"STUDY OF PREVALENCE OF THYROID PEROXIDE ANTIBODIES IN PRETERM DELIVERIES, IUD AND RECURRENT PREGNANCY LOSS"

Dissertation submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the requirement

for the award of

M.S. DEGREE – BRANCH – II

OBSTETRICS AND GYNAECOLOGY

GOVT.KILPAUK MEDICAL COLLEGE
KILPAUK, CHENNAI.

MAY 2018

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"STUDY OF PREVALENCE OF THYROID PEROXIDE ANTIBODIES IN PRETERM DELIVERIES, IUD AND RECURRENT PREGNANCY LOSS"** is the bonafide original work of **Dr.N.SATHYA** under the guidance of **Dr.VANI, DCH., MD., OG.,** Professor of Department of Obstetrics and Gynaecology, KMCH, Chennai in Partial fulfilment of the requirements for MS Obstetrics and Gynaecology, Branch II examination of the Tamilnadu Dr.MGR Medical university to be held in May 2018 .The period of Postgraduate study and training is from June 2015 to May 2018.

Prof.Dr.M.S.SORNAM, , MD., DGO.,
Professor & Head,
Department of Obstetrics and Gynaecology,
Kilpauk Medical College & Hospital,
Chennai-600106.

Prof.Dr.VANI, DCH., M.D., OG.,
Guide
Department of Obstetrics and Gynaecology,
Kilpauk Medical College & Hospital,
Chennai-600106.

Prof.Dr.P.VASANTHAMANI,
M. D., D.G.O., MNAMS., DCPSY., MBA
DEAN,
Governmant Kilpauk Medical College and Hospital,
Chennai-600010

DECLARATION

I solemnly declare that this **"STUDY OF PREVALENCE OF THYROID PEROXIDE ANTIBODIES IN PRETERM DELIVERIES, IUD AND RECURRENT PREGNANCY LOSS"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr.VANI, DCH., MD., OG.,** Professor, Department of Obstetrics and Gynaecology, Government Kilpauk Medical College and Hospital, Chennai. This dissertation is submitted to **The Tamil Nadu Dr.M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.S. (Obstetrics and Gynaecology).**

Place: Chennai

Date: **(Dr.N.SATHYA)**

ACKNOWLEDGEMENT

I start this thesis in the name of Almighty God, the most beneficent and forgiving. I thank God for giving me the privilege to learn from the able teachers in my department.

I express my sincere thanks to **Prof.Dr.P.VASANTHAMANI, M.D., D.G.O., MNAMS., DCPSY., MBA,** Dean, Government Kilpauk Medical College for allowing me to conduct the study using the available facilities.

I convey my heartfelt gratitude and sincere thanks to our **HOD Dr.M.S.SORNAM, MD., DGO.,** Department of Obstetrics and Gynaecology, Kilpauk Medical College for her constant support and guidance throughout the course of my study and preparation of the dissertation.

I convey my heartfelt gratitude and sincere thanks to my guide Professor, **Dr.VANI, DCH., MD., OG.,** Department of Obstetrics and Gynaecology, Kilpauk Medical College who with her exhaustive knowledge and Professional expertise has provided able guidance and constant encouragement throughout the preparation of this dissertation.

I am grateful to my Assistant Professors, colleagues and my friends for their advice and suggestions.

My heartful thanks to my family and friends, who have been a constant source of encouragement and immense help, for instilling in me a sense of commitment and for their belief in me.

Last but not the least I thank all **my Patients**, who formed the backbone of this study without whom this study would not have been possible.

(Dr. N.SATHYA)

ABBREVATION

TSH	-	thyroid stimulating hormone
TPOAb	-	thyroid peroxidase antibodies
TRH	-	thyroid releasing hormone
ACOG	-	american college of obstetrics and gynecology
IVF	-	in vitro fertilisation
ART	-	assisted reproductive technology
IUD	-	intrauterine death

CONTENTS

INTRODUCTION

- Maternal thyroid changes are substantial and physiologically altered gland structure and function are sometimes confused with thyroid abnormalities.
- In pregnancy, maternal serum concentration of thyroid-binding globulin are increased concomitantly with total or bound thyroid hormone levels.
- Thyrotropin, currently plays a central role in screening and diagnosis of many thyroid disorders. Serum TSH levels in early pregnancy decline because of weak TSH – receptor stimulation from massive quantities of human chorionic gonadotropin secreted by placental trophoblast. Because TSH levels does not cross the placenta, it has no direct fetal effects. But thyroxine crosses the placenta.
- During the first 12 weeks of gestation ,when hCG serum levels are maximal ,thyroid hormone secretion is stimulated.
- The resulting increased serum free thyroxine levels act to suppress hypothalamic thyrotropin-releasing hormone(TRH) and in turn limit pituitary TSH secretion. Accordingly, TRH is undetectable in maternal serum.

- Conversely, beginning at mid pregnancy, TRH becomes detectable in fetal serum, but levels are static and do not increase with advancing gestation.

Throughout pregnancy, maternal thyroxine is transferred to the fetus. Maternal thyroxine is important for normal fetal brain development, especially before development of fetal thyroid gland function. And even though the fetal gland begins concentrating iodine and synthesizing thyroid hormone after 12 weeks gestation, maternal thyroxine contribution remains important. In fact maternal sources account for 30% of thyroxine in fetal serum at term. Developmental risks associated with maternal hypothyroidism after mid pregnancy, however remain poorly understood.

ANTI THYROID ANTIBODIES

The most clinically revelant anti-thyroid peroxidase antibodies, thyrotropin antibodies, thyrotropin receptor antibodies and thyroglobulin antibodies.

Anti thyroid antibodies are commonly associated with the presence of antithyroid autoantibodies.

Anti TPO antibodies are the most common anti thyroid autoantibody ,present in approximately 90% of hashimoto's thyroiditis,75% of graves disease,10-20% of nodular goitre or thyroid carcinoma and 10-15% of normal individuals.

The majority of anti-TPO antibodies are produced by thyroid infiltrating lymphocytes, minor contributions from lymph nodes and bone marrow.

The presence of antithyroid antibodies is associated with an increased risk of unexplained subfertility, miscarriage, pretermbirth and postpartum thyroiditis.

AIMS OF MY STUDY

- To estimate the prevalence of thyroid peroxidase antibodies in the preterm deliveries, IUD and miscarriage.
- To assess the co-morbidities associated with the presence of TPOAb in mothers with abnormal outcomes.
- With the knowledge of association between the presence of TPOAb in pregnant women with poor outcomes, we will be able to understand the association of TPOAb and hypothyroidism and its adverse outcomes. Thereby we will be able to understand the importance of screening of TFT during pregnancy and prevent the poor fetomaternal outcomes.

INCIDENCE

Overt or symptomatic hypothyroidism has been reported to complicate 2 -10 %.

MATERNALEFFECTS

It is characterised by insidious non-specific clinical findings that include fatigue, constipation, cold intolerance, muscle cramps, and weight

gain, edema, dry skin, hair loss, and prolonged relaxation phase of deep tendon reflexes.

Overt hypothyroidism is confirmed by an abnormally high TSH, is accompanied by low thyroxine level.

THYROID STATUS IN PREGNANT AND NON PREGNANT WOMEN

Parameters	**TT4**	**TT3**	**FT4**	**FT3**	**TSH**
NON PRGNANT	87.42+/-30.11	2.83+/-1.27	14.96+/-6.21	6.38+/-2.98	2.68+/_1.11
PREGNANT					
1^{ST} TRIMESTER	79.22+/-38.42	2.91+/-1.12	14.81+/-4.11	6.91+/-2.63	1.87+/-1.02
2^{ND} TRIMESTER	91.76+/-38.42	3.42+/-1.25	12.56+/-3.96	4.79+/-2.10	2.22+/-1.19
3^{RD} TRIMESTER	122.18+/-49.32	2.95+/-1.43	9.54+/-4.12	3.72+/-1.33	2.49+/-0.94
OVERALL	102.17+/-40.11	3.31+/-1.30	11.78+/-4.48	5.09+/-2.02	2.15+/-1.03

SUBCLINICALHYPOTHYROIDISM

Subclinical hypothyroidism is defined by an elevated serum TSH level and normal serum thyroxine concentration. Included in the spectrum of subclinical thyroid disease are asymptomatic.

Included in the spectrum of subclinical thyroid disease are asymptomatic individuals with measurable antithyroid peroxidase or antithyroglobulin antibodies.

Euthyroid autoimmune thyroid disease represents a new investigative frontier in screening and treatment of thyroid dysfunction during pregnancy.

OVERTHYPOTHYROIDISM IN PREGNANCY

The most common cause of hypothyroidism in pregnancy is hashimoto thyroiditis, characterised by glandular destruction from autoantibodies, particularly antithyroid peroxidase antibodies.

Clinical identification of hypothyroidism is difficult during pregnancy because many of the signs or symptoms are also common to pregnancy itself.

Thyroid analysis testing should be performed on symptomatic women or those with a history of thyroid disease. Severe hypothyroidism during pregnancy is uncommon, probably because it is often associated with infertility and increased spontaneous abortion rates. Even women with treated hypothyroidism undergoing in vitro fertilization have a significantly decreased chances of achieving pregnancy.

TREATMENT

The American thyroid Association and American association of clinical endocrinologists recommended replacement therapy for hypothyroidism beginning with levothyroxine in doses of 1to 2 micro gm/kg/day or approximately100microgm/day. Women who are athyrotic after thyroidectomy or radioiodine therapy may require higher doses. Surveillance is with TSH levels measured at 4-6 week intervals, and the thyroxine dose is adjusted by 25 -50 microgm/day increments until TSH levels becomes normal. Pregnancy is associated with an increased thyroxine requirement in approximately a third of supplemented women. Because a similar increased requirement is seen in women with postmenopausal hypothyroidism after estrogen replacement, the increased demand in pregnancy is believed to be related to increased estrogen production.

* Increased thyroxine requirements begin as early as 5 weeks.

* In a randomized trial that provided an increased levothyroxine dose at pregnancy confirmation in 60 mothers, yassa and coworkers found that a 29 to 43 percent increase in the weekly dose maintained serum TSH values ,<5.0 mu/L during the first trimester in all women.

* Importantly, however, this increase caused TSH suppression in more than a third of women.

* Significant hypothyroidism may develop early in women without thyroid reserve such as those with prior radioiodine ablation, or thyroidectomy, those undergoing assisted reproductive techniques.

* Anticipatory 25-percent increases in thyroxine replacement at pregnancy confirmation will reduce this likelihood. All other women with hypothyroidism should undergo TSH testing at initiation of prenatal care.

PREGNANCY OUTCOME WITH OVERT HYPOTHYROIDISM

- Although limited, indicate that there are excessive adverse perinatal outcomes associated with overt thyroxine deficiency.
- With appropriate replacement therapy, however, adverse effects are not increased in most reports.
- There was an risk for some pregnancy complications even in women taking replacement theraphy.
- Most experts agree that adequate hormone replacement during pregnancy minimizes the risk of adverse outcomes and most complications.

FETAL AND NEONATAL EFFECTS

There is no doubt that maternal and fetal thyroid abnormalities are related. In both, thyroid function is dependent on adequate iodide intake, and its deficiency early in pregnancy can cause both maternal and fetal hypothyroidism. Maternal TSH-receptor blocking antibodies can cross the placenta and cause fetal thyroid dysfunction.

AUTOIMMUNE THYROIDITIS

Rovelli and colleagues evaluated 129 neonates born to women with autoimmune thyroiditis. They found that 28 percent had an elevated

TSH level on the third or fourth day of life, and 47 percent of these had TPO antibodies on day 15.still, auto antibodies were undetectable at 6 months of age, It seems paradoxical that despite these transient laboratory findings in the neonate, TPO and antithyroglobulin antibodies have little or no effect on fetal thyroid function. Indeed, prevalence of fetal hypothyroidism in women with Hashimoto's thyroiditis estimated to be only 1 in 180,000 neonates.

SUB CLINICAL HYPOTHYROIDISM

This thyroid condition is common in women, but its inci-dence can be variable depending on age, race, dietary iodine intake, and serum TSH thresholds used to establish the diag-nosis.

Its prevalence in pregnancy has been estimated to be between 2 and 5 percent.

The rate of progression to overt thyroid failure is affected by TSH level, age, other disorders such as diabetes, and presence and concentration of antithyroid antibodies.

STUDIES IN SUBCLINICAL HYPOTHYROIDISM

Diez and Iglesias prospectively followed 93 nonpregnant women with subclinical hypothyroidism for 5 years and reported that in a third, TSH values became normal. In the other two thirds, those women whose TSH levels were 10 to 15 m U/L developed overt disease at a rate of 19 per 100 patient-years. Those women whose TSH levels were < 10 mU/L developed overt hypothyroidism at a rate of 2 per 100 patient-Years.

The U.S. Preventative Services Task Force on screening for subclini-cal hypothyroidism also reported that nearly all patients who develop overt hypothyroidism within 5 years have an initial TSH level > 10 mU/ L . In a 20-year follow-up study of 5805 women who were screened in early pregnancy, only 3 percent developed thyroid disease.

Of the 224 women identified with subclinical .hypothyroidism during pregnancy, 36 (17 percent) developed thyroid disease in the next 20 years, and most of these had either TPO or TG antibodies during pregnancy. Consequently, the likelihood of progression to overt hypothy-roidism *during* pregnancy in otherwise healthy women with subclinical hypothyroidism seems unlikely.

Pregnancy Outcomes in Women with Untreated Subclinical Hypothyroidism and isolated Maternal Hypothyroxinemia Comparedwith Euthyroid Pregnant Women

Outcome	Euthyroid n=16,011	Subclinical Hypothyroidism n=598	p value	Isolated Hypothy-roxinemia n=233	p value
Hypertension (%)	9	9	0.68	11	0.53
Placental abruption (%)	0.3	1.0	0.03	0.4	0.75
Gestational age delivered (%)					
<36 weeks	6.0	7.0	0.09	6.0	0.84
< 34 weeks	2.5	4.3	0.005	2.0	0.44
< 32 weeks	1.0	2.2	0.13	1.0	0.47
RDS / ventilator (%)	1.5	2.5	0.05	1.3	0.78
Neonatal intensive care (%)	2.2	4.0	0.005	1.3	0.32

RDS = respiratory distress syndrome Data from Casey, 2007.

TSH LEVEL SCREENING IN PREGNANCY

Some professional organisations recommend routine prenatal screening and treatment for subclinical hypothyroidism.

The American College of Obstetricians and Gynecologists (2013) has reaffirmed that although observational data were consistent with the

possibility that subclinical hypothyroidism was associated with adverse neuropsychological development, there have been no interventional trials to demonstrate improvement.

The College thus has consistently recommended against implementation of screening until further studies are done to validate or refute these findings (American College of Obstetricians and Gynecologists, 2012).

The findings of the international multicenter Controlled Antenatal Thyroid screening (CATS} study of thyroid screening and treatment of subclinical hypothyroidism and isolated maternal hypothyroxinemia during pregnancy. The primary outcome was off- spring IQ scores are 3 years of age.

Cognitive function in the children was not improved with screening and treatment.

EUTHYROID AUTOIMMUNE THYROID DISEASE

Auto antibodies to TPO and TG have been identified in 6 to 20 percent of reproductive-aged women. Most who test positive for such antibodies, however, are euthyroid . That said, such women are at a two- to fivefold increased risk for early pregnancy loss. The presence of

thyroid antibodies has also been associated with preterm birth. In a randomized treatment trial of 115 euthyroid women with TPO antibodies, Negro and coworkers (2006) reported that treatment with levothyroxine astoundingly reduced the preterm birth race from 22 to 7 percent. Contrarily, Abbassi-Ghanavati and associates (201O) evaluated pregnancy outcomes in more than 1000 untreated women with TPO antibodies and did not find an increased risk for preterm birth compared with the risk in 16,000 euthyroid women without antibodies. These investigators, however, found a threefold increased risk of placental abruption in these women. As with nonpregnant subjects with TPO antibodies, these women are also at increased risk for progression of thyroid disease and postpartum thyroiditis.

