a study of Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications conducted in a total of 984 pregnant women; 11.7% were thyroid peroxidase antibody positive (TPOAb+). The TPOAb+ patients were divided into two groups: group A (n = 57) was treated with LT4, and group B (n = 58) was not treated. The 869 TPOAb− patients (group C) served as a normal population control group. Rates of obstetrical complications in treated and untreated groups were measured. They found that, at baseline, TPOAb+ had higher TSH compared with TPOAb−; TSH remained higher in group B compared with groups A and C throughout gestation. Free T4 values were lower in group B than groups A and C after 30 wk and after parturition. Groups A and C showed a similar miscarriage rate (3.5 and 2.4%, respectively), which was lower than group B (13.8%) [$P < 0.05$; relative risk (RR), 1.72; 95% confidence interval (CI), 1.13–2.25; and $P < 0.01$; RR = 4.95; 95% CI = 2.59–9.48, respectively]. Group B displayed a 22.4% rate of premature deliveries, which was higher than

group A (7%) ($P < 0.05$; RR = 1.66; 95% CI = 1.18–2.34) and group C (8.2%) ($P < 0.01$; RR = 12.18; 95% CI = 7.93–18.7). They concluded that the Euthyroid pregnant women who are positive for TPOAb develop impaired thyroid function, which is associated with an increased risk of miscarriage and premature deliveries. Substitutive treatment with LT4 is able to lower the chance of miscarriage and premature delivery.

7. R. Negro, G. Formoso, L. Coppola, G. Presicce, T. Mangieri, A. Pezzarossa, D. Dazzi in a study of Euthyroid women with autoimmune disease undergoing assisted reproduction technologies: The role of autoimmunity and thyroid function to assess if patients with autoimmune thyroid disease undergoing assisted reproduction technologies (ART) are afflicted by poor pregnancy and/or delivery rate and if the outcome is conditioned by pre-ART thyroid status. The study was retrospective (from January 2000 to January 2005) and was carried out at the Division of Physiopathology of Human Reproduction. Women who underwent ART were tested for TSH, free T4 (FT4), thyroid peroxidase antibodies (TPOAb) before and during pregnancy. A total of 416 euthyroid women were selected; 42 (10.1%) were TPOAb (+). Women >35 yr were excluded. The endpoints were pregnancy and delivery rates. Results: no differences in pregnancy and delivery rates were observed between women with and without antibodies. In TPOAb (+), women who failed to become pregnant or miscarried displayed higher TSH values before ART (2.8 mlU/l) compared to the ones who delivered (1.6

mlU/l; p=0.032) and compared to TPOAb (−) (1.1 mlU/l; p=0.018). Conclusions: in euthyroid women undergoing ART the pregnancy and delivery rates are not affected by the presence of TPOAb. In TPOAb (+) high-normal TSH values are associated with increased risk of unsuccessful pregnancy or subsequent miscarriage.

8. F.H. Rushworth, M. Backos, R. Rai I.T. Chilcott, N. Baxter L. Regan in a study of Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies with a purpose to determine the prevalence of thyroid antibodies in women with recurrent miscarriage and to observe whether their presence was predictive of future pregnancy outcome. A total of 870 consecutive, non-pregnant women with a history of three or more pregnancy losses and normal parental karyotypes were investigated for the presence of thyroglobulin antibodies (TgAb) and for thyroid microsomal antibodies (TmAb). Thyroid antibodies were found in 162 (19%) women. TgAb only were found in eight women (5%); TmAb only in 98 (60%) and both TgAb and TmAb were found in 56 (35%). Thirteen women had a history of thyroid disease and a further 15 women were found to have abnormal thyroid function. All 28 were excluded from the pregnancy outcome study. Among the remaining 134 thyroid antibody positive women, 36 women were not tested and normal thyroid stimulating hormone results were obtained for 98. In the group proven euthyroid, 14 of 24 untreated pregnancies resulted in live births (58%). Among the 710 thyroid

antibody negative women, 47 of 81 untreated pregnancies resulted in live births (58%). The future risk of pregnancy loss in women with unexplained recurrent miscarriage is not affected by their thyroid antibody status.

9. Amir Iravani, Maryam Saeedi, JalilPakravesh, SepehrHamidi, MehrshadAbbasi in Thyroid Autoimmunity and Recurrent Spontaneous Abortion in Iran: A Case-Control Study with objective to determine the association of thyroglobulin antibodies (TG-Ab) and thyroid peroxidase antibodies (TPO-Ab) with recurrent spontaneous abortion in a euthyroid, nonpregnant population of women in Iran. This case-control study conducted between November 2003 and September 2006 in Tehran, Iran, nonpregnant women with a history of 3 or more consecutive pregnancy losses and age-matched, healthy parous women without a history of reproductive problems were assessed. Thyroid function tests were performed, which included assessment of thyroid-stimulating hormone, triiodothyronine, thyroxine, and the presence of TG-Ab and TPO-Ab. A total of 641 patients and 269 controls were included. Mean age (± SD) was 30.6 ± 6.4 years (range, 16-51 years) in the patient group and 30.05 ± 6.6 years (range, 18-48 years) in the control group. Thyroid antibodies were present in 157 of 641 patients (24.5%) and in 34 of 269 controls (12.6%) (P<.001). The presence of thyroid antibodies was significantly associated with recurrent abortion independent of the impact of age with an odds ratio of 2.24 (95% confidence interval, 1.5-3.35). They concluded that TG-Ab

and TPO-Ab were identified more frequently in women with recurrent abortions compared with controls, and thyroid autoimmunity was independently associated with a higher risk of recurrent abortion.

10. ShakilaThangaratinam, Alex Tan, Ellen Knox, Mark D Kilby, ArriCoomarasamy in a study of Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence with an objective to evaluate the association between thyroid autoantibodies and miscarriage and preterm birth in women with normal thyroid function and to assess the effect of treatment with levothyroxine on pregnancy outcomes in this group of women. The study design was Systematic review and meta-analysis. With Data sources Medline, Embase, Cochrane Library, and SCISEARCH (inception-2011) without any language restrictions. They used a combination of key words to generate two subsets of citations, one indexing thyroid autoantibodies and the other indexing the outcomes of miscarriage and preterm birth. The Study selection included Studies that evaluated the association between thyroid autoantibodies and pregnancy outcomes were selected in a two stage process. Two reviewers selected studies that met the predefined and explicit criteria regarding population, tests, and outcomes. Data synthesis Odds ratios from individual studies were pooled separately for cohort and case-control studies with the random effects model.

Results included 30 articles with 31 studies (19 cohort and 12 case-control) involving 12 126 women assessed the association between thyroid autoantibodies and miscarriage. Five studies with 12 566 women evaluated the association with preterm birth. Of the 31 studies evaluating miscarriage, 28 showed a positive association between thyroid autoantibodies and miscarriage. Meta-analysis of the cohort studies showed more than tripling in the odds of miscarriage with the presence of thyroid autoantibodies (odds ratio 3.90, 95% confidence interval 2.48 to 6.12; P<0.001). For case-control studies the odds ratio for miscarriage was 1.80, 1.25 to 2.60; P=0.002). There was a significant doubling in the odds of preterm birth with the presence of thyroid autoantibodies (2.07, 1.17 to 3.68; P=0.01). Two randomised studies evaluated the effect of treatment with levothyroxine on miscarriage. Both showed a fall in miscarriage rates, and meta-analysis showed a significant 52% relative risk reduction in miscarriages with levothyroxine (relative risk 0.48, 0.25 to 0.92; P=0.03). One study reported on the effect of levothyroxine on the rate of preterm birth, and noted a 69% relative risk reduction (0.31, 0.11 to 0.90). They concluded that the presence of maternal thyroid autoantibodies is strongly associated with miscarriage and preterm delivery. There is evidence that treatment with levothyroxine can attenuate the risks.

MATERIALS AND METHODS

RESERCH DESIGN

Case control observational study

STUDY SETTING

The study was conducted in the Institute of Social Obstetrics in madras medical college between March2017 to March 2018 . The Study approved by Ethical committee of the hospital

INCLUSION CRITERIA

Patients with history of recurrent miscarriages (more than 3 in first trimester)presenting to antenatal clinic in Madras Medical College.