This group of euthyroid women with abnormally high thyroid autoantibody levels represents a new focus of thyroid research. Dosiou and colleagues performed a cost-effectiveness analysis of universal screening for autoimmune thyroid disease during pregnancy. Their results favored universal screening.

There is, however, a paucity of studies that show benefit co identifying and creating euthyroid women with thyroid autoantibodies.

Thus, calls for routine antibody screening seem premature. Currently, universal screening for the thyroid autoantibodies is not recommended by any professional organizations.

IODINE DEFICIENCY

Decreasing iodide fortification of table salt and bread products in the United Scares during the past 25 years has led to occasional iodide deficiency.

Importantly, the most recent National Health and Nutrition Examination survey indicated that, overall, the United Scares population remains iodine sufficient.

Even so, experts agree that iodine nutrition in vulnerable populations such as pregnant women requires continued monitoring.

* In 2011 the Office of Dietary Supplements of the National Institutes of Health sponsored a workshop to prioritize iodine research.

* Participants emphasized the decline in median urinary iodine to 125 µg/L in pregnant women and the serious potential impact on the developing fetus.

* Dietary iodine requirements are increased during pregnancy due to increased thyroid hormone production, increased renal losses, and fecal iodine requirements.

* Adequate iodine is requisite for fetal neurological development beginning soon after conception, and abnormalities are dependent on the degree of deficiency.

* The World Health Organisation (WHO) has estimated that at least 50 million people worldwide have varying degrees of preventable brain damage due to iodine deficiency.

✓ Although it is doubtful that*mild deficiency* causes intellectual impairment, supplementation does prevent fetal goiter.

✓ *Severe deficiency*, on the other hand, is frequently associated with damage typically encountered with *endemic cretinism* .

✓ It is presumed that *moderate deficiency* has intermediate adverse effects.

✓ Berbel and associates began daily supplementation in more than 300 pregnant women with moderate deficiency at three time periods-4 to 6 weeks, 12 to 14weeks, and after delivery.

- ✓ They found improved neurobehavioral development scores in offspring of women supplemented with 200 µg potassium iodide very early in pregnancy. Similarly, Velasco and coworkers found improved Bayley Psychomotor Development scores in offspring of women supplemented with 300 µg of iodide in the first trimester.

- ✓ In contrast, Murcia and colleagues identified lower psychomotor scores in, I-year-old infants whose mothers reported daily supplementation of more than 150 µg.

- ✓ There are two ongoing randomized controlled trials of iodine supplementation in mildly to moderately iodine-deficient pregnant women in India and Thailand. These studies should provide needed answers as to whether iodine supplementation in these women is beneficial.

- ✓ The Institute of Medicine recommends daily iodine intake during pregnancy of 220 µg/day, and 290 µg/day for lactating women.

- ✓ The Endocrine Society recommends an average iodine intake of 10 per day in childbearing-aged women, and this should be increased to 100 µg during pregnancy and breast feeding.

- ✓ The American Thyroid Association has recommended that 150 µg of iodine be added to prenatal vitamins to achieve this average daily intake.

- ✓ According to Leung and coworkers, however, only 51 percent of the prenatal multivitamins in the United States contain iodine.

- ✓ It has even been suggested that because most cases of maternal hypothyroxinemia world- wide are related to relative iodine deficiency, supplementation may obviate the need to consider thyroxine treatment in such women.

- ✓ On the other hand, experts caution against over supplementation. Teng and associates contend char excessive iodine intake-defined as > 300 µg/day-may lead to subclinical hypothyroidism and autoimmune thyroiditis. And the Endocrine Society, in accordance with the WHO, advises against exceeding twice the daily recommended intake of iodine.

CONGENITAL HYPOTHYROIDISM

- ➢ Because the clinical diagnosis of hypothyroidism in neonates is usually missed, universal newborn screening was introduced in 1974 and is now required by law in all.

- Congenital hypothyroidism develops in approximately 1 in 3000 newborns and is one of the most preventable causes of mental retardation. Developmental disorders of the thyroid gland such as agenesis and hypoplasia account for 80 to 90 percent of these cases.

- The exact underlying etiology of thyroid dysgenesis remains unknown. The remaining ·primary congenital hypothyroidism cases are caused by hereditary defects in thyroid hormone production. The list of identified gene mutations that cause hypothyroidism continues to grow rapidly.

- Early and aggressive thyroxine replacement is critical for infants with congenital hypothyroidism.

- Still, some infant identified by screening programs with severe congenital hypo thyroidism who were treated promptly will exhibit cognitive defects into adolescence.

- Therefore, in addition to riming of treatment the severity of congenital hypothyroid is an important factor in long-term cognitive outcomes. Accordingly, in infants with screening results suggestive of severe hypothyroidism , therapy should be started

immediately without waiting for confirmatory reported that 8 percent of 1420 infants with congenital hypothyroidism also had other major congenital malformations.

ABORTION

Abortion is defined as the spontaneous or induced termination of pregnancy before fetal viability.

It thus is appropriate that miscarriage and abortion are terms used interchangeably in a medical context. But because popular use of *abortion* by lay persons implies a deliberate infact pregnancy termination, many prefer *miscarriage* for spontaneous fetal loss.

Newer terms made sonography and human chorionic gonadotropin measurements that identify extremely a pregnancies include *early pregnant loss*, *wastage* or *failure.*

FIRST TRIMESTER SPONTANEOUS ABORTION

PATHOGENESIS

More than 80 percent of spontaneous abortions occur within the first 12 weeks of gestation. With first-trimester losses, death or the embryo or fetus nearly always precedes spontaneous expulsion. Death is

usually accompanied by hemorrhage into the decidua basalis. This is followed by adjacent tissue necrosis that stimulates uterine contractions and expulsion. An intact gestational sac is usually filled with fluid and may or may not contain an embryo or fetus. Thus, the key to determining the cause of early miscarriage is to ascertain the cause of fetal death. In contradiction, in later pregnancy losses, the fetus usually does not die before expulsion, and thus other explanations are sought.

INCIDENCE

Statistics regarding the incidence of spontaneous abortion according to the diligence used for its recognition. Wilcox and colleagues studied 221 healthy women through 707 menstrual cycles and found that 31 percent of pregnancies were lost after implantation.

They used highly specific assays for minute concentrations of maternal serum β-hCG and reported chat two thirds of these early losses were *clinically silent.*

Currently, there are factors known to influence clinically apparent spontaneous abortion, however, it is unknown it these same factors affect clinically silent miscarriages. By way of example, the rate of clinical miscarriages is almost doubled when either parent is older than 40 years .

But, it is not known it clinically silent miscarriages are similarly affected by parental age.

FETAL FACTORS

As approximately half of miscarriages are *anembryonic*, that is, with no identifiable embryonic elements. Less accurately, the term *blighted ovum* may be used.

The ocher 50 percent are *embryonic* miscarriages, which commonly display a developmental abnormality of the zygote, embryo, fetus, or at times, the placenta. Of embryonic miscarriage, half of these- 25 percent of all abortuses - have chromosomal anomalies and thus are *aneuploid abortions.* The remaining cases are *euploid abortions,* that is, carrying a normal chromosomal complement.

CHROMOSOMAL FINDINGS IN FIRST – TRIMESTER ABORTUSES

Chromosomal Studies	Incidence Range (%)
Embryonic	50
Euploid	
46,XY and 46,XX	45 to 55
Aneuploid	
Autosomal trisomy	22 to 32
Monosomy X (45,X)	5 to 20
Triploidy	6 to 8
Tetraploidy	2 to 4
Structural anomaly	2
Anembryonic (blighted ovum)	**-50**

Date from Eiben, 1990, Kajii, 1980, Simpson, 1980, 2007.

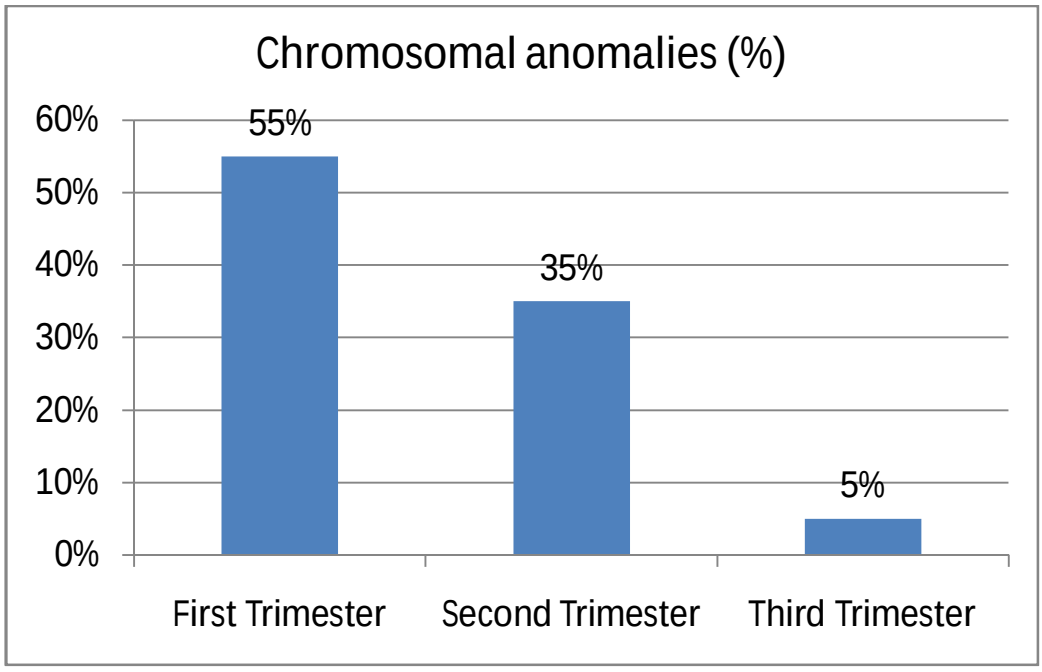


Figure 18-1 Frequency of chromosomal anomalies in abortuses and stillbirths during each trimester. Approximate percentages for each group are shown. (Data from Eiben, 1990; Fantel, 1980; Warburton, 1980).

INFECTION

Some common viral, bacterial, and other infectious agents that invade the normal human can cause pregnancy loss. Many are systemic and infect the fetoplacental and by blood- borne organisms. Others may infect locally through genitourinary infection or colonization. However, despite the numerous infections acquired in pregnancy, these uncommonly cause early abortion. *Brucellaabortus, Campylobacter fetus* ,and *Toxoplasma gondii*infections cause abortion in livestock, but their role in human pregnancy is less- clear**.**

There appear to be no abortifacient effects of infections caused by *Listeria monocytogenes,* parvovirus, cytomegalovirus, or herpes simplex virus.

One possible exception is infection with *Chlamydia trachomatis,* which was found to be present in 4 percent of abortuses compared with < 1 percent of controls.

Another is polymicrobial infection from periodontal disease that has been linked with a two- to fourfold increase.

MEDICAL DISORDERS

In general, early abortions are rarely due to chronic was ting diseases such as tuberculosis or cancer. There are a few specific disorders possibly linked with increased early pregnancy loss. Those associated with diabetes mellitus and thyroid disease are discussed subsequently. Another examples *celiac disease,* which has been reported to cause recurrent abortions as well as both male and female infertility.

Unrepaired cyanotic heart disease is likely a risk for abortion, and in some, this may persist after repair.

Eating *disorders-anorexianervosa* and *bulimianervosa-have* been linked with subfertility, preterm delivery, and fetal-growth restriction. Their association with miscarriage, however, is less well studied.

Inflammatory bowel disease and systemic lupus erythematosus may increase the risk.

Chronic hypertension does not appear to confer significant risk.

Perhaps related, women with a history of recurrent miscarriages were reported to be at increased risk for fetal-growth restriction.

Another possible link with vascular disease is that women with multiple miscarriages are more likely to suffer a myocardial infarction.

MEDICATIONS

Only a few medications have been evaluated concerning a role with early pregnancy loss. Oral contraceptive or spermicidal agents used in contraceptive creams and jellies are not associated with an increased miscarriage rate. Similarly, non steroidal anti inflammatory drugs or ondansetron are not linked. A pregnancy with an intra uterine device (IUD) in situ has an increased risk of abortion and specifically of septic abortion.

With the newer IUDs, reported that only 2 of 6 intact pregnancies aborted before 20 weeks. Finally, studies have shown no increase in pregnancy loss rates with meningococal conjugate or trivalent inactivated influenza vaccines.

CANCER

Therapeutic doses of radiation are undeniably abortifacient, but doses that cause abortion are not precisely known. According to Brent (2009), exposure to< 5 rads does not increase the risk.

Cancer survivors who were previously created with abdomino pelvic radiotherapy may later be at increased risk for miscarriage.

The effects of chemotherapy in causing abortion are not well defined. Particularly worrisome *art* women with an early normal gestation erroneously treated with methotrexate for an ectopic pregnancy.

A report of eight such cases, two viable-size fetuses had multiple malformations. In the remaining six cases, three each had a spontaneous or induced abortion (Nurmohamed, 2011).

DIABETES MELLITUS

The abortifacient effects of uncontrolled diabetes are well- known. Optimal glycemic control will mitigate much of this loss. Spontaneous abortion and major congenital malformation rates are both increased in women with insulin-dependent diabetes. This is directly related to the degree of periconceptional glycemic and metabolic control.

THYROID DISORDERS

These have long been suspected to cause early pregnancy loss and other adverse pregnancy outcomes. Severe iodine deficiency, which is infrequent in developed countries, has been associated with increased

miscarriage rates. Varying degrees of thyroid hormone insufficiency are common in women. Although the worst-overt hypothyroidism-is infrequent in pregnancy, subclinical hypothyroidism has an incidence of 2 to 3 percent.

Both are usually caused by autoimmune *Hashimoto thyroiditis,* in which both incidence and severity accrue with age. Despite this common prevalence, any increased risks for miscarriage due to hypothyroidism are still unclear.

That said, De Vivo (20IO) reported that subclinical thyroid hormone deficiency may be associated with very early pregnancy loss.

The prevalence of abnormally high serum levels of antibodies to thyroid peroxidase or thyroglobulin is nearly 15 percent in pregnant women.

Although most of these women are eurhyroid, those with clinical hypothyroidism tend to have higher concentrations of anti-bodies.

Even in euthyroid women, however, antibodies are a marker for increased miscarriage.

This has been confirmed by two prospective studies, and preliminary data from one suggest that thyroxine supplementation decreases this risk.

'Effects associated with thyroid disorders in women with *recurrent miscarriage*.

SURGICAL PROCEDURES

The risk of miscarriage caused by surgery is not well studied. There is extensive interest in pregnancy outcomes following bariatric *surgery*, obesity is an uncontested risk factor for miscarriage. However, currently, it is not known if this risk is mitigated by weight-reduction surgery.

It is likely that *uncomplicated* surgical procedures performed during early pregnancy do not increase the risk for abortion.

Ovarian tumors can generally be resected with out causing miscarriage. An important exception involves early removal of the corpus luteum or the ovary in which it resides.

If performed before 10 weeks gestation, supplemental progesterone should be given. Between 8 and 10 weeks, a single 150-mg intramuscular

injection of 17 – hydroxyl progesterone caproate is given at the time of surgery. If between 6 to 8 weeks, then two additional 150-mg injections should be given 1 and 2 weeks after the first. Other progesterone regimens include: (I) oral micronized progesterone (Prometrium), 200 or 300 mg orally once daily, or (2) 8-percent progesterone vaginal gel (Crinone) given intra- vaginally as one premeasured applicator daily *plus* micronized progesterone 100 or 200 mg orally once daily continued until 10 weeks' gestation.

Trauma seldom causes first-trimester miscarriage. Major trauma- especially abdominal- can cause fecal loss, but is more likely as pregnancy advances.

NUTRITION

Extremes of nutrition-severe dietary deficiency and morbid obesity - are associated with increased miscarriage risks. Dietary quality may also be important, as this risk may be reduced in women who consume fresh fruit and vegetables daily.

Sole deficiency of one nutrient or moderate deficiency of all does not appear to increase risks for abortion. Even in extreme cases-for example, *hyperemesis gravidarum -abortion* is rare (Maconochie).

Obesity is associated with adverse pregnancy outcomes . These include subfertility and an increased risk of miscarriage and recurrent abortion.

In a study of 6500 women who conceived with in vitro fertilization (IVF), live birth races were reduced progressively for each body mass index (BMI) unit increase.

As noted earlier, although the risks for many adverse late-pregnancy outcomes are decreased after bariatric surgery, any salutary effects on the miscarriage rate are not clear.

SOCIAL AND BEHAVIORAL FACTORS

Lifestyle choices reputed to be associated with an increased miscarriage risk are most commonly related to chronic and especially heavy use of *legal* substances.

The most common used is alcohol, with its potent tetarogenic effects. That said, an increased miscarriage risk is only seen with regular or heavy use.

In fact, low-level alcohol consumption does not significantly increase the abortion risk.

At least 15 percent of pregnant women admit to *cigarette smoking*.

It seems intuitive, but unproven, that cigarettes could cause early pregnancy loss by a number of mechanisms chat cause adverse late-pregnancy outcomes (Carov, 2008).

Excessive caffeine consumption- not well defined-has been associated with an increased abortion risk. There are reports that heavy intake of approximately five cups of coffee per day-about 500 mg of caffeine-slightly increases the abortion risk.

Studies of "moderate"-less than 200 mg daily-did not increase the risk. Currently, the American College of Obstetricians and Gynecologists (2013b) has concluded that moderate consumption likely is not a major abortion risk and that any associated risk with higher intake is unsettled.

OCCUPATIONAL AND ENVIRONMENTAL FACTORS

It is intuitive to limit exposure of pregnant women to any toxin. That said, although some environmental toxins such as benzene are implicated in fetal malformations, data with miscarriage risk is less clear. The major reason is that it is not possible to accurately assess environmental exposures. Earlier reports that implicated some chemicals as increasing miscarriage risk include arsenic, lead, formaldehyde,

benzene, and ethylene oxide (Barlow, 1982). More recently, there is evidence chat DDT-dichlorodiphenyltrichloroethane may cause excessive miscarriage rates (Eskenazi, 2009). In fact, use of DDT- containing insecticides had been suspended. But in 2006, it was again and is still endorsed by the World Health Organization (2011) for mosquito control for malaria prevention.

There are even fewer studies of occupational exposures and abortion risks. In a follow-up of the Nurses Health Study II, Lawson and associates (2012) reported slightly increased miscarriage risks in nurses exposed to antineoplastic drugs, sterilizing agents, and x-rays. Some of these found that exposure to *video display terminals* or to *ultrasound* did not increase miscarriage rates.

Increased miscarriage risk was found for dental assistants exposed to more than 3 hours of nitrous oxide daily if there was no gas-scavenging equipment.

Conclusions from a metaanalysis were that there is a small incremental risk for spontaneous abortion in women who worked with *cytotoxic antineoplastic chemotherapeutic agents*.

IMMUNOLOGICAL FACTORS

The immune, tolerance of the mother to the paternal haploid fetal combination remains enigmatic.

There is, however, an increased risk for early pregnancy loss with some immune-mediated disorders. The most potent of these are antiphospholipid antibodies directed against binding proteins in plasma (Erkan, 2011).

These along with clinical and laboratory findings provide criteria for the *antiphospholipid antibody syndrome-APS* (American College of Obsterricians and Gynecologists, 2012).

INHERITED THROMBOPHILIAS

Although thrombophilias were initially linked to various pregnancy outcomes, most putative associations have been refuted. Currently, the American College of Obstericians and Gynecologists is of the opinion that there is not a definitive causal link between these thrombophilias and adverse pregnancy outcomes in general, and abortion in particular.

UTERINE DEFECTS

Various inherited and acquired uterine defects are known to cause both early and late recurrent miscarriages.

RECURRENT MISCARRIAGE

Other terms that have been used to describe repetitive early spontaneous pregnancy losses include *recurrent spontaneous abortion, recurrent pregnancy loss,* and *habitual abortion.* It is generally accepted that approximately I percent of fertile couples have recurrent miscarriages classically defined as three or more consecutive pregnancy losses at 20 weeks or with a fetal weight < 500 grams. Most of these are embryonic or early losses, and the remainder either are anembryonic or occur after 14 weeks. Studies are difficult to compare because of non standardized definitions. For example, some investigators include women with two instead of three consecutive losses, and yet others include women with three *nonconsecutive* losses. Documentation of pregnancy with β-hCG levels, sonography, and pathological examination also varies widely.

At minimum, recurrent miscarriage should be distinguished from sporadic pregnancy loss that implies intervening pregnancies that reached viability. Although women in the later category were thought to have a much lower risk of yet another abortion.

In two studies, the risk for subsequent miscarriage is similar following either two or three pregnancy losses. Remarkably, the chances for a successful pregnancy are > 50 percent even after five losses.

The American Society for Reproductive Medicine (2008) proposed that recurrent pregnancy loss be defined as two or more failed clinical pregnancies confirmed by either sonographic or histopathological examination. A thorough evaluation certainly is warranted after three losses, and treatment is initiated earlier in couples with concordant subfertility.

ETIOLOGY

There are many putative causes of recurrent abortion, how- ever, only three are widely accepted: parental chromosomal.

Predicted Miscarriage Rate in Scottish Women with Their Next Pregnancy According to Number of Prior Miscarriages

	Number of Prior Pregnancy Losses			
	0	1	2	3
Initial pregnancy with miscarriage (n)	143,595	6577	700	115
Subsequent risk for miscarriage	7%	14%	26%	28%

Other suspected but not proven causes are alloimmunity, endocrinopathies, environment toxins, and various infections. Infections seldom cause even sporadic loss. Thus, most are unlikely to cause recurrent miscarriage, especially since maternal antibodies usually have developed. For years, various inherited thrombophilia mutations chat include factor V Leiden, prothrombin G202 IOA, protein C and S deficiency, and antithrombin deficiency were suspected. But large studies have refuted an association between increased pregnancy wastage and these thrombophilias (American College of Obstetricians and Gynecologists, 20 l3a).

There is some evidence to support a role for various poly morphisms of gene expression in miscarriages. Just a few examples include polymorphisms that alter VEGF-A expression, those that exaggerate platelet aggregation, and those with a specific maternal type of Th1 and Th2 immune response.

The timing of recurrent loss may offer clues, and in some women, each miscarriage may occur near the same gestation age.

Genetic factors usually result in early embryonic losses, whereas autoimmune or uterine anatomical abnormalities more likely cause second-trimester losses.

As mentioned, first-trimester losses in recurrent miscarriage have a significantly lower incidence of genetic abnormalities than sporadic losses-25 versus 50 percent.

That said, routine chromosomal evaluation of abort uses is costly and may not accurately reflect the fetal karyotype.

PARENTAL CHROMOSOMAL ABNORMALITIES

Although these account for only 2 to 4 percent of recurrent losses, karyotypic evaluation of both parents is considered by many to be a critical part of evaluation. In an earlier study, balanced reciprocal translocation s accounted for half of chromosomal abnormalities, robertsonian translocations for a fourth, and X chromosome mosaicism-47, XXY or *Klinefelter syndrome-for* 12 percent. These chromosomal abnormalitis are repetitive for consecutive losses.

After thorough generic counseling, couples with an abnormal karyotype can usually be managed with IVF followed by pre· implantation genetic diagnosis.

ANATOMICAL FACTORS

Several genital tract abnormalities have been implicated in recurrent miscarriage and other adverse pregnancy outcomes, but not infertility. According to Devi Wold and colleagues (2006), 15 percent of women with three or more consecutive miscarriages will be found to have a congenital or acquired uterine anomaly.

Of acquired abnormalities, uterine *synechiae-Asherman syndrome-usually* result from destruction of large areas of endometrium. This can follow uterine curettage. Characteristic multiple filling defects are seen with hysrero salpingography or saline-infusion sonography. Treatment is done using directed hysteroscopiclysis of adhesions.

*Uterine leiomyomas*are found in a large proportion of adult women and can cause miscarriage, especially if located near the placental implantation site. That said, data indicating them to be a significant cause of recurrent pregnancy loss are not convincing. Uterine cavity distortion is apparently not requisite for bad outcomes. But in women undergoing IVF, pregnancy outcomes were adversely affected by submucous but not subserosal or intramural leio-myomas most agree that consideration be given to excision of submucosal and intracavitary leiomyomas in women with recurrent losses. Ironically, women undergoing uterine artery

embolization of myomas had an increased risk for miscarriage in a subsequent pregnancy.

In contrast, congenital genital tract anomalies commonly originate from abnormal mullerian duct formation or abnormal fusion. These have an overall incidence of approximately 1 in 200 women. Depending on their anatomy, some may increase risks for early miscarriage, whereas others may cause midtrimester abortion or preterm delivery. Unicornuate, bicornuate and septate uterus are associated with all three types of loss. Looked at another way, developmental uterine anomalies were found in approximately 20 percent of women with recurrent pregnancy losses compared with about 7 percent of controls.

It has proven difficult to demonstrate that correction of uterine anomalies improves early pregnancy outcome.

Estimated Prevalence and Pregnancy Loss Rate for Some Congenital Uterine Malformations

Uterine Anomaly [a]	Proportion of All Anomalies (%)	Pregnancy Loss Rate (%) [b]
Bicornuate	39	40-70
Septate or Unicornuate	14-24	34-88
Didelphys	11	40
Arcuate	7	
Hypo – or aplastic	4	

[a] Estimated overall prevalence 1:200 women.

[b] Included first – and second trimester losses.

Data from Bradshaw, 2012; Buttram, 1979; Nahum,

1998, Reddy, 2007; Valli, 2001.

IMMUNOLOGICAL FACTORS

In their analysis of published studies, determined that 15 percent of more than 1000 women with recurrent miscarriage had recognized autoimmune factors. Two primary pathophysiological models are the

autoimmune theory immunity directed against self, and the *alloimmune theory immunity* against another person.

As miscarriages are more common in women with systemic lupus erythematosus, an autoimmune disease.

Many of these women were found to have *antiphospholipid antibodies,* a family of auto- antibodies that bind to phospholipid-binding plasma proteins.

Women with recurrent spontaneous pregnancy loss have a higher frequency of these antibodies compared with normal controls - 5 to 15 versus 2 to 5 percent, respectively.

The *antiphospholipid antibody syndrome (APS)* is defined by these antibodies found together with various forms of reproductive *losses* along with substantively increased risks for venous thrombo embolism (American College of Obstetricians and Gynecologists, 201 Id, 2013a).

ENDOCRINE FACTORS

According to Arredondo and Noble (2006), 8 to 12 percent of recurrent miscarriages are caused by endocrine factors. Studies to evaluate these have been inconsistent and generally under- powered. Two examples, both controversial, are progesterone deficiency caused *by* a

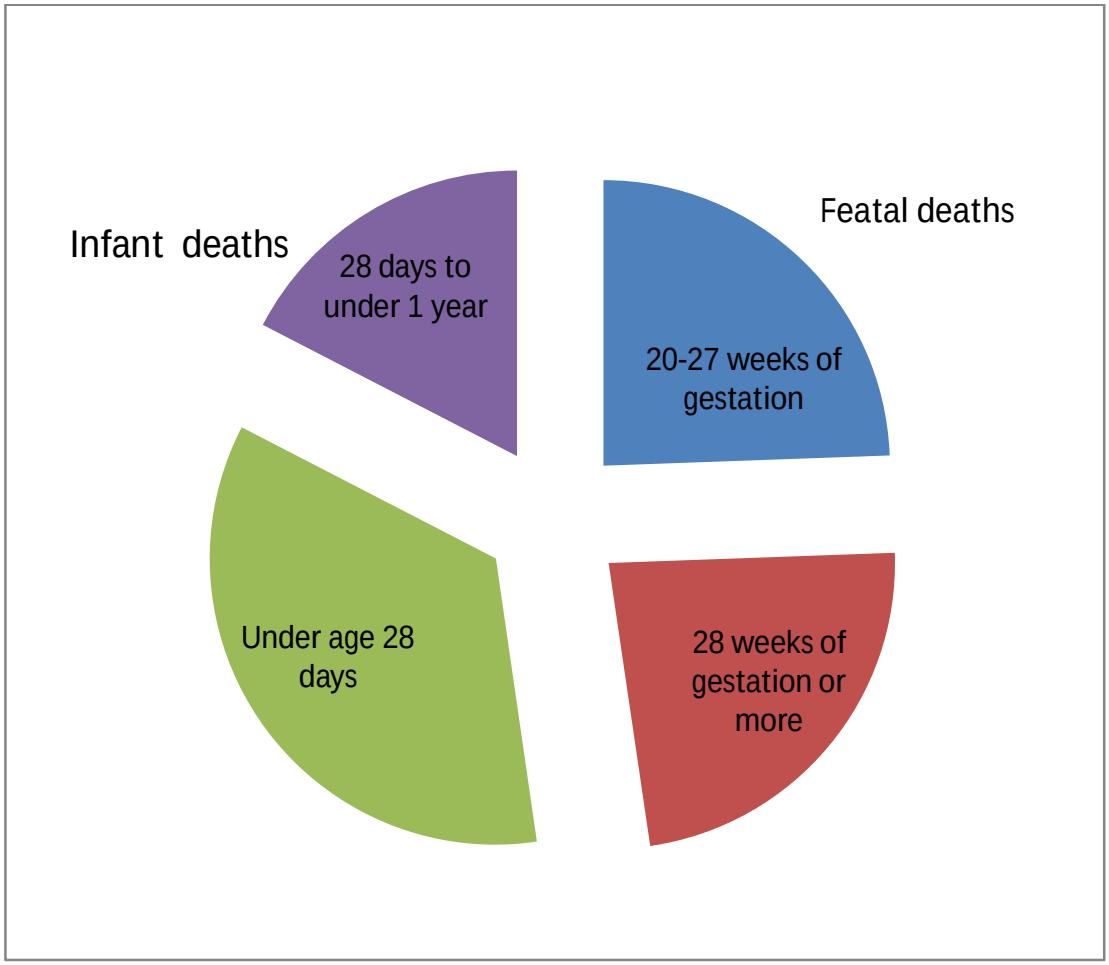
luteal-phase defect and *poly cystic ovarian syndrome.*

Likewise, the effects on early pregnancy loss of overt hypo-thyroidism and severe iodine deficiency are well known. Also, the effects of subclinical hypothyroidism and antithyroid antibodies are sporadic, and thus any effects on recurrent miscarriage rates have been debated (Garber, 202). That said, however, two recent metaanalyses reported convincingly positive associations between these antibodies and an increased risk for sporadic and recurrent miscarriages. Less convincing are preliminary data regarding thyroid hormone treatment for antibody positive women.

STILLBIRTH

Fetal death means death prior to complete expulsion or extraction from the mother of a product of human conception irrespective of the duration of pregnancy and which is not an induced termination of pregnancy. The death is indicated by the fact that after such expulsion or extraction, the fetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Heartbeats are to be distinguished from transient cardiac contractions, respiration are to be distinguished from fleeting respiratory efforts or gasps.

Fetal mortality is generally divided into three periods early, or <20 completed weeks, intermediate, 20-27 weeks, and late, 28 weeks or more. The fetal death rate after 28 weeks has declined since 1990, whereas deaths from 20 to 27 weeks are largely unchanged.