EXCLUSION CRITERIA

Those with

1.anatomical uterine defects

2.Overt hypothyroid

3.Anti phospholipid antibody syndrome

4. other auto immune disorders

SAMPLE SIZE

100

METHOD

All patients provided written informed consent. 50 women who presented with history of recurrent miscarriage were taken as cases &50 mothers without such history were taken as controls.

Those with anatomic uterine defects, overt hypothyroidism, antiphospholipids syndrome and other autoimmune diseases were excluded from cases.

Under quality control and safety procedures for sample collection 10ml venous blood sample was collected in vaccutainertubes .Serum samples were sent for anti-TPO and TSH assay. Serum TSH levels were determined using Micro particle Enzyme Immunoassay (MEIA) kits.

Normal reference range in pregnancy for TSH: 0.35-2.5μIU/ml (as per our hospital reference value), values >2.5 μIU/ml were considered high for pregnancy. Anti- TPO antibodies quantitative determination was done using CLIA (Chemiluminescemt Immunoassay) kits . TPO levels >34 iu/ml were considered abnormal and these women were considered TPO+VE. Cases\ were evaluated for obstetrics complications such as

preeclampsia and preterm labour.

RESULTS AND DISCUSSION

The collected data were analysed with IBM.SPSS statistics software 23.0 Version.To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. To find the significance in categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact was used. In all the above statistical tools the probability value .05 is considered as significant level.

AGE:

A total of 100 patients were recruited for the study. 50 patients were in control group and 50 patients were case group.

The Age distribution among the patients.

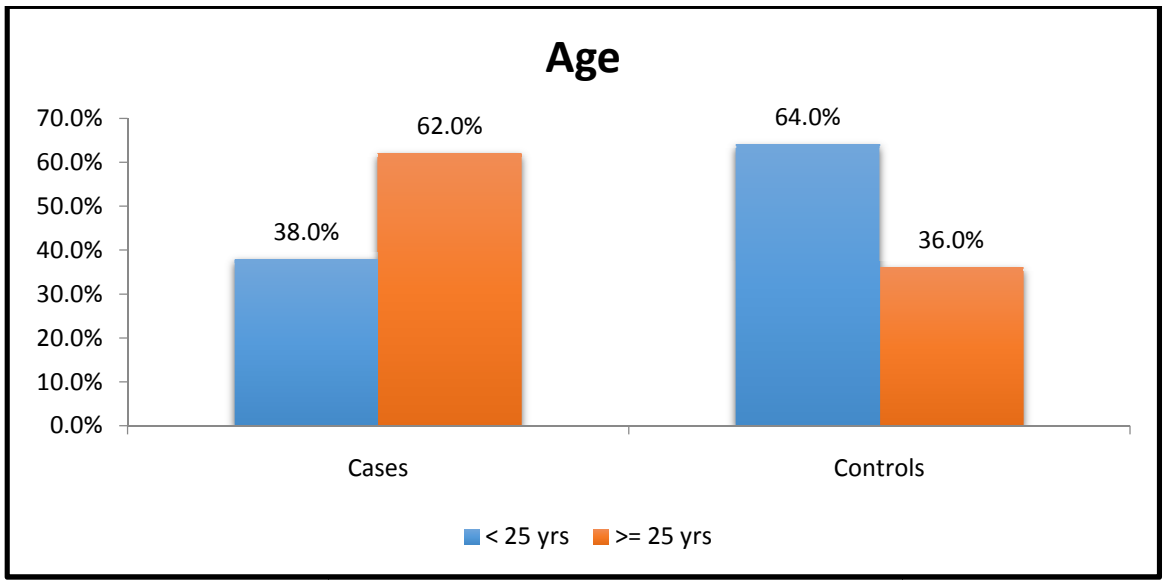
			Groups		**Total**
			Cases	**Controls**	
Age	< 25 yrs	Count	19	32	51
		%	38.0%	64.0%	51.0%
	>= 25 yrs	Count	31	18	49
		%	62.0%	36.0%	49.0%
P value Chi Square test			0.009		

Majority of the study subjects in control group were in the age group of <25 years (n=32, 51.0%) and in case group were in the age group of >=25 years (n=31, 62.0%).

Below the age group of 25 years 51 patients were recruited of which 19(38%) were in case group and 32 (64%) were in control group.

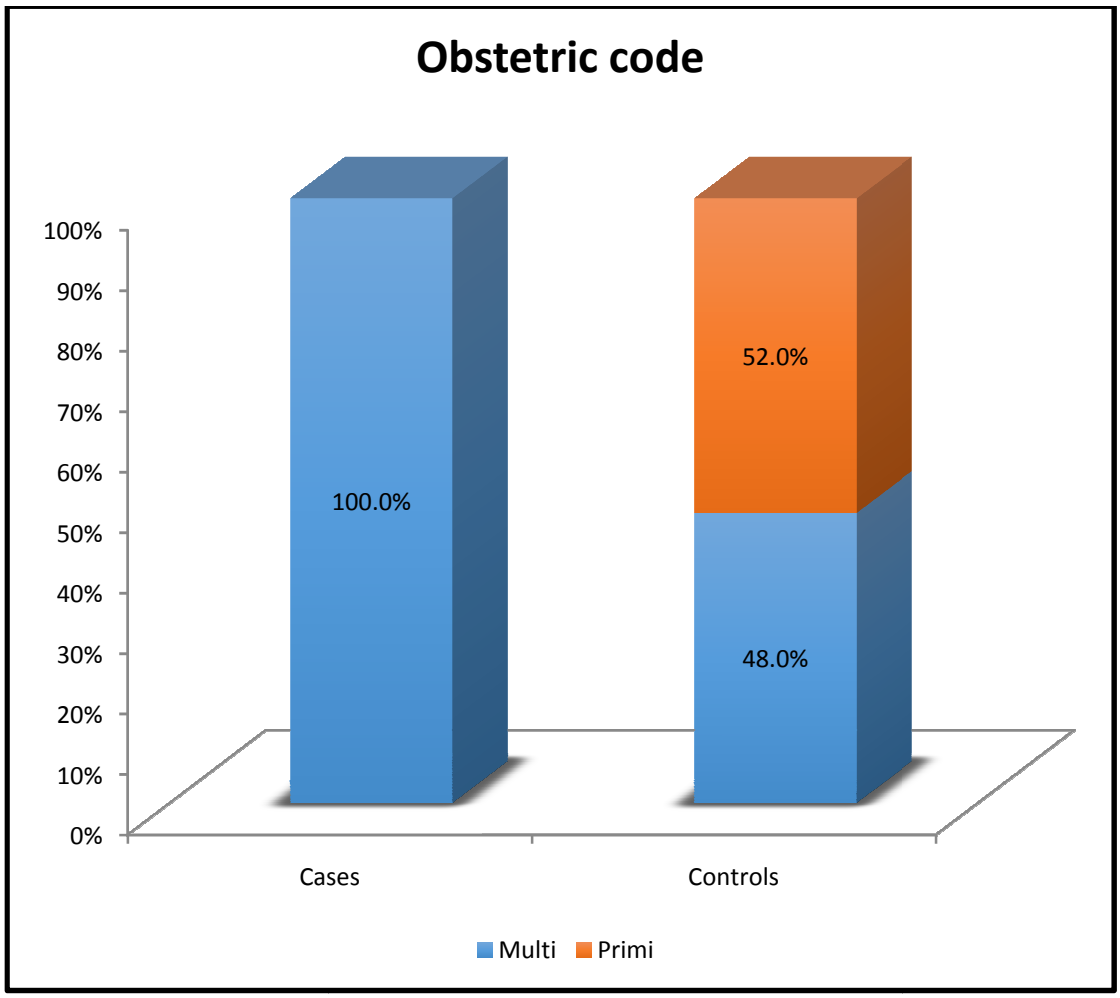
Above the age group of 25 years 49 patients were recruited of which 31 (62%) were in case group and 18 (36%).