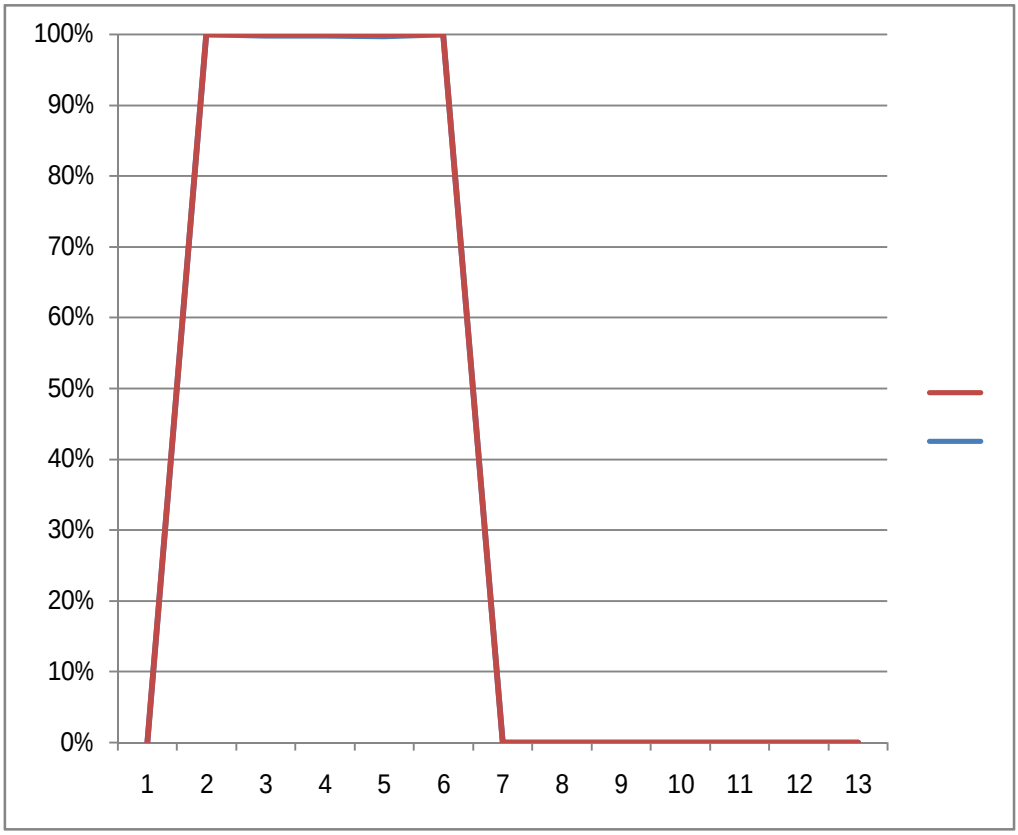
Percent distribution of fetal deaths at 20 weeks gestation or more, and infant deaths, United States 2006. (From MacDorman, 2012).

CAUSES OF FETAL DEATH

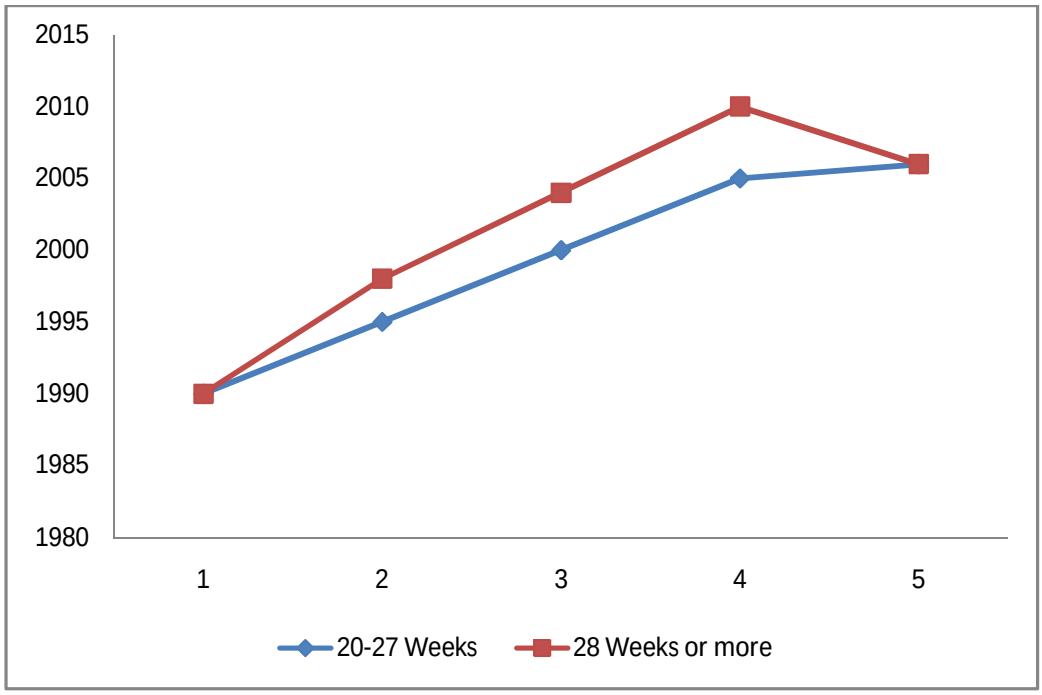
The Eunice *Kennedy Shriver* National institute of Child Health and Human Development (NICHD) created the Stillbirth Collaborative Research Network co ascertain stillbirth causes in a racially and geographically diverse population in the United States. From this, the Stillbirth Collaborative Research Writing Group (2011b) ascertained stillbirths at 20 weeks or later between 2006 and 2008 ·in 59 tertiary care and community hospitals in five scares. Standardized evaluations that included autopsy, placental histology, and testing of maternal or fetal blood/tissues- including feral karyotyping-were performed in 500 women with 512 stillbirths. Of these, 83 percent were before labor and were considered antepartum stillbirths.

CAUSES OF STILLBIRTH WERE DIVIDED INTO EIGHT CATEGORIES

These categories were then classified as probable, possible, or unknown. As an example, diabetes was considered a *probable cause* if the fetus had diabetic embryopathy with lethal anomalies or the mother had diabetic ketoacidosis, but it was a *possible cause* if the mother had poor glycemic control and the fetus had abnormal growth. Overall, a probable or possible source was identified in 76 percent of cases.



Fetal mortality rate per 1000 births by single weeks of gestation. United States, 2006.(From MacDorman, 2012).



Fetal mortality rates by period of gestation United States 1990-2006 (From MacDorman, 2012).

Each cause of fetal death assigned is reasonably straightforward and comprehensible except for placental abnormalities," which includes "uteroplacental insufficiency" as well as a few other entities less clearly defined. This aside, the leading reasons for fetal death were obstetrical complications that primarily included abruption, multifetal gestation, and spontaneous labor or ruptured membranes before viability· The major contribution of this study was char systematic evaluation led to a likely cause in approximately three fourths of stillbirths. This rate is considerably higher than most analyses of stillbirth etiologies and serves to emphasize the importance of careful evaluations.

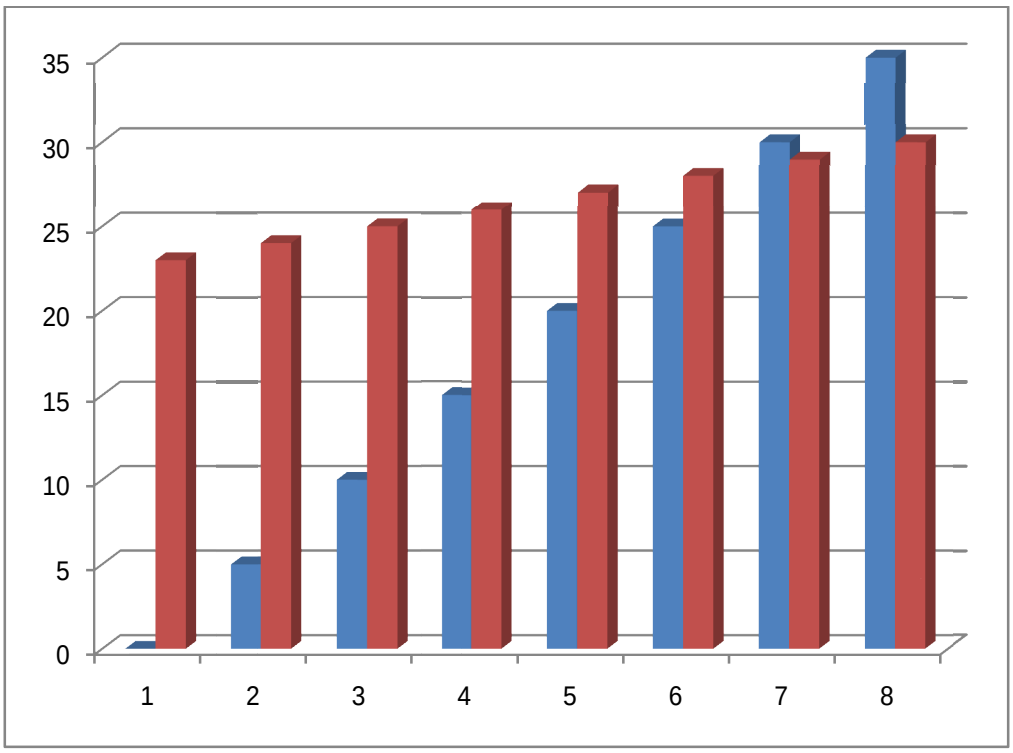
RISK FACTORS FOR FETAL DEATH

Factors char have been associated with an increased risk of antepartum stillbirth include advanced maternal age; Africans American race; smoking; illicit drug use; maternal medical conditions.

Causes of 512 Stillbirths in the Stillbirth Collaborative Research Network Study

Cause	Examples	Percent
Obstetrical complications	Abruption, multifetal gestation, ruptured preterm membranes at 20-24 weeks	29
Placental abnormalities	Uteroplacental insufficiency, maternal vascular disorders	24
Fetal malformations	Major structural abnormalities and / or genetic abnormalities	14
Infection	Involving the fetus or placenta	13
Umbilical cord abnormalities	Prolapse, stricture, thrombosis	10
Hypertensive disorders	Preeclampsia, Chronic hypertension	9
Medical complications	Diabetes, antiphospholipid antibody syndrome	8
Undetermined	NA	24

diseases-such as overt diabetes or chronic hypertension; assisted reproductive technology; nulliparity; obesity; and previous adverse pregnancy outcomes-such as prior preterm birth or growth-restricted newborn .



Distribution of livebirths and stillbirths in the National Institute of Child Health and Development Safe Labor Consortium according to gestational age.(From Reddy, 2010).

Diabetes			
Insulin+diet	2.4	6-35	1.7-7.0
Systemiclupuserythematosus	<1	40-150	6-20
Renaldisease	<1	15-200	2.2-30
Thyroiddisease	0.2-2	12-20	2.2-3.0
Thrombophilia	1-5	18-40	2.8-5.0
Cholestasisofpregnancy	<0.1	12-30	1.8-4.4
Smoking>10cigarettes	10-20	10-15	1.7-3.0
Obesity			
BMI25-29.9 kg/m^2	21	12-15	1.9-2.7
BMI>30	20	13-18	2.1-2.8
Education(<12yvs;::12y)	30	10-13	1.6-2.0
Priorgrowth-restrictedinfant(<100/o)	6.7	12-30	2-4.6
Priorstillbirth	0.5-1	9-20	1.4-3.2
Multifetalgestation			
Twins	2.7	12	1.0-2.8
Triplets	0.14	34	2.8-3.7
Maternalage(reference<35y)			
35-39y	15-18	11-14	1.8-2.2
40y	2	11-21	1.8-3.3
Black women compared with white women	15	12-14	2.0-2.2

Odds ratio of the factor present compared with the risk factor absent. From Fretts, 2005, with permission.

PRE TERM LABOR

DEFINITION OF PRETERM

A *preterm* or *premature infant* was defined by preterm infants were those delivered before 37 completed weeks.

This definition, which has now been in use for almost 40 years, was first promulgated in 1976 by the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FICO).

This definition was based on a statistical analysis of gestational age distribution at birth. It lacks a specific functional basis and should be clearly distinguished from the concept of prematurity.

Prematurity represents incomplete development of various organ systems at birth. The lungs are particularly affected, leading to the respiratory distress syndrome.

Beginning in 2005, in recognition that infants born between $34^{0/7}$ weeks and $36^{6/7}$ weeks experience morbidities and mortality characteristic of premature infants, pre- term births were subdivided. Those before $33^{6/7}$ weeks are labeled-early *preterm* ,and those occurring between 34 and 36 completed *weeks-late preterm.* Most recently, Spong (2013) observed, "it has become apparent that infants born between 37 weeks 0 days and 38 weeks 6 days gestation experience morbidities that are associated with prematurity compared to births at 39 weeks 0 days through 40 weeks 6 days when infant mortality is lower than at any other rime in human gestation." Those births $37^{0/7}$ weeks through $38^{6/7}$ weeks are now defined as *early term* and those 39 weeks 0 days through 40 weeks 6 days are defined as *term.*

MORBIDITY IN PRETERM INFANTS

Various morbidities, largely due to organ system immaturity, are significantly increased in infants born before 37 weeks' gestation compared with those delivered at term.

For approximately 40 years, complications in infants born before 34 weeks have been the primary focus. Only recently (2005) have *late preterm* infants-34 to 36 weeks-gained attention because of their increased morbidity. Attention has also been given to increasingly small preterm infants-very *low birth- weight* and *extremely low birth weight.* These very small infants suffer disproportionately not only the immediate complications of prematurity bur also long-term sequelae such as neuro developmental disability. Indeed, live births once considered "abortuses" because they weighed < 500 g are now classified as live births.

Remarkable studies have been made in neonatal survival for infants born preterm. This is especially true for chose born after 28 weeks. Importantly, the results are shown as a function of both birthweight*and* gestational age. After achieving a birth weight of 2: 1000 g or a gestational age of 28 weeks for females or 30 weeks for males, survival rates reach 95 percent.

Resources used to care for low-birth weight infants are a measure of the societial burden of preterm birth. The economic consequences of preterm birth that reach beyond the newborn period into infancy, adolescence, and adulthood are difficult to estimate. However, they must be enormous when the effects of adult diseases associated will maturity, such as hypertension and diabetes, are considered.

MAJOR SHORT AND LONG – TERM PROBLEMS IN VERY – LOW – BIRTH WEIGHT INFANTS

Organ or System	Short Term Problems	Long – Term Problems
Pulmonary	Respiratory distress syndrome, air leak, bronchopulmonary dysplasia, apnea of prematurity	Bronchopulmonary dysplasia, reactive airway disease, asthama
Gastrointestinal or nutritional immunological	Hyperbilirubinemia, feeding intolerance, necrotizing enterocolitis, growth failure Hospital – acquired infection, immune deficiency, perinatal infection	Failure to thrive, short bowel syndrome, cholestasis
Central nervous system	Intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus	Respiratory syncytial virus infection, branchiolitis
Ophthalmological Cardiovascular	Retinopathy of prematurity Hypotension, Patent ductusarteriosus, pulmonary	Cerebral palsy, hydrocephalus, cerebral atrophy, neuro developmental

Organ or System	Short Term Problems	Long – Term Problems
	hypertension	delay, hearing loss Blindness, retinal detachment, myopia, strabismus Pulmonary hypertension, hypertension in adulthood
Renal	Water and electrolyte imbalance, acid base disturbances	Hypertension in adulthood
Hematological	latrogenic anemia, need for frequent transfusions, anemia of prematurity	
Endocrinological	Hypoglycemia, transiently low thyroxine levels, cortisol deficiency	Impaired glucose regulation, increased insulin resistance

CAUSES OF PRETERM DELIVERY

There are four main direct reasons for preterm births in the United Scares. These include:

(1) spontaneous unexplained preterm labor with intact membranes,

(2) idiopathic preterm premature rupture of membranes (PPROM),

(3) delivery for maternal or feral indications, and

(4) twins and higher-order multiferal births. Of all preterm births, 30 to 35 percent are indicated, 40 to 45 percent are due to spontaneous pre-term labor, and 30 to 35 percent follow preterm membrane rupture (Goldenberg, 2008). Indeed, much of the increase in the singleton preterm birth rare in the United States is explained by rising numbers of indicated preterm births (Ananth, 2005).

Reasons for preterm birth have multiple, often interacting, antecedents and contributing factors. This complexity has greatly confounded efforts to prevent and manage this complication. This is particularly true for preterm ruptured membranes and spontaneous preterm labor which together lead to 70 to 80 percent of preterm births. For example, in 2004, there were 508,356 preterm births, and of these, 86, 116 or 17 percent were from multifetal pregnancies. Many of these pregnancies were achieved using ovulation-inducing drugs and assisted reproductive technologies (ART).

Analogous to other complex disease processes, multiple coexistent generic alterations and environment may lead co preterm birth.

There are poly morphisms in genes associated with inflammation and infection and in those associated with collagen turnover (Velez, 2008).

Inherited mutations in genes regulating collagen assembly may predispose individuals to cervical insufficiency or prematurely ruptured membranes.

BASIC SCIENCE OF SPONTANEOUS PRETERM LABOR

For both clinical and research purposes, pregnancies with intact feral membranes and spontaneous preterm labor must be distinguished from those complicated by preterm prematurely ruptured membranes. Even so, chose with spontaneous preterm labor do not constitute a homogeneous group characterized singularly by early initiation of parturition (American College of Obstetricians and Gynecologists, 2012b). This certainly is one reason why preventative therapies and clinical tools to assess the risks for preterm birth have been difficult to identify. Among the more common associated finding area multifetal pregnancy, intrauterine infection, bleeding, placental infarction, premature cervical dilatation, cervical insufficiency, hydramnios, uterine fundal abnormalities, and fetal anomalies. Severe maternal illness as a result of infections, autoimmune diseases, and gestational hypertension also increases preterm labor risks.

Although there are unique aspects to each cause of preterm labor, these diverse processes culminate in a common end point, which is

premature cervical dilatation and effacement and premature activation of uterine contractions. It seems important co emphasize char the actual process of preterm labor should be considered a final step that results from progressive or acute changes that could be initiated days or even weeks before labor onset. Indeed, many forms of spontaneous preterm labor that result from premature initiation of phase 2 of parturition may be viewed in this light. Although the end result in preterm birth is the same as at term, namely cervical ripening and myometrial activation, recent studies in animal models support the idea that preterm birth is not always an acceleration of the normal process. Diverse pathways to instigate parturition exist and are dependent on the etiology of preterm birth. Identification of both common and uncommon factors has begun to explain the physiological processes of human parturition at term and preterm. Four major causes of spontaneous preterm labor include uterine distention, maternal-fetal stress, premature cervical changes, and infection.

UTERINE DISTENTION

There is no doubt that multifetal pregnancy and hydramnios lead to an increased risk of preterm birch. It is likely that early uterine distention acts to initiate expression of contraction-associated proteins

(CAPs) in the myometrium. The *CAP* genes that are influenced by strech include chose coding for gap-junction proteins such as connexin 43, for oxytocin receptors, and for prosraglandin synthase. Recent reports suggest char gamin-releasing peptides (GRPs) are increased with screech to promote myometrial contractility and char GRP antagonists can inhibit uterine contractility. There is also a stretch-induced potassium channel-TREK-1-rhar is upregulated during gestation and down regulated in labor. This pattern of expression is consistent with a potential role in uterine relaxation during pregnancy (Buxton, 2010). Expression of TREK- I splice variants char block function of the full-length TREK- I have been recently identified in myometrium from women with preterm labor. This further implicates a role for TREK-I in uterine quiescence (Wu, 2012). Although these and other regulatory factors remain to be validated, it is clear that excessive uterine strech causes premature loss of myometrial quiescence.

Excessive uterine stretch also leads co early activation of the placental- fetal endocrine cascade. The resulting early rise in maternal corticotropin- releasing hormone and estrogen levels can further enhance the expression of myometrial *CAP* genes.

Finally, the influence of uterine stretch should be considered with regard to the cervix. For example, cervical length is an important risk factor for preterm birth in multi- fetal pregnancies.

Prematurely increased stretch and endocrine activity may initiate events char shift the timing of uterine activation, including premature cervical ripening.

MATERNAL - FETAL STRESS

Stress is defined as a condition or adverse circumstance char disturbs the normal physiological or psychological functioning of an individual. But the complexities of measuring "mess" are what cause difficulty in defining its exact role.

As discussed earlier, the last trimester is marked by rising maternal serum levels of placental-derived corricotropin-releasing hormone (CRH). This hormone works with adrenocorticotropic hormone (ACTH) to increase adult and fetal adrenal steroid hormone production, including the initiation of fetal cortisol biosynthesis. Rising levels of maternal and feral cortisol further increase placental CRH secretion. Rising levels of CRH further stimulate fetal adrenal dehydroepiandrosreronesulfate

(DHEA-S) biosynthesis, which acts as substrate to increase maternal plasma estrogens, particularly estriol.

It has been hypothesized that a premature rise in cortisol and estrogens results in an early loss of uterine quiescence. Because of large variations in CRH levels among pregnant women, however, a single CRH measurement has low sensitivity.

It may be that the *rate of increase* in maternal CRH levels is possibly a more accurate predictor of preterm birth. Confounding factors include CRH variability among ethnic groups.

Another is that placental CRH enters the feral circulation-albeit at lower levels than in the maternal circulation. In vitro studies have shown char CRH can directly stimulate feral adrenal production of DHEA-S and cortisol.

Thus, current studies do not support the idea that CRH levels alone have a positive-predictive value for preterm birth risk.

If preterm delivery is associated with early activation of the feral adrenal-placental endocrine cascade, maternal estrogen levels would likely be prematurely elevated. This is indeed the case. An early rise in serum estriol concentrations is noted in women with subsequent preterm

labor. Physiologically, this premature rise in estrogen levels may alter myometrial quiescence and accelerate cervical ripening.

Taken together, these observations suggest that preterm birth is associated, in many cases, with a maternal-fetal biological stress response. The stressors that activate this cascade likely are broad, and the stress response is dependent on the stressor.

For example, CRH or estriol levels are prematurely elevated in preterm birth due to infection and multifetal pregnancies bur nor in pregnant women with perceived stress.

Chronic, psychological stress- resulting for example from racial discrimination-appears to promote impaired cellular immune competence (Christian, 2012b). A growing body of work in the area of psychoneuro immunology will perhaps enhance the understanding of pathways that link stress with adverse birth outcomes.

INFECTION

There is great interest in the role of infection as a primary cause of preterm labor in pregnancies with intact membranes.

In some cases, there is histological evidence of inflammation in the feral membranes, decidua, or umbilical cord, whereas other cases are deemed "subclinical." More recently, new technologies based on genomic analysis of a mixed population of microorganisms have shown that the non pregnant vaginal tract hosts a complex microbial community that can differ widely between women who are all healthy.

The application of the field of *metagenomics*to understanding microbiome complexity in term and preterm birth and to identifying microbe populations that may mediate subclinical infection holds great promise.

There are considerable data chat associate chorioamnionitis with preterm labor. In such infections, the microbes may invade maternal tissue only and not amnionic fluid. Despite this, endotoxins can stimulate amnionic cells to secrete cytokines that enter amnionic fluid. This scenario may serve co explain the apparently contradictory observations concerning an association between amnionic fluid cytokines and preterm labor, in which microbes were not detectable in the amnionic fluid.

Sources for Intrauterine Infection. The patency of the female reproductive tract, although essential for achievement of pregnancy and delivery, is theoretically problematic during phase 1 of parturition.

It has been suggested that bacteria can gain access to intrauterine tissues through:

(1) transplacental transfer of maternal systemic infection,

(2) retrograde flow of infection into the peritoneal cavity via the fallopian cubes, or

(3) ascending infection with bacteria from the vagina and cervix. The lower pole of the feral membrane-decidual junction is contiguous with the cervical canal orifice, which is patent to the vagina. This anatomical arrangement provides a passageway for microorganisms, and ascending infection is considered to be the most common. A thoughtful description of the potential degrees of intrauterine infection has been provided by Goncalves and associates (2002). They categorize intrauterine infection into four stages of microbial invasion that include bacterial vaginosis-stage I, decidual infection- stage II, amnionic infection-stage III, and finally, fecal systemic infection-stage IV. As expected, progression of these stages is thought to increase rates of preterm birth and neonatal morbidity.

Microbes Associated with Preterm Birth. Some micro-organisms-examples include *Gardnerella vaginalis, Fusobacterium, Mycoplasma hominis,* and *Ureaplasma urealyticum-are* detected more frequently than others in amnionic fluid of women with preterm labor.

This finding was interpreted by some as presumptive evidence that specific microorganisms are more commonly involved as pathogens in the induction of preterm labor. Another interpretation, however, is that given direct access to the membranes after cervical dilatation, selected microorganisms, such as fusobacteria, that are more capable of burrowing through these exposed tissues will do so. Fusobacteria are found in the vaginal fluid of only 9 percent of women but in 28 percent of positive amnionic fluid cultures from pregnancies with preterm labor and intact membranes (Chaim, 1992). Knowledge from metagenomic studies will better define these interactions in the future. In addition, host responses to pathogens with respect to mucosal immunity, barrier protection of ceivical and vaginal epithelia, and expression of antimicrobial peptides is likely to provide insights. Specifically, the mechanisms that render some women more susceptible to infection-mediated preterm birth may be found.

Intrauterine Inflammatory Response. The initial inflammatory response elicited by bacterial toxins is mediated, in large measure, by specific receptors on mononuclear phagocytes, decidual cells, cervical epithelia, and trophoblasts. These *Toll-like receptors* represent a family that has evolved to recognize pathogen -associated molecules Janssens, 2003). Toll- like receptors are present in the placenta on trophoblast cells, in the cervical epithelia, and on fixed and invading leukocytes.

PRETERM PREMATURE RUPTURE OF MEMBRANES

This term defines spontaneous rupture of the fetal membranes before 37 completed weeks and *before labor onset* (American College of Obstetricians and Gynecologists, 2013d). Such rupture likely has various causes, but intrauterine infection is believed by many to be a major predisposing event. There are associated risk factors that include low socioeconomic status, body mass index 19.8, nutritional deficiencies, and cigarette smoking. Women with prior preterm premature rupture of membranes (PPROM) are at increased risk for recurrence during a subsequent pregnancy (Bloom, 2001). Despite these known risk factors, none is identified in most cases of preterm rupture.

MOLECULAR CHANGES

Preterm membrane rupture pathogenesis may be related to increased apoptosis of membrane cellular components and to increased levels of specific proteases in membranes and amnionic fluid. Most tensile strength of the membranes is provided by the amniontic extracellular matrix and interstitial amnionic collagens- primarily type I and III-which are produced in mesenchymal cells (Casey, 1996). For that reason, collagen degradation has been a focus of research. The matrix metalloproteinase (MMP) family is involved with normal tissue remodeling and particularly with collagen degradation. The MMP-1, MMP-2, MMP-3, and MMP-9 members of this family are found in higher concentrations in amnionic fluid from pregnancies with preterm prematurely ruptured membranes (Maymon, 2000; Park, 2003; Romero, 2002). MMP activity is in pan regulated by tissue inhibitors of matrix metalloproteinases-TIMPs. Several of these inhibitors are found in lower concentrations in amniotic fluid from women with ruptured membranes. Elevated MMP levels found at a time when protease inhibitor expression decreases supports further that their expression alters amniotic tensile strength. Studies of amniochorion explants have demonstrated char the expression of MMPs can be increased by treatment with ·IL-1, TNF-a, and IL-6.

In pregnancies with PPROM, the amnion exhibits a higher degree of cell death and more apoptosis markers than that in term amnion.

In vitro studies indicate that apoptosis is likely regulated by bacterial endotoxin, IL- I, and TNF-a. Last, there are proteins involved in the synthesis of mature cross-linked collagen or matrix proteins that bind collagen and thereby promote tensile strength. These proteins are altered in membranes with premature rupture.

Taken together, these observations suggest that many PPROM cases result from collagen degradation, altered collagen assembly, and cell death, which all lead to a weakened amnion.

INFECTION

Several studies have been done to ascertain the incidence of infection-induced premature membrane rupture. Bacterial cultures of amnionic fluid support a role for infection in significant proportion.

Overall, there is compelling evidence that infection causes a significant proportion of PPROM cases. The inflammatory response that leads to membrane weakening is currently being defined. Research is focused on mediators of this process with a goal to identify early risk markers for PPROM.

MULTIFETAL GESTATION

Twins and higher-order multifetal births account for approximately 3 percent of infants born in the United Scares (Martin, 2009a). The majoriry-95 percent-of these births are twins. Compared with 1980, the rates of multiple births increased steadily and peaked in 1998. Current rates have declined since then, but remain higher than the 1980s. The increased rate of multifetal births is due to the increased number of women having babies after the age of 30. In addition, the use of fertility treatments has contributed to the elevated rates of multifetal pregnancies. Preterm delivery continues to be the major cause of the excessive perinatal morbidity and mortality with multifetal pregnancies.

ANTECEDENTS AND CONTRIBUTING FACTORS

Myriad generic and environmental factors affect the frequency of preterm labor.

THREATENED ABORTION

Vaginal bleeding in early pregnancy is associated with increased adverse outcomes later. Weiss (2004) reported outcomes with vaginal bleeding at 6 to 13 weeks in nearly 14,000 women. Both light and heavy bleeding were associated with subsequent preterm labor, placental abruption, and subsequent pregnancy loss before 24 weeks.

REVIEW OF LITERATURE

The prevalence of anti-thyroid peroxidase antibodies in subclinical and clinical hypothyroid patients.

Jayashankar C.A.1, Avinash S.2*, Shashidharan B.3, Vijaya Sarathi.4, Shruthi K.R.5, Nikethan D.5, Harshavardhan J.5

INTRODUCTION

Subclinical hypothyroidism is a state of mild thyroid failure and is essentially a laboratory diagnosis with elevated serum thyroid stimulating hormone (TSH) and a normal free thyroxine (FT4) concentration.1 Subclinical hypothyroidism is much more common than overt hypothyroidism and hence the early diagnosis and treatment of the condition may prevent the onset of overt hypothyroidism and its associated effects. Patients with subclinical hypothyroidism with high titre of antithyroperoxidase (anti-TPO) antibodies are more likely to progress to overt hypothyroidism. Most of the hypothyroid patients have an elevated anti-TPO titre, suggesting an autoimmune etiology for hypothyroidism. Literature evidence substantiates the positive association between serum anti-TPO levels and the activity of chronic autoimmune thyroiditis.

ABSTRACT

Background: Subclinical hypothyroidism is a state of mild thyroid failure and is essentially a laboratory diagnosis with elevated serum thyroid stimulating hormone (TSH) and a normal free thyroxine (FT4) concentration. The main objective of study is to evaluate the prevalence of anti-thyroid peroxidise (anti-TPO) antibodies among patients with clinical and subclinical hypothyroidism. Methods: A prospective study was conducted involving 50 patients with biochemical evidence of hypothyroidism. Subclinical hypothyroidism was defined as thyroid stimulating hormone (TSH) >5.0 μIU/ml with normal FT4 and clinical hypothyroidism as free thyroxine (FT4) and high TSH. A detailed history, clinical examination, and investigations comprising of complete haemogram, fasting plasma glucose, fasting FT4, TSH, anti-TPO antibodies and lipid profile were done for all the patients. Results: Out of 50 cases, 28 subjects had clinical hypothyroidism (25 females and 3 males) and 22 had subclinical hypothyroidism (14 females and 8males). Among the 50 subjects with clinical and subclinical hypothyroidism, 33 were anti-TPO positive. The corresponding percentage of anti-TPO positivity noted in the clinical hypothyroidism and subclinical hypothyroidism groups were 80 % and 50% respectively. Conclusions: Serum TSH and anti-TPO analyses are essential in determining the

etiology of hypothyroidism and risk of progression to overt hypothyroidism in patients with subclinical.