The p value was 0.009 which is significant. The women with age more than 25 years are at a higher risk for abortions. The mean age



OBSTETRIC CODE:

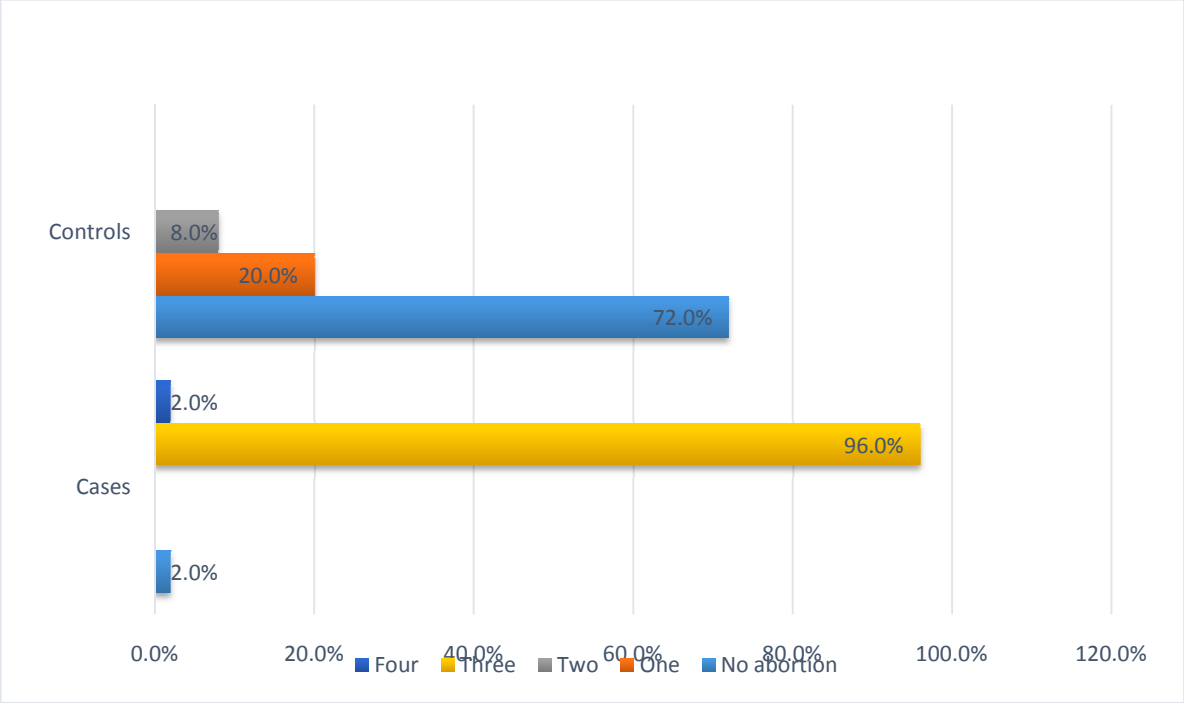
			Groups		Total
			Cases	**Controls**	
Obst code	MULTI	Count	50	24	74
		%	100.0%	48.0%	74.0%
	PRIMI	Count	0	26	26
		%	0.0%	52.0%	26.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%



In the control group of the 50 patients 24 (48%) were Multigravida and 26 (52%).

ABORTION HISTORY

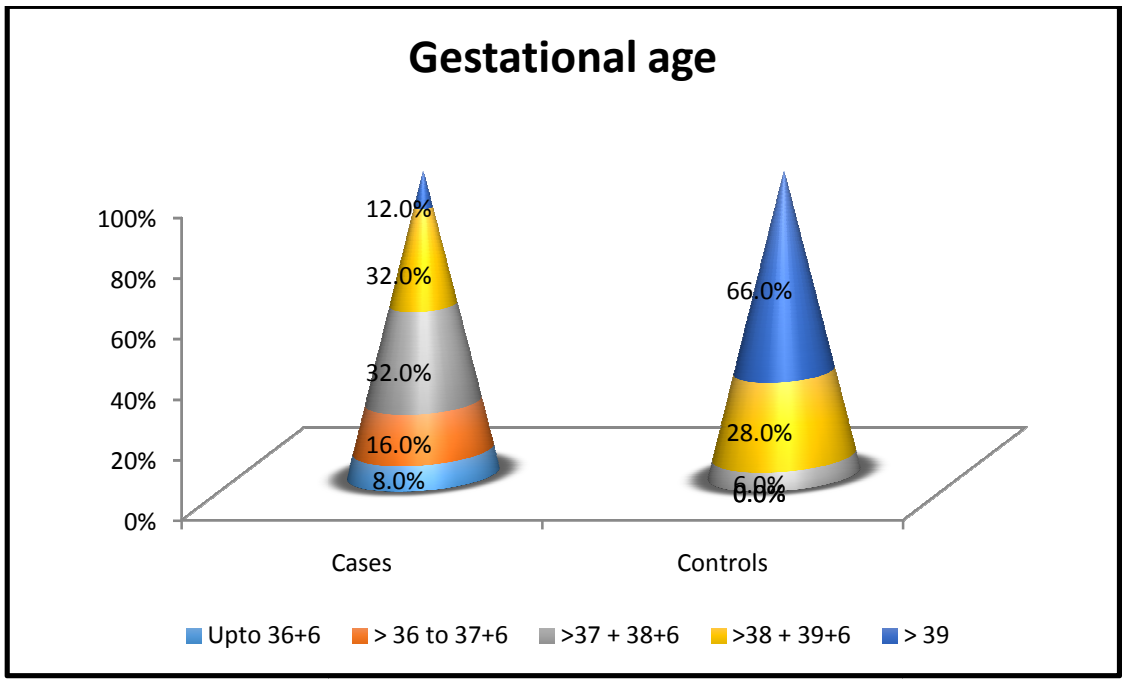
			Groups		Total
			Cases	**Controls**	
ABORTIONS	0	Count	0	36	36
		%	0.0%	72.0%	36.0%
	1	Count	0	10	10
		%	0.0%	20.0%	10.0%
	2	Count	0	4	4
		%	0.0%	8.0%	4.0%
	3	Count	48	0	48
		%	96.0%	0.0%	48.0%
	4	Count	2	0	2
		%	4.0%	0.0%	2.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%



The P Value is 0.0005. The p Value is significant. Case population history of abortions is found to be significant than control population.

GESTATIONAL AGE AT THE TIME OF DELIVERY

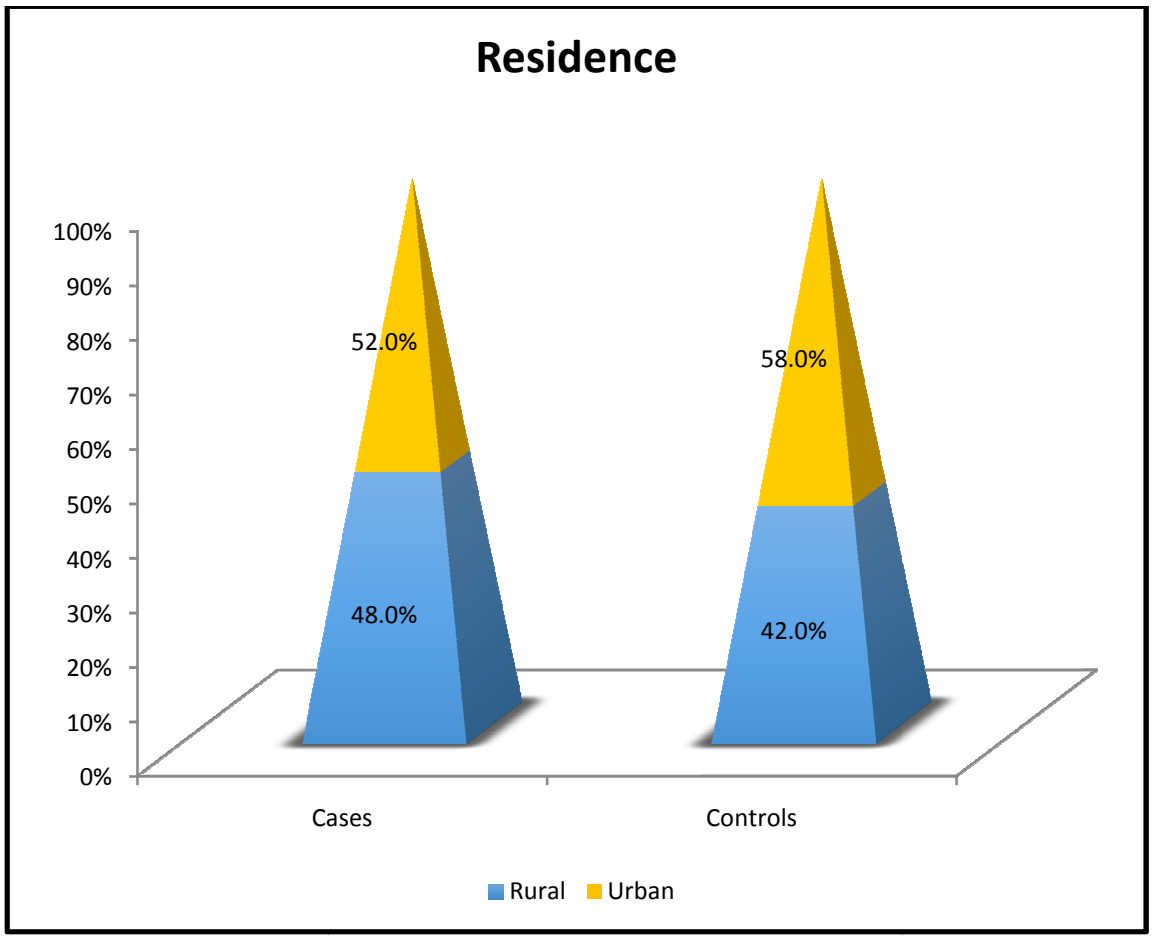
			Groups		Total
			Cases	**Controls**	
GA	Upto 36+6	Count	4	0	4
		%	8.0%	0.0%	4.0%
	> 36 to 37+6	Count	8	0	8
		%	16.0%	0.0%	8.0%
	>37 + 38+6	Count	16	3	19
		%	32.0%	6.0%	19.0%
	>38 + 39+6	Count	16	14	30
		%	32.0%	28.0%	30.0%
	> 39	Count	6	33	39
		%	12.0%	66.0%	39.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%



In the case group 4 (8%) patients were in the preterm group. the p Value is 0.0005. Patients with recurrent spontaneous abortion have a significant chance of having preterm labour.

THE PLACE OF RESIDENCE

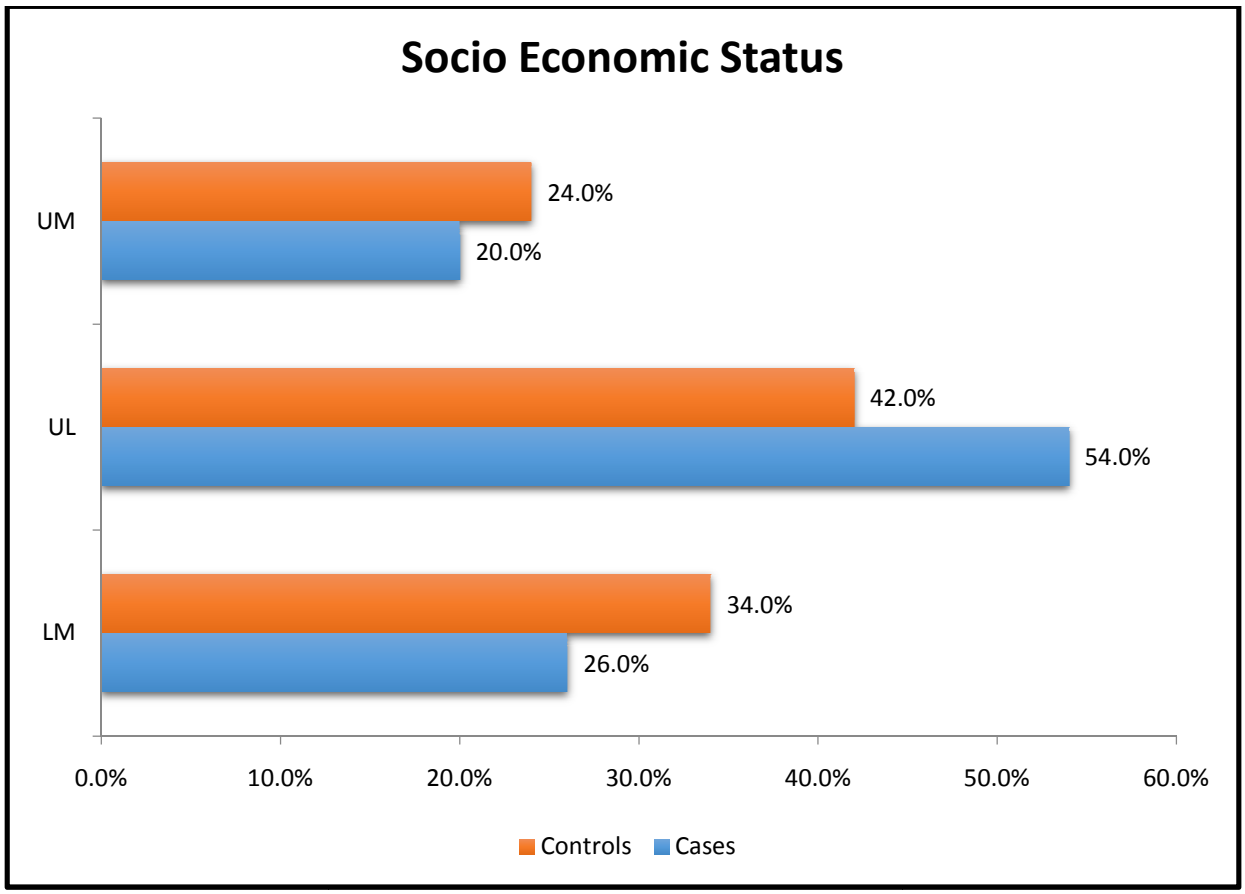
			Groups		Total
			Cases	**Controls**	
RESIDENCE	Rural	Count	24	21	45
		%	48.0%	42.0%	45.0%
	Urban	Count	26	29	55
		%	52.0%	58.0%	55.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%



Of the Total 100 patients in the study 45 patients were from the rural population and 55 patients were in urban population. This shows that the place of residence is insignificant with recurrent spontaneous miscarriage.

SOCIO ECONOMIC STATUS

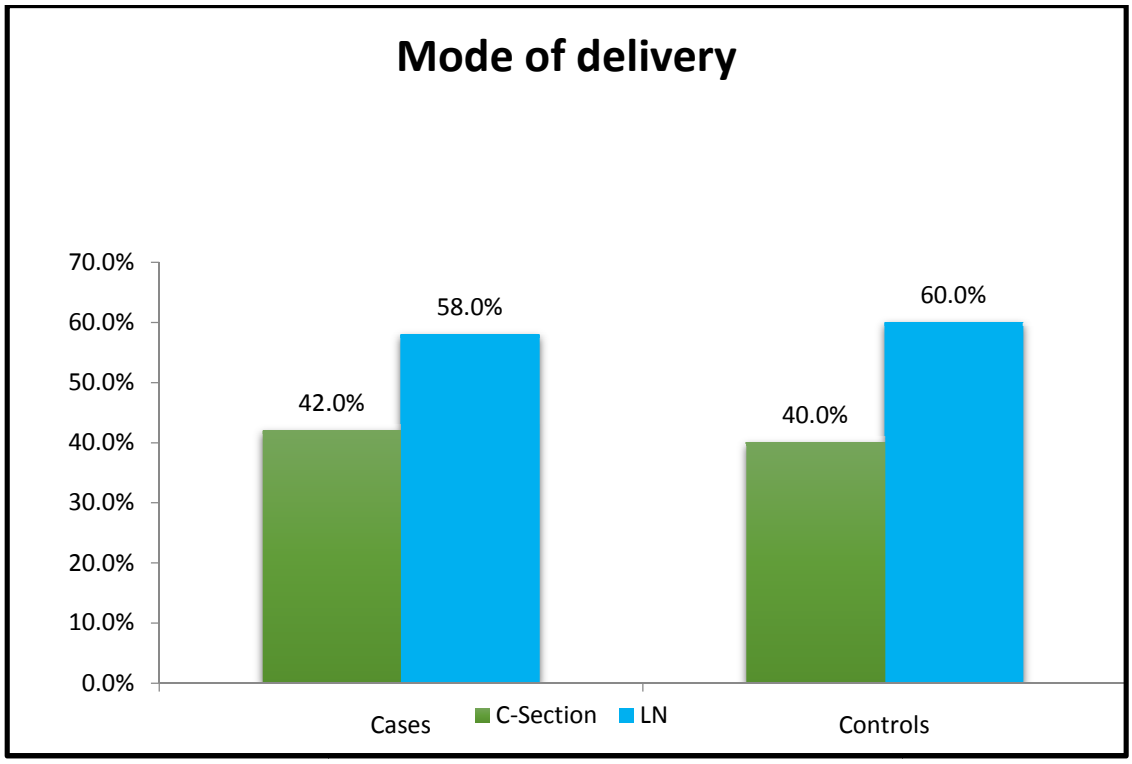
			Groups		Total
			Cases	Controls	
socio economic status	LM	Count	13	17	30
		%	26.0%	34.0%	30.0%
	UL	Count	27	21	48
		%	54.0%	42.0%	48.0%
	UM	Count	10	12	22
		%	20.0%	24.0%	22.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%



Out of 100 patients 30% were in low middle class, 48% were in upper lowerclass , 22 % in upper middle class . Thus, socio economic status found be insignificant in recurrent spontaneous miscarriage.