Keywords: Clinical hypothyroidism, Subclinical hypothyroidism, Anti-TPO antibodies 1Associate Professor, 2Senior Resident, 3Professor, 5Postgraduate student, Department of General Medicine, Vydehi Institute of Medical sciences and research centre, Whitefield, Bangalore Karnataka, India 4Assistant Professor, Department of Endocrinology, Vydehi Institute of Medical sciences and research centre, Whitefield, Bangalore Karnataka, India

Received: 02 October 2015 Accepted: 17 November 2015

*Correspondence: Dr. Avinash S, E-mail: avinashtwins05@gmail.com

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20151399

Jayashankar CA et al. Int J Res Med Sci. 2015 Dec;3(12):3564-3566

TYPE OF STUDY

Cross sectional study

PERIOD OF STUDY

JANUARY 2017-AUGUST 2017

PLACE OF STUDY

LABOUR WARD & PN WARD, Department of Obstetrics and Gynecology, Kilpauk Medical College & Hospital, Chennai.

INCLUSION CRITERIA

- Pregnant women of all ages,
- Both primi and multigravida,
- Both euthyroid and hypothyroid,
- Patients with preterm deliveries,
- Post natal and postabortal women,
- First trimester abortions and recurrent pregnancy losses,
- Preterm and term IUD'S.

EXCLUSION CRITERIA

- Pre eclampsia
- Diabetes
- PROM

- Antepartum haemorrhage
- Infections
- Incompetent cervix
- Uterine anomalies

SAMPLE SIZE

With the prevalence of TPOAb in pregnant women of 9.3% with an absolute precision of 5% at 95% confidence interval, the estimated sample size is 130. Assuming a non response of 10%, the sample size will be 143.

$N = Z^2 * p * (1-p) / d^2$

$= 1.96^2 * 9.3 * 90.7 / 5^2$

$= 129.56$

~ 130

With 10% non response, N = 130 * 0.1(130) = 143

MATERIALS AND METHODS

1) All patients who had preterm deliveries, IUD, miscarriages irrespective of gestational age.

2) Detailed history;

   Antenatal history, past history, treatment history

   General examination;

   Obstetric examination;

3) Blood is drawn for basic investigations like CBC, RFT, LFT, thyroid profile, thyroid peroxidase antibodies.

4) Routine urine analysis, urine spot PCR if needed.

STATISTICAL ANALYSIS

With the prevalence of TPOAb in pregnant women of 9.3% with an absolute precision of 5% at 95% confidence interval, the prevalence of TPOAb among the preterm deliveries, IUD ‘s, miscarriages were analysed. And also the associated co-morbidities were also analysed.

RESULTS

PROFILE OF THE STUDY CASES

TABLE 1

Lifestyle

AGE CATEGORIES

	Frequency	Percent
< 20 years	13	10.0
20 - 22 years	35	26.9
23 - 25 years	48	36.9
26 - 28 years	25	19.2
> 28 years	9	6.9
Total	130	100.0

Of the 130 cases,48 (36.9) were in the age group between 23-25 years.

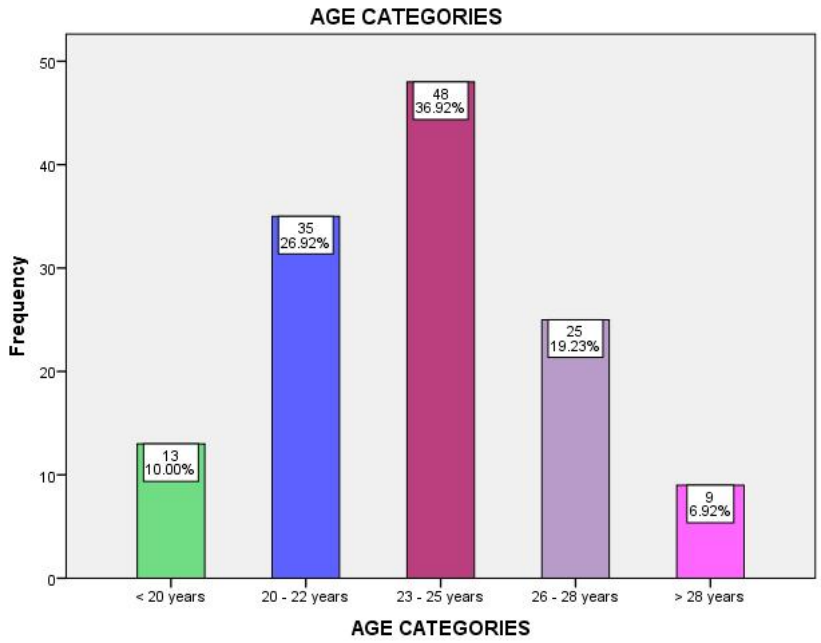


TABLE 2

PARITY

	Frequency	Percent
PRIMI	85	65.4
G2P1	1	0.8
G2P1L1	34	26.2
G3A2	1	0.8
G3P1L1A1	3	2.3
G3P2L2	5	3.8
Total	130	100.0

Of the 130 cases 85 cases (65.4%) were primi.

TABLE 3

GRAVIDA

	Frequency	Percent
1	85	65.4
2	36	27.7
3	9	6.9
Total	130	100.0

Of the 130 cases 85 (65.4%) were primi.

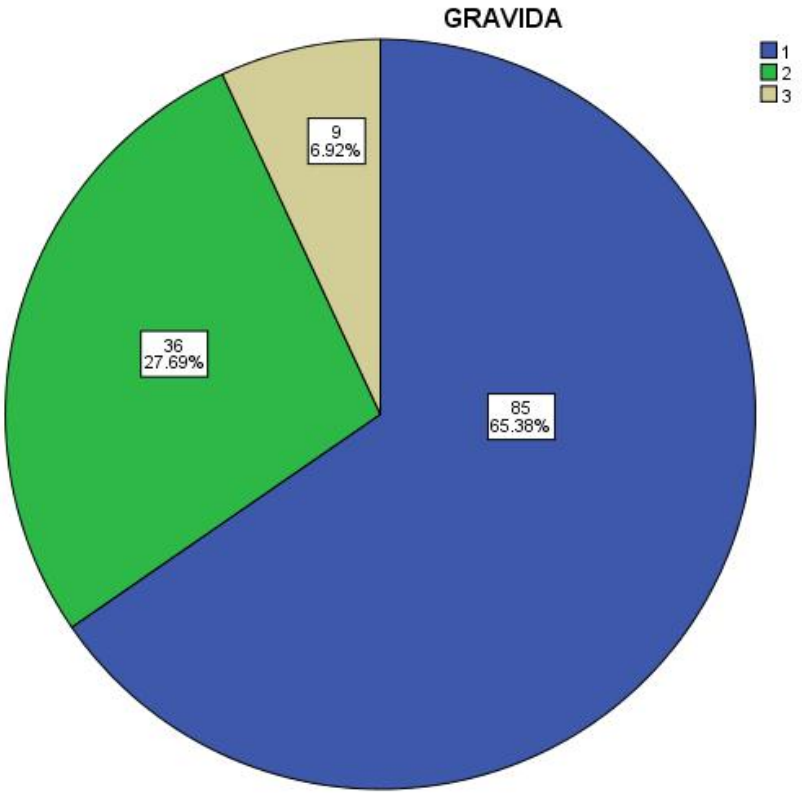


TABLE 4

PARITY

	Frequency	Percent
1	38	88.4
2	5	11.6
Total	43	100.0

Of the 43 cases 38(88.4%) were primipara.

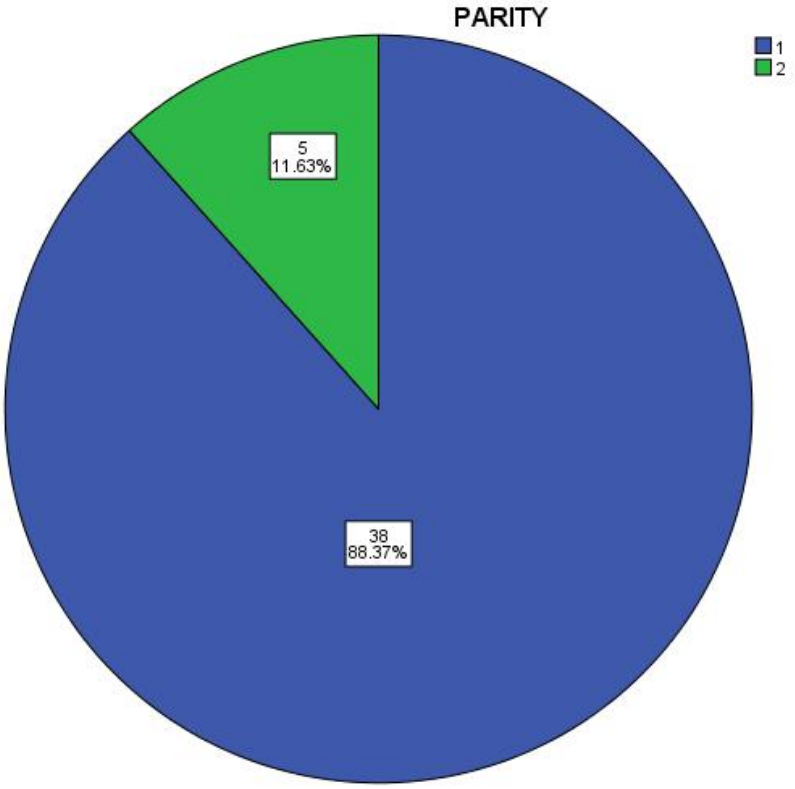


TABLE 5

LIVE BIRTHS

		Frequency	Percent
Valid	1	37	88.1
	2	5	11.9
	Total	42	100.0

Of the 42 cases 37(88.1%) are live births.

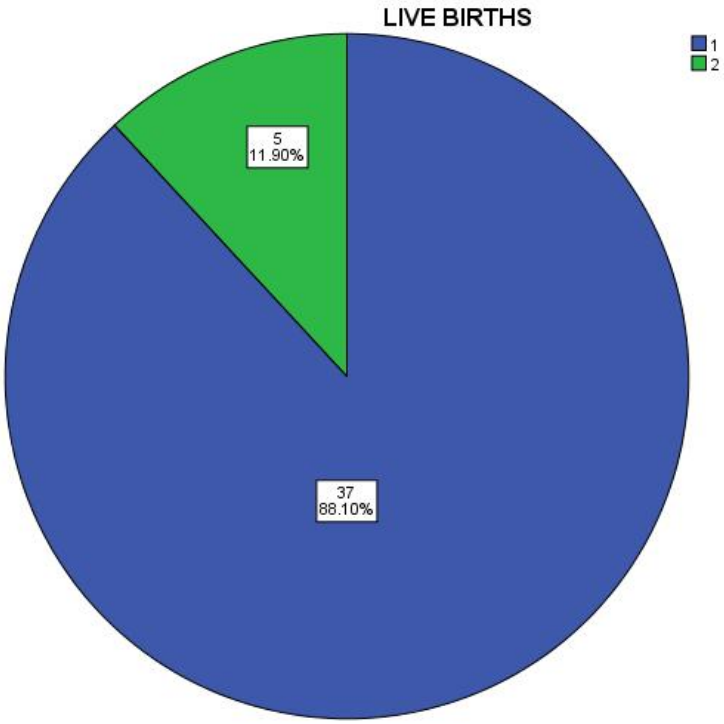


TABLE 6

ABORTIONS

		Frequency	Percent
Valid	primi	4	80
	multipara	1	20
	Total	5	100

Of the 5 cases 4(80%) were primigravida.

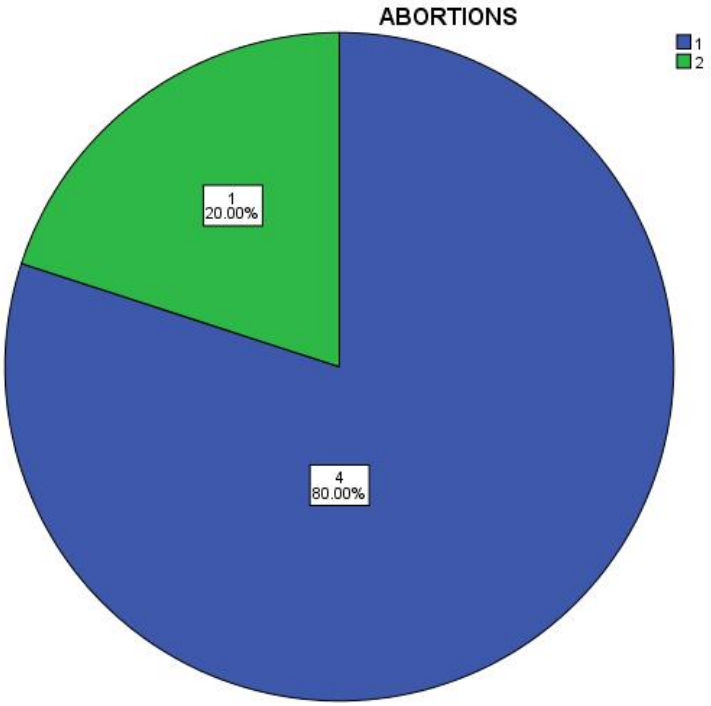


TABLE 7

MODE OF DELIVERY

	Frequency	Percent
LN	80	61.5
LSCS	11	8.5
ABORTION	19	14.6
IUD	20	15.4
Total	130	100.0

Out of 130 cases 80 were labour natural, 11 were LSCS, 19 were abortions, 20 were IUD.

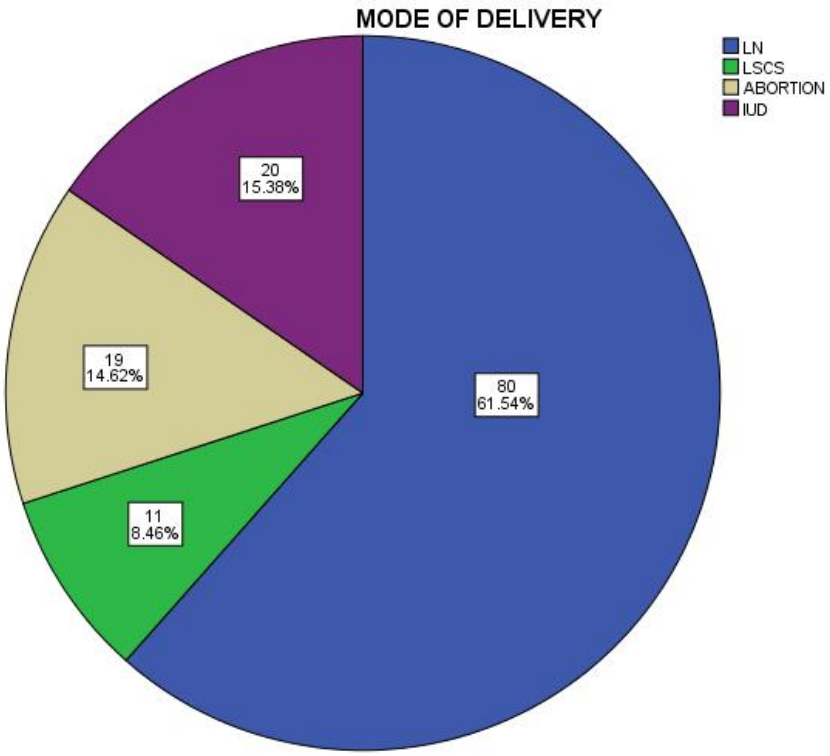


TABLE 8

	N	Minimum	Maximum	Mean	Std. Deviation	Median
TPOAB	130	0	1000	19.58	124.23	0.37
T3	130	67.24	298.6	144.24	40.11	139.1
T4	130	2.86	18.19	10.41	3.06	9.69
TSH	130	0.08	27.97	3.06	3.85	1.9

TABLE 9

TPOAB

	Frequency	Percent
HIGH	16	12.3
NORMAL	114	87.7
Total	130	100.0

Of the 130 cases TPOAb were high in 16(12.3%)

TABLE 10

T3

	Frequency	Percent
HIGH	13	10.0
NORMAL	115	88.5
LOW	2	1.5
Total	130	100.0

Of the 130 cases T3 were high in 13 (10%)

TABLE 11

T4

	Frequency	Percent
HIGH	41	31.5
NORMAL	85	65.4
LOW	4	3.1
Total	130	100.0

Of the 130 cases T4 is high in 41(31%)

TABLE 12

TSH

	Frequency	Percent
HIGH	19	14.6
NORMAL	103	79.2
LOW	8	6.2
Total	130	100.0

Of the 130 cases TSH were high in 19(14.6%)

TABLE 13

ASSOCIATION OF AGE WITH TPOAB

AGE CATEGORIES	**TPOAB**		**Total**	**Fisher exact p value**
	HIGH	**NORMAL**		
< 20 years	0 (0%)	13 (100%)	13 (100%)	0.0009
20 - 22 years	2 (5.71%)	33 (94.28%)	35 (100%)	
23 - 25 years	4 (8.33%)	44 (91.66%)	48 (100%)	
26 - 28 years	8 (32%)	17 (68%)	25 (100%)	
> 28 years	2 (22.22%)	7 (77.77%)	9 (100%)	
Total	16 (12.3%)	114 (87.69%)	130 (100%)	

Out of 130 cases 16 have high TPOAB is statistically significant and it is not age specific.