Bar diagram showing Socio economic status

Mode of delivery

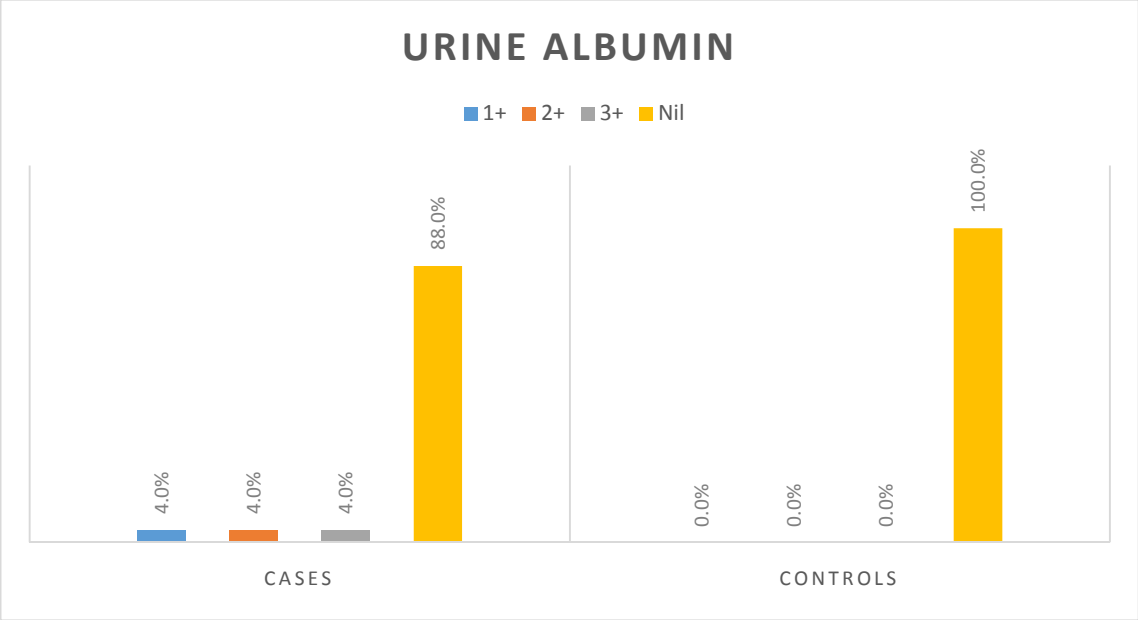


In case group Labour natural was 42% and caesarean section was 58%.

In control group labour natural was 40% and casesarean section 60%.

URINE ALBUMIN

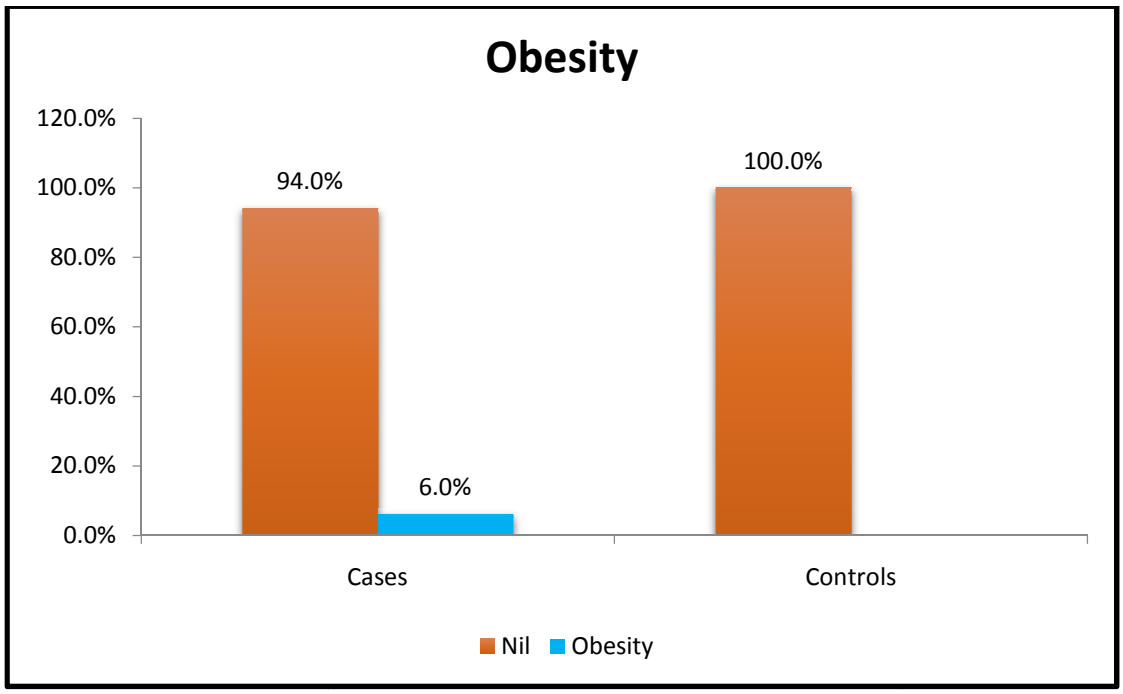
			Groups		Total
			Cases	Controls	
urine albumin	1+	Count	2	0	2
		%	4.0%	0.0%	2.0%
	2+	Count	2	0	2
		%	4.0%	0.0%	2.0%
	3+	Count	2	0	2
		%	4.0%	0.0%	2.0%
	Nil	Count	44	50	94
		%	88.0%	100.0%	94.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%



Urine albumin was found to be more than 1+ in 12% in case group. among the case group 4% were urine albumin 1+, 4 % were 2+, 4% were 3 +.

MATERNAL RISK FACTORS

			Groups		
			Cases	**Controls**	**Total**
COMORBIDITIES	Nil	Count	47	50	97
		%	94.0%	100.0%	97.0%
	Obesity	Count	3	0	3
		%	6.0%	0.0%	3.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%

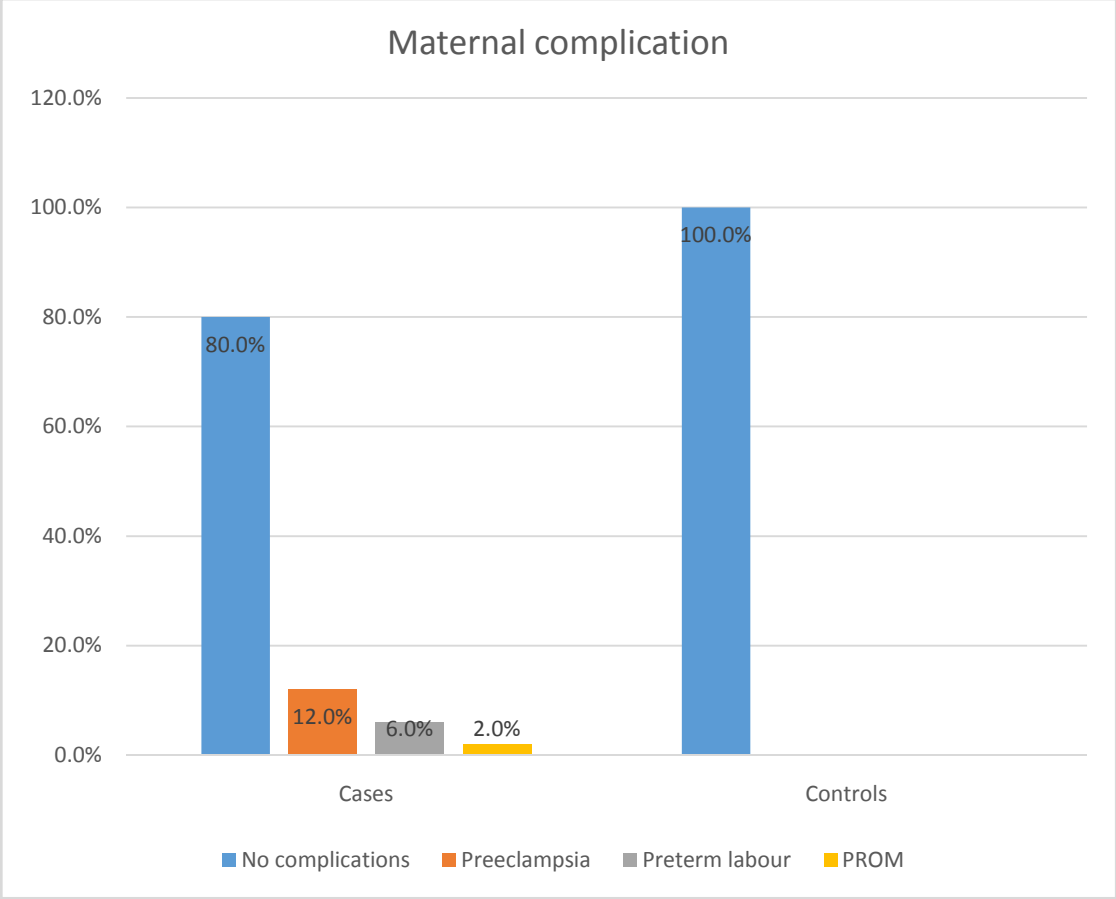


In case group only 6% of the population. (Obese – BMI >25). Obesity was statistically insignificant with recurrent spontaneous miscarriage.

MATERNAL COMPLICATIONS:

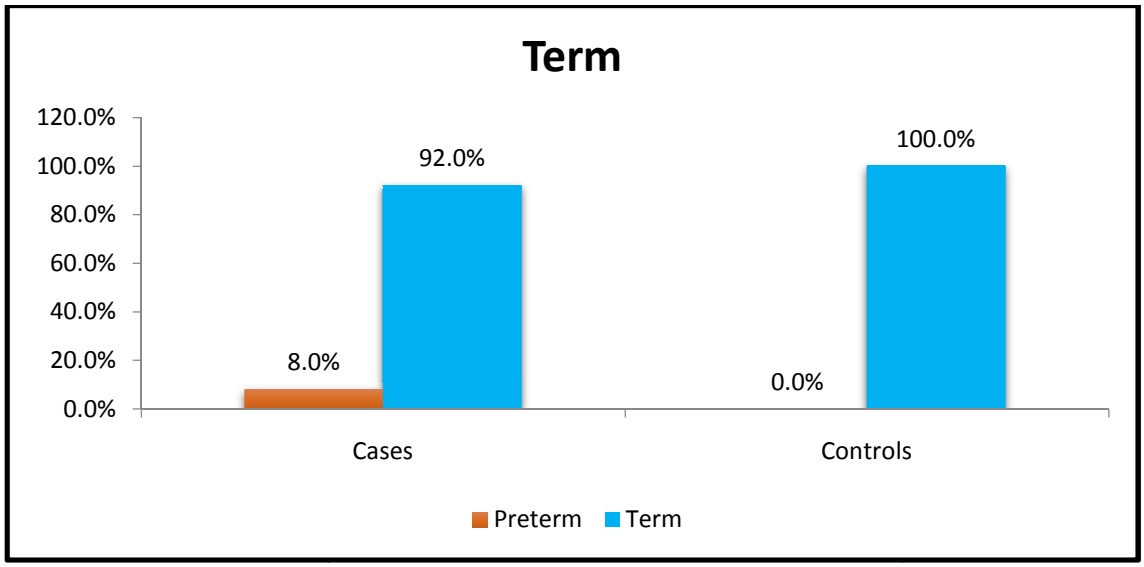
			Groups		Total
			Cases	Controls	
Maternal complication	No complications	Count	40	50	90
		%	80.0%	100.0%	90.0%
	Preeclampsia	Count	6	0	6
		%	12.0%	0.0%	6.0%
	Preterm labour	Count	3	0	3
		%	6.0%	0.0%	3.0%
	PROM	Count	1	0	1
		%	2.0%	0.0%	1.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%

Preeclampsia was noted among 12% of mothers of with recurrent spontaneous miscarriages,. Preterm labour was noted in 6% of the case population and Preterm rupture of membranes was seen in 2% of the case population. The p value was 0.011. which is significant. The incidence of complication among women with recurrent spontaneous miscarriage is higher than the general population.



	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	11.111[a]	3	.011
Likelihood Ratio	14.976	3	.002
N of Valid Cases	100		

Pre -term labour



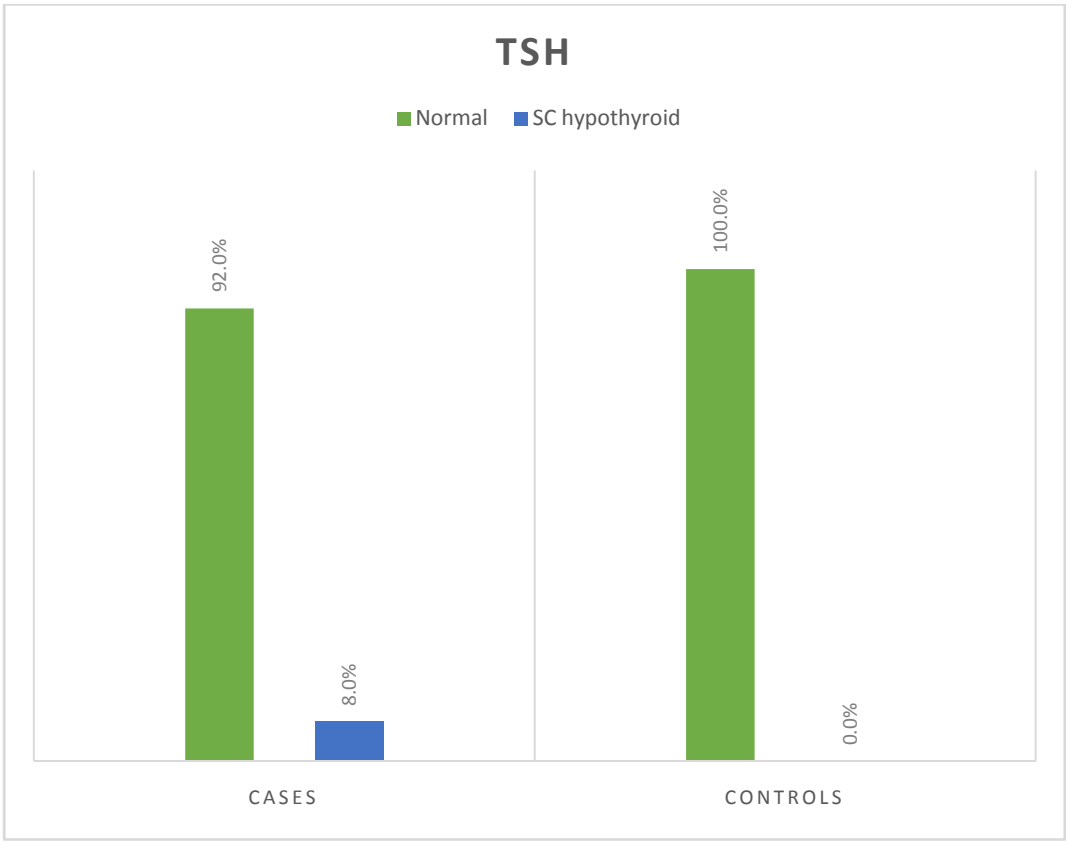
Out of 50 patients in RSM group 4(8%) developed preterm labour.

			Groups		Total
			Cases	Controls	
TERM	preterm	Count	4	0	4
		%	8.0%	0.0%	4.0%
	term	Count	46	50	96
		%	92.0%	100.0%	96.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%

TSH

			Groups		
			Cases	**Controls**	**Total**
TSH	Normal	Count	46	50	96
		%	92.0%	100.0%	96.0%
	Sub clinical hypothyroid	Count	4	0	4
		%	8.0%	0.0%	4.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%

OUT of 50 cases 4 (8%) of recurrent spontaneous miscarriages were found to be subclinical hypothyroid. TSH was found to normal in 46(92%)of RSM.