TABLE 14

COMPARISON OF AGE IN HIGH AND NORMAL VALUES OF TPOAB

CHARACTERISTIC	HIGH		NORMAL		p VALUE BY Mann Whitney 'U' TEST
	MEAN	S.D.	MEAN	S.D.	
AGE	26.69	4.60	23.48	3.42	0.001

TABLE 15

ASSOCIATION OF TPOAB WITH GRAVIDA

GRAVIDA	TPOAB		Total	Fisher exact p value
	HIGH	NORMAL		
1	6 (7.05%)	79 (92.94%)	85 (100%)	0.0585791
2	10 (27.77%)	26 (72.22%)	36 (100%)	
3	0 (0%)	9 (100%)	9 (100%)	
Total	16 (12.3%)	114 (87.69%)	130 (100%)	

TABLE 16

PARA	TPOAB		Total	Chi sq test p value
	HIGH	NORMAL		
1	10 (26.31%)	28 (73.68%)	38 (100%)	0.19040081
2	0 (0%)	5 (100%)	5 (100%)	
Total	10 (23.25%)	33 (76.74%)	43 (100%)	

Out of 130 cases 10 in second gravida and 10 in primi have high TPOAB which is statistically not significant.

TABLE 17

LIVE	TPOAB		Total	Chi sq test p value
	HIGH	NORMAL		
1	10 (27.02%)	27 (72.97%)	37 (100%)	0.18293117
2	0 (0%)	5 (100%)	5 (100%)	
Total	10 (23.8%)	32 (76.19%)	42 (100%)	

TABLE 18

ABORTIONS	TPOAB (NORMAL)
1	4 (100%)
2	1 (100%)
Total	5 (100%)

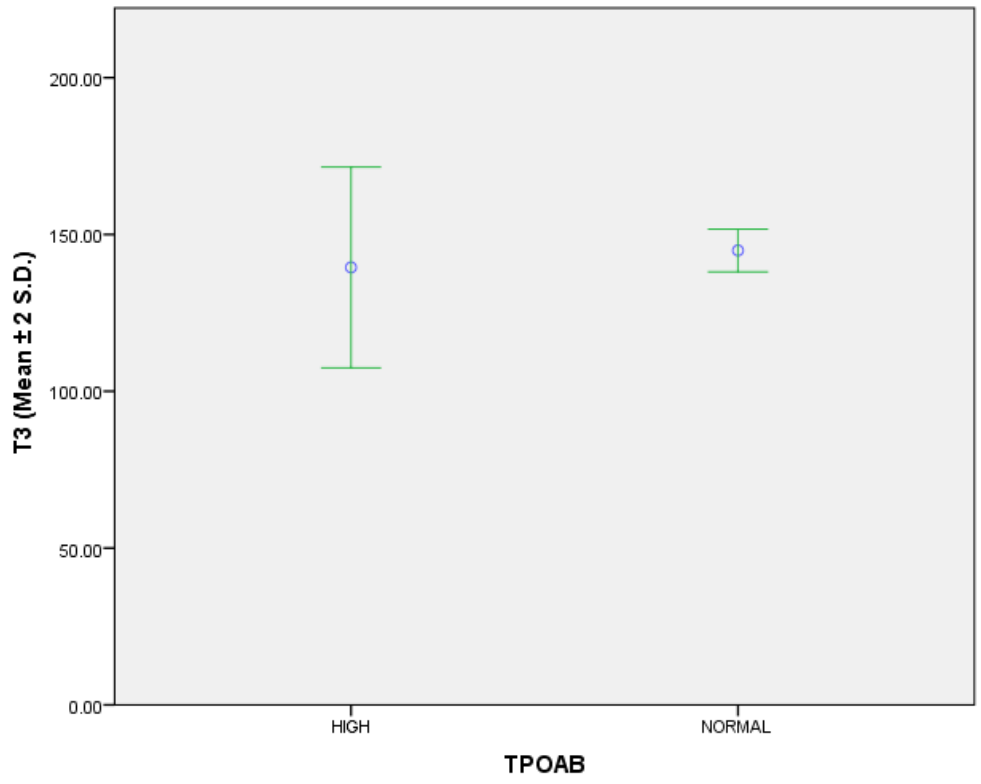
TABLE 19

CATEGORIES	HIGH TPOAb	Total
Preterm birth	13	91
IUD	1	20
MISCARRIGE	2	19
TOTAL	16	130

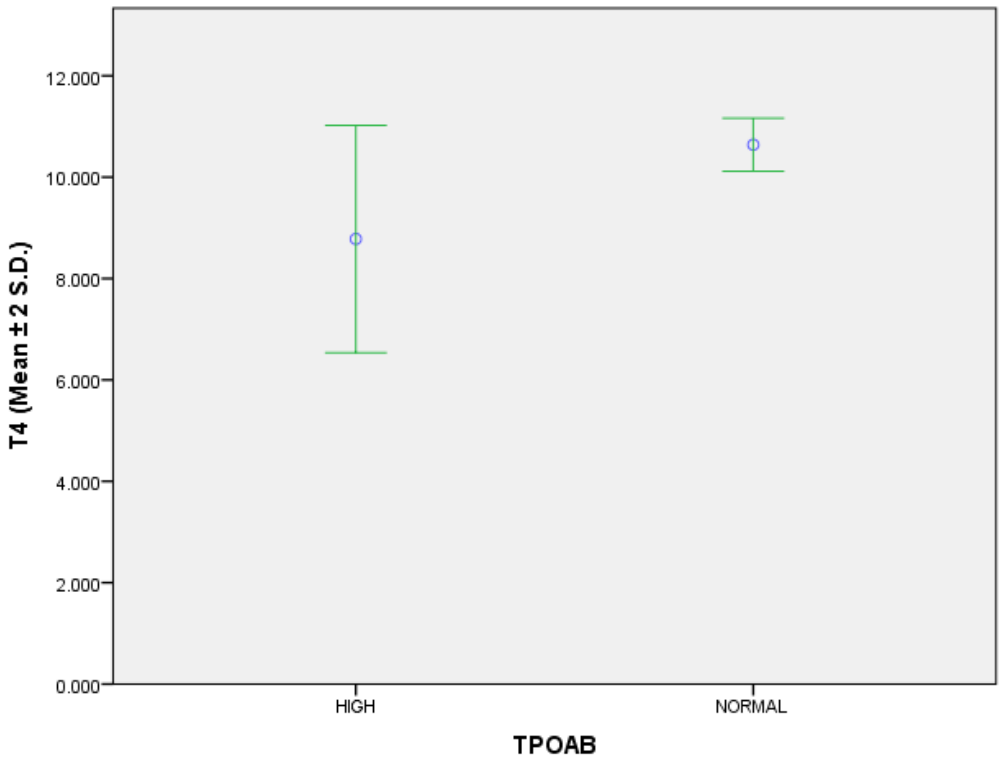
TABLE 20

MODE	TPOAB		Total	Fisher exact p value
	HIGH	NORMAL		
LN	10 (12.5%)	70 (87.5%)	80 (100%)	0.072
LSCS	3 (27.27%)	8 (72.72%)	11 (100%)	
ABORTION	2 (10.52%)	17 (89.47%)	19 (100%)	
IUD	1 (5%)	19 (95%)	20 (100%)	
Total	16 (12.3%)	114 (87.69%)	130 (100%)	

Out of 130 cases TPOAB are high in 10 labornatural, 3 in LSCS ,2 in abortions and 1 in IUD.


200.00
150.00
100.00
50.00
0.00
T3 (Mean ± 2 S.D.)
HIGH
NORMAL
TPOAB

.


12.000
10.000
8.000
6.000
4.000
2.000
0.000
T4 (Mean ± 2 S.D.)
HIGH
NORMAL
TPOAB

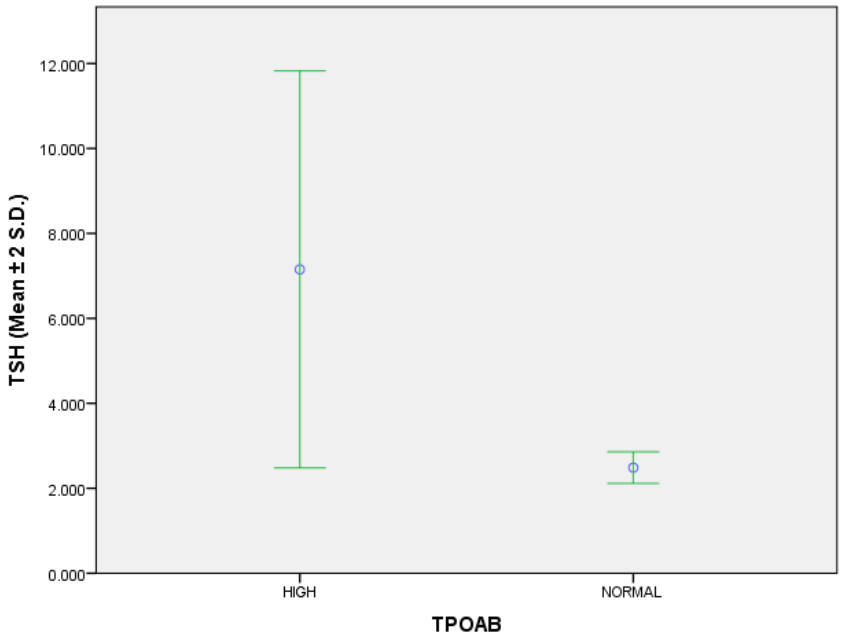


TABLE 19

ASSOCIATION OF T3, T4 AND TSH

VARIABLE		TPOAB		Fisher exact p value
		HIGH	NORMAL	
T3	**HIGH**	3 (23.08%)	10 (76.92%)	<0.0001
	NORMAL	11 (9.57%)	104 (90.43%)	
	LOW	2 (100%)	0 (0%)	
T4	**HIGH**	2 (4.88%)	39 (95.12%)	<0.0001
	NORMAL	12 (14.12%)	73 (85.88%)	
	LOW	2 (50%)	2 (50%)	
TSH	**HIGH**	6 (31.58%)	13 (68.42%)	<0.0001
	NORMAL	10 (9.71%)	93 (90.29%)	
	LOW	0 (0%)	8 (100%)	

The association between the T3,T4and TSH is statistically significant.

CONCLUSION

In our setup the following results are obtained in my study

1-Irrespective of age TPOAB high in all age groups.

2-Irrespective of parity TPOAB are prevalent.

3-Among the preterm deliveries both by labour natural and LSCS 0ut of 91, 13 were TPOAB high. Among 19 abortions 2 have high TPOAB high. Among 20 IUD 1 have high TPOAB high

4-The TPOAB association with T3, T4 and in TSH, it is more associated with TSH significantly.

- In my study out of 130 cases 36.6% were in age group between 23-25 yrs, 26.2% were second gravida, 88.1% were preterm births,19% abortions, 61.1% labour natural,20% IUD.
- TPOAB were high in 12.3%, T3 were high in 10%,T4 were high in 31.5%,TSH were high in 14.6%.
- TPOAB are prevalent in age 26-28 years, 5% IUD, 10% in abortions.
- The association of TPOAB with TSH is high and significant.

- Hence from this study I conclude that screening for thyroid is important in pregnancy.
- To avoid subclinical hypothyroidism and its complications screening for TPOAB is also important.

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[1]Endocrine Research Center, Research Institute for Endocrine Sciences, Shaheed Beheshti University of Medical Sciences, P.O. Box 19395-4763, Tehran, Iran

[2]Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3]Departments of Oncology, Medicine, Obstetrics, Gynecology, Pharmacology, and Physiology, Georgetown University Medical Center, Washington, DC 20057, USA

Received 19 December 2012; Accepted 27 March 2013

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MASTER CHART

S. NO	NAME	AGE	PARITY	MODE	TPO AB	T3	T4	TSH
1	SANGEETHA	24	G2P1L1	LN	0.36	124	8.19	1.65
2	MEENA	22	PRIMI	IUD	0.52	128.60	9.62	1.22
3	NAZRINBANU	27	G2P1L1	ABORTION	0.20	152.70	12.27	1.310
4	DEVI	22	PRIMI	ABORTION	0.17	109.4	9.69	1.660
5	JAYALAKHSMI	33	G2P1L1	LN	0.49	143.9	9.30	1.07
6	PAVITHRA	22	PRIMI	LN	2.89	152.9	15.34	0.353
7	FARZHANA	26	G2P1L1	IUD	0.49	163.7	13.85	3.06
8	AMMU	28	G2P1L1	ABORTION	>1000	132.0	8.37	9.04
9	PRIYADHARSHINI	19	PRIMI	LN	0.32	220.6	15.14	1.85
10	MANIMEGALAI	21	PRIMI	LN	0.41	188.8	16.22	0.66
11	VIJAYA	23	PRIMI	LN	0.24	81.59	8.67	1.61
12	MAHESHWARI	36	G2P1L1	ABORTION	0.56	107.1	9.14	1.90
13	NAVINA	23	PRIMI	IUD	0.48	81.04	7.14	1.70
14	VASANTHA	37	G2P1L1	LSCS	43.51	67.24	4.81	4.31
15	AMALA	26	G2P1L1	LN	10.91	213.8	18.19	1.28
16	SHARMILA	27	G2P1L1	LN	0.27	121.7	8.28	0.896
17	SATHYA	22	PRIMI	IUD	0.49	140.1	11.30	0.619
18	JANANI	23	PRIMI	ABORTION	4.46	185.70	13.42	0.945
19	DHIVYA BHARATHI	22	PRIMI	LN	0.29	154.40	10.70	1.600
20	PRIYA DHARSHINI	21	PRIMI	LN	5.38	174.90	10.26	2.480
21	SANDHYA	19	PRIMI	IUD	0.26	134.30	8.26	0.666
22	PARAMESHWARI	23	PRIMI	LN	0.20	168.60	13.48	5.910
23	DURGA	21	PRIMI	IUD	0.19	108.50	6.87	1.650
24	PARVATHY	24	PRIMI	ABORTION	0.46	184.84	11.11	6.230
25	MANJU	25	G2P1L1	LN	0.24	142.60	10.05	1.920
26	GRACY	23	PRIMI	LN	0.06	162.00	11.36	4.380
27	DEVI	26	G2P1L1	LSCS	6.42	138.10	9.47	0.388
28	ANUPRIYA	19	PRMI	ABORTION	0.23	110.40	8.32	0.706
29	GLORY	23	PRIMI	IUD	0.20	132.00	10.39	2.040
30	USHA	22	PRIMI	LN	0.19	89.38	6.78	1.330
31	JAYANTHI	24	PRIMI	LN	10.74	99.13	9.67	1.090
32	KALAIVANI	30	G2P1L1	LN	0.35	140.90	10.57	6.270