TSH
Normal
SC hypothyroid
92.0%
8.0%
100.0%
0.0%
CASES
CONTROLS

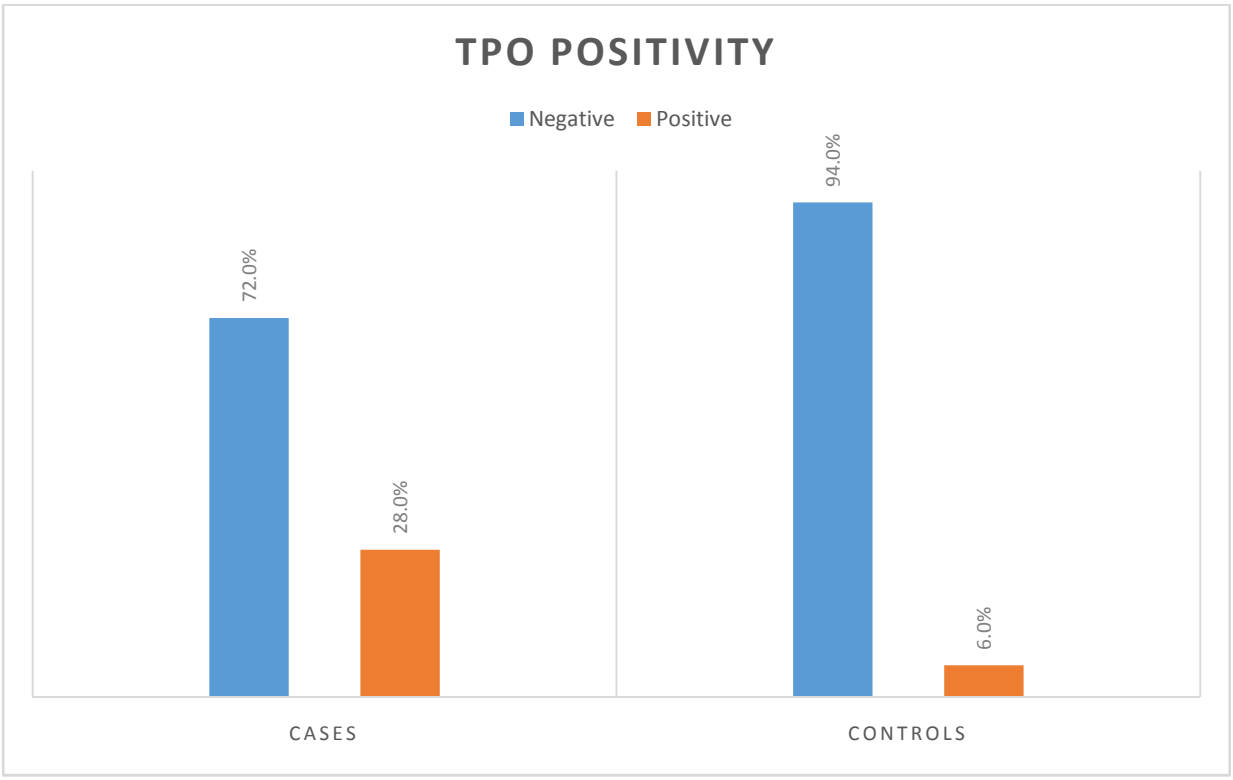
ANTI TPO POSITIVITY:

			Groups		Total
			Cases	**Controls**	
ANTI TPO POSITIVE	Negative	Count	36	47	83
		%	72.0%	94.0%	83.0%
	Positive	Count	14	3	17
		%	28.0%	6.0%	17.0%
Total		Count	50	50	100
		% within Groups	100.0%	100.0%	100.0%

Out of 50 patients in case group 14 (28%) were ANTI TPO positive and 36 (72%) were ANTI TPO negative.

Out of 50 patients in control group, 3(6%)were ANTI TPO POSITIVE and 47(94%)were ANTI TPO negative. P value 0.006 shows that ANTI TPO POSITIVITY were significant in RSM group.

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.575[a]	1	.003		
Continuity Correction[b]	7.087	1	.008		
Likelihood Ratio	9.185	1	.002		
Fisher's Exact Test				.006	.003
N of Valid Cases	100				



GROUP STATISTICS:

Groups		N	Mean	Std. Deviation	Std. Error Mean
AGE	Cases	50	25.92	2.702	.382
	Controls	50	24.18	1.380	.195
HEIGHT	Cases	50	158.50	5.100	.721
	Controls	50	158.72	6.075	.859
WEIGHT	Cases	50	69.06	8.594	1.215
	Controls	50	68.34	4.856	.687
SBP	Cases	50	113.80	14.576	2.061
	Controls	50	106.60	6.581	.931
DBP	Cases	50	72.10	11.819	1.671
	Controls	50	71.40	6.392	.904
BIRTH WEIGHT	Cases	50	2.917	.3599	.0509
	Controls	50	2.982	.3022	.0427

SUMMARY

The study population consisted of apparently healthy pregnant women with a history of unexplained recurrent miscarriage during the first trimester (5 – 13 weeks of gestation). Depending on the increased necessity of the thyroid gland for normal development, growth and metabolic homeostasis during in pregnancy and fetal life, changes associated with pregnancy require an increased availability of thyroid hormones by 40% to 100% in order to meet the needs of mother and fetus during pregnancy.

The relation of the thyroid antibodies with miscarriage is an important issue that has attracted the interest of many investigators. A number of researches have been published concerning the relation of thyroid autoimmunity and miscarriage which include healthy women, women with recurrent miscarriage and those undergoing assisted reproductive techniques. All these studies are not easily comparable due to the different selection criteria employed for specific aims for each study, but most studies have shown a significant positive association between the presence of thyroid autoantibodies and miscarriage rate.

It was suggested that those autoantibodies, which can also be higher in the euthyroid patients, may produce a threat for miscarriage in the subsequent pregnancy. Thyroid peroxidase antibodies target the thyroid peroxidase enzyme that assists in the production and metabolism of thyroid

hormone. Although they are widely seen in autoimmune thyroid disorders, thyroid peroxidase antibodies are not necessarily a sign of disease. In up to 26 percent of healthy women, low levels of TPO antibodies are seen. In our study the control group the TPO was positive in among 6 percent of the study population.

In the normal healthy population, when TPO antibodies are accompanied by a higher TSH level (> 2.0 mu/L); they suggest an increased risk for developing Hashimoto's thyroiditis. In spite of many studies available regarding the physiological changes in the thyroid function during pregnancy, it is uncertain if functional disorders of the thyroid gland play a role in the aetiology of spontaneous miscarriages. However, this study was about evaluating the thyroid peroxidase antibody in recurrent spontaneous miscarriage, risk factors and the obstretric complication in the study population.

In our study showed the mean age of was 25.92 in case population and in control population was 24.18. In our that significant correlation the age of the women and the incidence recurrent spontaneous miscarriages.

The mean height was 158.5 cm in cases and 158.72 cm in controls. The weight 69.06 kg in cases and 68.34 kg in control group. The was no significance about the of height and weight of the women with recurrent spontaneous miscarriage

The residence of the women has no significance with recurrent spontaneous miscarriage. In our study the case population resided in urban was 52% and in rural 48% and in the control population the urban was 58% and rural population was 42%.

There was no significance with socioecomic status of the women.

In the case group 12 (6) percentage developed preeclampsia. Among these 6 women 2 women had severe preeclampsia. These 2 women developed severe preeclampsia at 37 weeks of gestation and pregnancy was terminated. Urine albumin was 3+ in 2 women. Urine albumin was 1+ and 2 + was seen in 4 women. Among the 6 women who developed preeclampsia 4 patients were ANTI TPO positive.

Three women developed preterm labour. One women at 35Weeks and other two at 36 all three women had vaginal delivery and babies had good apgar. Among these 3 women who had preterm labour 2 patients had ANTI TPO positive after ruling out other causes of Pre term labour.

Among case population one women developed PREMATURE RUPTURE OF at MEMBRANES AT 38 weeks and delivered by caesarean delivery with good apgar and the women was ANTI TPO POSITIVE.

In our study the incidence of subclinical hypothyriods was 4%.The ANTI TPO positive in a total of 17, patients in the case population 14

patient were anti TPO positive and 3patients were ANTI TPO positive in the control population. The p value was 0.006. The TPO positivity is significant in the recurrent spontaneous miscarriage.

In our study the prevalence of TPO positivity was higher in women with history of RSM than those with uneventful pregnancy history. Again those with TPO positive have higher prevalence of subclinical hypothyroidism.

Thyroid hormones are essential for the developing fetus. Hence a pregnant woman needs thyroxine more than non-pregnant lady to provide T4 to both herself and her developing fetus. The fetus's thyroid gland is not fully functional until after 12 weeks of pregnancy. If the mother does not have sufficient thyroid hormones, she may be at increased risk of miscarriage. Since the majority of women are not sure that they are pregnant until four to six weeks after the last menstrual period, they do not go to see doctors and test their thyroid function until the first trimester is more than half over.

It is advisable to suggest thyroid investigation to the pregnant women with history of recurrent miscarriage as soon as possible after knowing they are pregnant. Management of thyroid diseases during pregnancy requires special considerations because pregnancy induces major changes in thyroid function, and maternal thyroid disease can have adverse effects on the

pregnancy and the fetus. Care requires coordination among several healthcare professionals.

Avoiding maternal and fetal thyroid dysfunction is of major importance because of potential damage to fetal neural development, an increased incidence of miscarriage, and preterm delivery.

CONCLUSION

Thyroid autoimmunity and subclinical hypothyroid can be considered as risk marker for recurrent spontaneous miscarriage. Euthyroid women in early stage of pregnancy with TPO antibody positive are still at risk of developing hypothyroidism later. There serum TSH level needs to monitored.

The TSH levels were found to be normal in miscarriage women compared with healthy pregnant women. The feedback mechanism of thyroid-pituitary glands is profound or not properly works in recurrent miscarriage women.

The thyroid antibodies can only affect pregnant women when their serum TSH level is relatively within the actual normal range.

The total thyroid hormones (TT4 and TT3) as well as decreased in recurrent miscarriage women compared to the control subjects.

Most of women with recurrent miscarriage were euthyroid

In patients with recurrent miscarriage and if all the other work up for recurrent pregnancy loss have turned out to be negative then tests for detecting anti TPO should be considered even with normal TSH levels. And if anti TPO antibodies turns out to be positive, treatment with Tablet levothyroxine can be considered.

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ANNEXURES:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.K.Manjula
Post Graduate in M.S. O & G
Madras Medical College
Chennai 600 003

Dear Dr.K.Manjula ,

The Institutional Ethics Committee has considered your request and approved your study titled **"ANTI – THYROID PEROXIDASE POSITIVITY IN RECURRENT MISCARRIAGES AND ASSOCIATED OBSTETRIC COMPLICATIONS" - NO.16012017 (IV).**

The following members of Ethics Committee were present in the meeting hold on **31.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.S.Suresh,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PROFORMA

Name: Educational status:

Age:

Residence:

Socio economic status:

LMP:

DEE:

GA:

Obstetric history;

1st:

2nd:

3rd:

4th :

Present history:

h/o labour pain

h/o draining pv

h/o bleeding pv

h/o imminent symptoms

Past history:

Diabetes: Yes ( ) No ( )

Hypertension: Yes ( ) No ( )

Renal disease: Yes ( ) No ( )

Thyroid disorder: Yes ( )Hyper ( ) Hypo ( ). Other ( ) No ( )

Congenital abnormality: Yes ( ) No ( )

APLA positivity: Yes ( ) No ( )

Clinical examination:

Height	General condition:
Weight:	Pallor:
BMI:	Pedal edema:
Temperature:	Icterus:
BP:	
PR:	
RR:	

Systemic examination:

CVS:

RS:

Per abdomen:

Per speculum:

Per Vaginal:

Investigations

Urine albumin

TSH

FT3

FT4

ANTI TPO

Other routine investigations:

Maternal complication

MODE OF DELIVERY

LN ( ) C- SECTION ( )

FOETAL OUTCOME

Alive/

Term/ preterm

Boy/girl

Apgar

Birth weight

INFORMATION SHEET

We are conducting a study on **"ANTI-THYROID PEROXIDASE POSITIVITY IN RECURRENT MISCARRIAGE AND ASSOCIATED OBSTERICS COMPLICATIONS"** among the patients in Institute of Obstetrics and Gynaecology, Madras Medical College, Chennai and for that your clinical details may be valuable to us.

We are selecting certain patients and if you are found eligible, we may be using your clinical details in such a way so as to not affect your final report or management.

The privacy of the patient in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in the study is voluntary. You are free to decide whether to participate in the study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The result of the special study may be intimated to you at the end of the study period or during the study. If anything is found abnormal, which may aid in management or treatment.

Signature of Investigator: Signature of Participant:

Date :

நோயாளி தகவல் தாள்

மீண்டும் மீண்டும் கருச்சிதைவு ஏற்படுதலில் எதிர்ப்பு தைராய்டு பெராக்ஸிடேஸ் பாசிட்டிவிட்டி மற்றும் அதன் தொடர்புடைய மகப்பேறியல் சிக்கல்கள்

நோயாளிகளுக்கான தகவல் :

உங்களை இந்த ஆராய்ச்சியில் பங்கு கொள்ள அழைக்கிறோம். நாங்கள் உங்களுக்கு கொடுக்கும் இந்த படிவத்தில் உள்ள விவரங்களைக் கொண்டு நீங்கள் இந்த ஆராய்ச்சிக்கு உட்படலாமா அல்லது நிராகரிக்கலாமா என்பதை நீங்களே முடிவு செய்யலாம். மேலும் உங்களின் சந்தேகங்களையும் எங்களிடம் கேட்கலாம். நீங்கள் எங்கள் ஆராய்ச்சிக்கு தகுதி உள்ளவராகும் பட்சத்தில், சென்னை மருத்துவ கல்லூரியில்நடைபெறும் இந்த ஆராய்ச்சியில் உங்களை பங்கெடுத்துக்கொள்ள செய்வோம்.

CONSENT FORM

“ANTI-THYROID PEROXIDASE POSITIVITY IN RECURRENT MISCARRIAGE AND ASSOCIATED OBSTERICS COMPLICATIONS”

STUDY CENTRE :
Institute of Obstetrics and Gynaecology,
Madras Medical College, Chennai

PARTICIANT NAME: AGE:
MRD No.:

I confirm that I have understood the purpose of the procedure for the above study. I have an opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complication that may occur during the procedure. I understand that my participation in the study in voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the Ethics Committee will not need my permission to look at my health records both in the respective current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties of published, unless as required under the law. I agree not to restrict the use of any or results that arise from the study.

I hereby consent to participate in the study of **“ANTI-THYROID PEROXIDASE POSITIVITY IN RECURRENTMISCARRIAGE AND ASSOCIATED OBSTERICS COMPLICATIONS”**
SIGNATURE OF THE PARTICIPANT:
DATE :
PLACE:

NAME OF THE INVESTIGATOR:
INSTITUTION:

<u>சுய ஒப்புதல் படிவம்</u>

மீண்டும் மீண்டும் கருச்சிதைவு ஏற்படுதலில் எதிர்ப்பு தைராய்டு பெராக்ஸிடேஸ் ஆன்டிபாடி பாசிட்டி விட்டி மற்றும் அதன் தொடர்புடைய மகப்பேறியல் சிக்கல்கள்
ஆய்வு நடத்தபடும் இடம்: சென்னை மருத்துவக் கல்லூரி, சென்னை.

பங்குபெறுபவரின் பெயர் :
பங்குபெறுபவரின் வயது :

பங்குபெறுபவரின் எண் :

இந்த ஆய்வில் குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ அதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கையை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என்பதை அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் முடிவை பயன்படுத்திக்கொள்ள மறுக்கமாட்டேன்.

இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் சாட்சிகளின் கையொப்பம்

இடம் : இடம் :

தேதி : தேதி :

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் :

ஆய்வாளரின் கையொப்பம்

URKUND

Urkund Analysis Result

Analysed Document:	MANJU PLAGI (Repaired).docx (D42568255)
Submitted:	10/15/2018 1:00:00 PM
Submitted By:	manju19.k@gmail.com
Significance:	6 %

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