S. NO	NAME	AGE	PARITY	MODE	TPO AB	T3	T4	TSH
33	SANGEETHA	19	PRIMI	LN	0.64	122.40	9.69	1.950
34	ANUSHYA	18	PRIMI	LN	0.45	157.00	13.48	1.540
35	NANDHINI	24	G2P1L1	IUD	0.13	189.20	12.95	2.360
36	LALITHA	26	G3P1L1A1	ABORTION	0.36	170.70	13.56	0.080
37	SARANYA	19	PRIMI	LN	0.17	187.30	13.92	2.450
38	UMAMAHESHWARI	23	PRIMI	LSCS	0.31	99.31	7.62	3.570
39	JANAKI	25	PRIMI	LN	0.32	102.20	7.28	1.540
40	JAYANTHI	27	G3P2L2	LN	0.21	154.10	14.70	1.720
41	LAKHSMI	26	G2P1L1	LN	0.92	219.60	13.09	4.970
42	SARANYARAMALINGAM	20	PRIMI	LN	0.36	107.70	8.57	0.335
43	JAHURAAKTAR	28	G2P1L1	LN	47.79	108.00	6.92	27.970
44	GANGA	21	PRIMI	IUD	0.37	102.20	7.10	1.780
45	GIRIJA	22	PRIMI	ABORTION	1.50	232.30	13.40	8.140
46	ANBARASI	23	PRIMI	IUD	0.19	96.17	7.33	2.400
47	AKLIMA	25	G2P1L1	LN	0.23	123.50	9.52	2.900
48	KANIMOZHI	25	PRIMI	LN	0.22	207.00	15.35	1.030
49	SUJATHA	25	PRIMI	LN	0.22	120.80	9.15	6.750
50	PREMA	28	G3P2L2	LN	0.34	147.80	12.95	2.590
51	NADHIYA	23	PRIMI	LN	0.15	175.60	13.42	3.670
52	CHITHRAVIJAYASANKAR	27	G3P1L1A1	IUD	0.23	128.20	10.47	1.720
53	SARANYA	20	PRIMI	LSCS	0.18	206.90	11.85	2.840
54	CHITHRA	22	PRIMI	LN	174.93	113.60	8.71	4.770
55	PARVEEN NISHA	22	PRIMI	LN	0.41	105.10	10.92	1.200
56	DEVI RAJAMANI	23	PRIMI	LN	5.12	129.8	9.070	0.494
57	JAYANTHI	23	PRIMI	IUD	0.32	127.6	8.33	2.26
58	PARVATHY	24	PRIMI	ABORTION	0.29	166.1	12.85	2.01
59	PACHAIYAMMAL	24	PRIMI	ABORTION	0.69	147.20	9.41	0.261
60	MENAKA	24	PRIMI	IUD	2.48	113.90	8.45	3.140
61	JENCY	21	PRIMI	LN	0.42	143.87	11.88	3.624
62	SATHYA	23	PRIMI	LN	0.29	154.87	8.46	2.740
63	NITHYA	24	PRIMI	LN	3.23	164.88	7.32	7.210
64	PRIYA	23	PRIMI	LSCS	6.43	174.8	9.043	3.201
65	PRABHA	23	PRIMI	IUD	4.12	124.78	13.45	2.786
66	PREETHI	22	PRIMI	LN	2.23	113.76	7.45	0.214

S. NO	NAME	AGE	PARITY	MODE	TPO AB	T3	T4	TSH
67	PUSHPA	22	PRIMI	LN	1.46	114.34	8.67	8.246
68	JAYANTHI	21	PRIMI	LN	0.42	232.42	3.86	9.72
69	SAGUNTHALA	20	PRIMI	LN	3.46	146.80	14.98	0.12
70	JEGATHAMBBAL	27	G2P1L1	LN	0.67	132.80	9.65	3.21
71	ANITHA	32	G3P2L2	IUD	3.24	124.76	8.09	4.1
72	AMUTHA	23	PRIMI	ABORTION	7.43	298.6	3.46	8.96
73	ARUNA	24	G2P1	LSCS	2.12	183.8	15.86	4.07
74	JEYAMMA	26	G2P1L1	LN	0.23	120.3	12.64	3.21
75	PRABHA	24	PRIMI	LN	3..42	132.9	8.42	2.69
76	PRIYA	21	PRIMI	LN	6.43	128.4	4.42	9.34
77	SHEEBHA	20	G2A1	ABORTION	0.45	183.2	2.86	1.83
78	SHINY	20	G3A2	IUD	2.45	163.8	9.42	0.345
79	PONNI	19	PRIMI	IUD	0.67	99.3	11.86	1.45
80	NITHYAPRIYA	22	PRIMI	LN	1.82	108.4	5.86	4.29
81	SANGEETHA	24	G2P1L1	LN	0.36	124	8.19	1.65
82	MEENA	22	PRIMI	LN	0.52	128.60	9.62	1.22
83	NAZRINBANU	27	G2P1L1	LN	0.20	152.70	12.27	1.310
84	DEVI	22	PRIMI	LSCS	0.17	109.4	9.69	1.660
85	JAYALAKHSMI	33	G2P1L1	ABORTION	0.49	143.9	9.30	1.07
86	PAVITHRA	22	PRIMI	ABORTION	2.89	152.9	15.34	0.353
87	FARZHANA	26	G2P1L1	IUD	0.49	163.7	13.85	3.06
88	AMMU	28	G2P1L1	LN	>1000	132.0	8.37	9.04
89	PRIYADHARSHINI	19	PRIMI	LN	0.32	220.6	15.14	1.85
90	MANIMEGALAI	21	PRIMI	LN	0.41	188.8	16.22	0.66
91	VIJAYA	23	PRIMI	LN	0.24	81.59	8.67	1.61
92	MAHESHWARI	36	G2P1L1	LN	0.56	107.1	9.14	1.90
93	NAVINA	23	PRIMI	LN	0.48	81.04	7.14	1.70
94	VASANTHA	37	G2P1L1	LN	43.51	67.24	4.81	4.31
95	AMALA	26	G2P1L1	LN	10.91	213.8	18.19	1.28
96	SHARMILA	27	G2P1L1	LSCS	0.27	121.7	8.28	0.896
97	SATHYA	22	PRIMI	LN	0.49	140.1	11.30	0.619
98	JANANI	23	PRIMI	LN	4.46	185.70	13.42	0.945
99	DHIVYA BHARATHI	22	PRIMI	LSCS	0.29	154.40	10.70	1.600
100	PRIYA DHARSHINI	21	PRIMI	LN	5.38	174.90	10.26	2.480
101	SANDHYA	19	PRIMI	LN	0.26	134.30	8.26	0.666

S. NO	NAME	AGE	PARITY	MODE	TPO AB	T3	T4	TSH
102	PARAMESHWARI	23	PRIMI	LN	0.20	168.60	13.48	5.910
103	DURGA	21	PRIMI	LN	0.19	108.50	6.87	1.650
104	PARVATHY	24	PRIMI	ABORTION	0.46	184.84	11.11	6.230
105	MANJU	25	G2P1L1	IUD	0.24	142.60	10.05	1.920
106	GRACY	23	PRIMI	LN	0.06	162.00	11.36	4.380
107	DEVI	26	G2P1L1	LN	6.42	138.10	9.47	0.388
108	ANUPRIYA	19	PRMI	LN	0.23	110.40	8.32	0.706
109	GLORY	23	PRIMI	LN	0.20	132.00	10.39	2.040
110	JAYANTHI	24	PRIMI	LN	10.74	99.13	9.67	1.090
111	KALAIVANI	30	G2P1L1	LSCS	0.35	140.90	10.57	6.270
112	SUPRIYA	19	PRIMI	ABORTION	0.64	122.40	9.69	1.950
113	ANU	18	PRIMI	ABORTION	0.45	157.00	13.48	1.540
114	NANCY	24	G2P1L1	LN	0.13	189.20	12.95	2.360
115	LAKHSMI	26	G3P1L1A1	LN	0.36	170.70	13.56	0.080
116	SARALA	19	PRIMI	LN	0.17	187.30	13.92	2.450
117	MAHESHWARI	23	PRIMI	LN	0.31	99.31	7.62	3.570
118	JANCY	25	PRIMI	LN	0.32	102.20	7.28	1.540
119	JAYA	27	G3P2L2	LN	0.21	154.10	14.70	1.720
120	LAKHSMIPRIYA	26	G2P1L1	LN	0.92	219.60	13.09	4.970
121	SULOCHANA	20	PRIMI	LSCS	0.36	107.70	8.57	0.335
122	JOSHNA	28	G2P1L1	IUD	47.79	108.00	6.92	27.970
123	GAYATHRI	21	PRIMI	LN	0.37	102.20	7.10	1.780
124	KANCHANA	22	PRIMI	LN	1.50	232.30	13.40	8.140
125	ANGUPRIYA	23	PRIMI	LN	0.19	96.17	7.33	2.400
126	BHUVANA	25	G2P1L1	LN	0.23	123.50	9.52	2.900
127	KUMARI	25	PRIMI	LN	0.22	207.00	15.35	1.030
128	SUMALATHA	25	PRIMI	LN	0.22	120.80	9.15	6.750
129	PRIYANKA	28	G3P2L2	ABORTION	0.34	147.80	12.95	2.590
130	NANDHANA	23	PRIMI	LN	0.15	175.60	13.42	3.670

ANNEXURE

PROFOMA

NAME :

AGE :

IP NO :

ADDRESS

SOCIOECONOMIC STATUS :

MENSTURAL HISTORY :

MARITAL HISTORY :

OBSTETRIC HISTORY :

1) Gravida/Parity/Gestational age

2) Regular ANC

3) LMP EDD

4) Living children

5) Abortion

6) Still birth

7) Previous h/o medical complications

PAST HISTORY

- Diabetes
- Hypertension
- Heart disease
- Tuberculosis
- Chronic renal disease
- Obesity
- Drug intake
- Thyroid status

General examination

Febrile	:	Height :
Pallor	:	Weight :
Pedal edema	:	BMI :
CVS	:	
RS	:	
Per abdomen	:	
Blood investigation	:	
Thyroid profile	:	
Thyroid peroxidase ab	:	

SIGNATURE OF THE INVESTIGATOR:

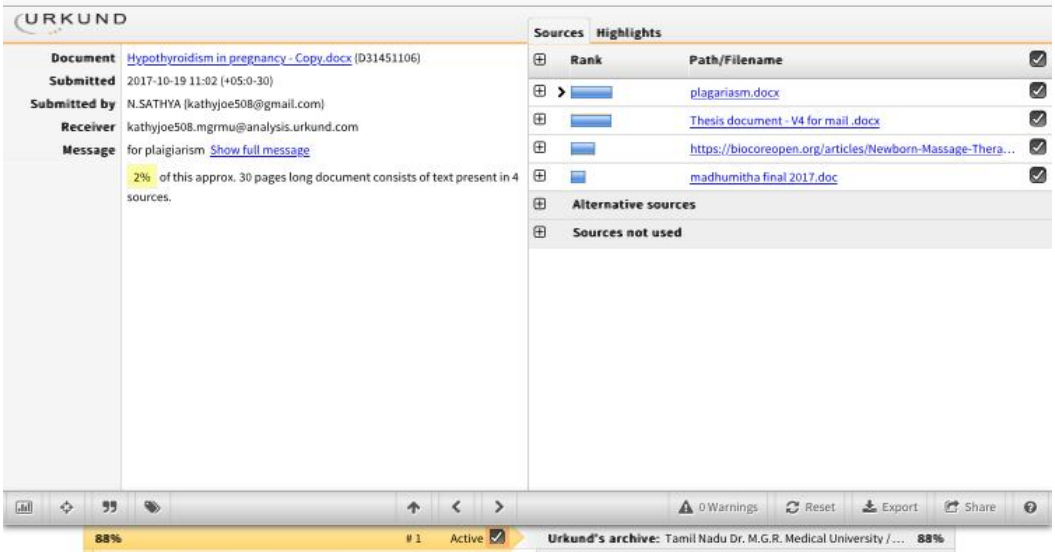
SIGNATURE OF THE GUIDE:

DATE:

CERTIFICATE – II

This is to certify that this dissertation work titled entitled dissertation **"STUDY OF PREVALENCE OF THYROID PEROXIDE ANTIBODIES IN PRETERM DELIVERIES, IUD AND RECURRENT PREGNANCY LOSS"** of the candidate **Dr.N.SATHYA** with Registration Number **221516155** for the award of **M.S** degree in the branch of **OBSTETRICS & GYNAECOLOGY**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **2%** of plagiarism in this dissertation.

Guide & Supervisor sign with Seal



Reichman, 2010). Looked at another way, developmental uterine anomalies were found in approximately 20 percent of women with recurrent pregnancy losses compared with about 7 percent of controls (Salim , 2003).

It has proven difficult to demonstrate that correction of uterine anomalies improves early pregnancy outcome.

TABLE 18-5 Estimated Prevalence and Pregnancy Loss Rate for Some Congenital Uterine Malformations

Uterine Anomaly a Proportion of All Anomalies (%) Pregnancy Loss Rate (%) b Bicornuate Septate or Unicornuate Didelphys Arcuate Hypo – or aplastic 39 14-24 11 7 4 40-70 34-88 40

a Estimated overall prevalence 1:200 women. b Included first – and second trimester losses. Data from Bradshaw, 2012; Buttram, 1979; Nahum, 1998, Reddy, 2007; Valli, 2001.

Immunological Factors

In their analysis of published studies, Yetman and Kuneh (1996) determined that 15 percent of more than 1000 women with recurrent miscarriage had recognized autoimmune factors. Two primary pathophysiological models are the autoimmune theory immunity directed against self, and the alloimmune theory immunity against another person.

As miscarriages are more common in women with systemic lupus erythematosus, an autoimmune disease (Clowse, 2008; Warren, 2004). Many of these women were found to have antiphospholipid antibodies, a family of auto antibodies that bind to phospholipid-binding plasma proteins (Erkan, 2011).

Women with recurrent spontaneous pregnancy loss have a higher frequency of these antibodies compared with normal controls-5 to 15 versus 2 to 5 percent, respectively (

Branch, 2010). The antiphospholipid antibody syndrome (APS) is defined by these antibodies found together with various forms of reproductive losses along with substantively increased risks for venous thromboembolism (American College of Obstetricians and Gynecologists, 201 Id, 2013a).

Endocrine Factors

According to Arredondo and Noble (2006), 8 to 12 percent of recurrent miscarriages are caused by endocrine factors. Studies to evaluate these have been inconsistent and generally under powered. Two examples, both controversial, are progesterone deficiency caused by a luteal-phase defect and poly cystic ovarian syndrome(Bukulmez, 2004; Cocksedge, 2008; Nawaz, 2010

Likewise, the effects on early pregnancy loss of overt hypo thyroidism and severe iodine deficiency are well known. Also, the effects of subclinical hypothyroidism and antithyroid antibodies are sporadic, and thus any

INSTITUTIONAL ETHICS COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No.09/2017 Meeting held on 03.03.2017

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval **"Study of Prevalance of Thyroid Peroxide Antibodies in Preterm Deliveries, IUD and Recurrent Pregnancy Loss. "** submitted by Dr.N.Sathya, M.S. (O&G), PG Student, GKMC, Chennai-10

The Proposal is APPROVED

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

DEAN 23/3/17
Govt. Kilpauk Medical College,
Chennai-10.

23/3/17