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Effect of Overt and Subclinical Hypothyroidism on Pregnancy and Childbirth

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Abstract
Aim: *Our study is to find out the effect of overt and subclinical thyroid dysfunction on pregnancy and outcomes in our hospital.*
Materials and Methods: *This is a case control study conducted in Sree Avittom Thirunal Hospital, Government Medical College, Thiruvananthapuram and study period was for one year.*
Results: *In our study hypothyroidism was detected in 71.8% of cases <30 years and the mean age was 26.29 years, median was 25.5 years, age group varied froml8 to 33 years. Mean age was 24.88 years, median was 27 years and the age group varied from 20 to 34 years among the controls. Religion wise, socioeconomic class wise and parity wise cases and controls were comparable. Cases had 3.6 the risk of developing threatened abortion, 3.8 times the risk of developing gestational hypertension, 3.6 times the risk of getting postpartum haemorrhage.25.6% of cases and 20.5% of the controls developed preterm labour.5.1% of cases and 2.6% of controls had abruption with a higher risk among the cases. Caesarean section was done in 51.3% of cases and 28.2% of the controls. Congenital goiter was seen in 2.6% of cases and 1.3% of controls. Congenital malformations were observed in 7.7% of cases and 5.1% of controls. Congenital hyperbilirubinemia was seen in 6.4% of cases and 2.6% of controls. Congenital hypothyroidism was observed in 5.1% of cases and 2.1% of controls. Early neonatal deaths were seen in 5.1% of cases and 3.8% of controls. Stillbirths were observed in 6.4% of cases and 5.1% of the controls.*
Conclusion: *This study recommends treatment for all women who have overt thyroid disease. Antenatal women who are diagnosed and treated hypothyroidism will probably need an increased dosage of thyroid medication during pregnancy, and should be periodically tested and treated. Women with thyroid conditions requires the care of a high-risk obstetrician. Women who are hypothyroid should give birth at a hospital that is experienced in the postnatal care of babies. Women should use prenatal vitamins containing iodine, which is essential for thyroid function.*

Introduction

A number of important physiological and hormonal changes in pregnancy alters thyroid function. Thyroid function tests therefore must be interpreted with caution during pregnancy[1]. Thyroid function tests change during pregnancy due to the influence of two main hormones: human chorionic gonadotropin (hCG) and estrogen, the main female hormone. HCG can weakly turn on the thyroid and the high circulating hCG levels in the first trimester may result in a slightly low TSH[2]. When this occurs, the TSH will be slightly decreased in the first trimester and then return to normal throughout the duration of pregnancy .Estrogen increases the amount of thyroid hormone binding proteins in the serum which increases the total thyroid hormone levels in the blood since >99% of the thyroid hormones in the blood are bound to these proteins. However, measurements of "Free" hormone usually remains normal. The thyroid gland is functioning normally if the TSH, Free T4 and Free T3 are all normal throughout pregnancy.

The thyroid gland can increase in size during pregnancy. However, pregnancy-associated goiters occur much more frequently in iodine-deficient areas of the world. If very sensitive imaging techniques (ultrasound) are used, it is possible to detect an increase in thyroid volume. This is usually only a 10-15% increase in size and is not typically apparent on physical examination by the physician. However, sometimes a significant goiter may develop and prompt the doctor to measure tests of thyroid function.

Upto 12 weeks of gestation thyroid hormone completely is derived from the maternal thyroid galand. once second trimester starts the fetus starts to produce thyroid hormone but it is entirely dependent on maternal iodine intake which is must for thyroid hormone production The World Health Organization (WHO) recommends 250 mcg of iodine daily during pregnancy and lactation. The National Academy of Medicine (formerly the Institute of Medicine) recommends daily iodine intake of 220 mcg during pregnancy and 290 mcg during lactation. Commonest cause of hypothyroidism is Hashimotos thyroiditis which is a autoimmune disorder. When iodine nutrition is adequate, the most common cause of hypothyroidism during pregnancy is chronic autoimmune (Hashimoto's) thyroiditis. In iodine-deficient areas, iodine deficiency itself is associated with hypothyroidism and goiter. Other causes of hypothyroidism, such as prior radioiodine ablation, prior surgical removal of the thyroid, or disorders of the pituitary or hypothalamus, can also occur in pregnant women.

The diagnosis of primary hypothyroidism during pregnancy is based upon the finding of an elevated serum TSH concentration, defined using population and trimester-specific TSH reference ranges for pregnant women. For women with a TSH above the population and trimester-specific upper limit of normal, or above 4.0 mU/L when local reference ranges are not available, we also measure a free T4.Overt hypothyroidism is defined as an elevated population and trimester-specific TSH concentration in conjunction with a decreased free T4 concentration (below assay normal using reference range for pregnant women). Subclinical hypothyroidism is defined as an elevated population and trimester-specific serum TSH concentration and a normal free T4 concentration.[17]

Those mothers with mild hypothyroidism will be asymptomatic and doesn't show any or minimal symptoms associated with pregnancy. Complications are more with untreated severe hypothyroidism. These can present with maternal anemia, muscle weakness, congestive cardiac failure, preeclampsia, intra uterine growth retardation, or small for gestation babies and postpartum hemorrhage.[4]

Congenital hypothyroidism is a preventable condition. If detected early and treated at the earliest the problem of cognitive, neurological and developmental of the baby can be prevented to a certain extent. All newborns according to the government of Kerala is screened and thyroid replacement is started at the eariest.

Maternal iodine deficiency especially due to iodine deficiency can lead to impaired brain development. This is true even in case of mild untreated hypothyroidism during pregnancy[5]. At this time there is no general consensus of opinion regarding screening all women for hypothyroidism during pregnancy. Ideally all pregnant women and woman with established hypothyroidism should have a TSH test once pregnancy is confirmed, as thyroid hormone requirements increase during pregnancy, often leading to the need to increase the levothyroxine dose and if the TSH is normal, no further checkup of thyroid hormones is typically required.

Once hypothyroidism is diagnosed, the woman should be treated with levothyroxine to normalize her TSH and Free T4 values .Adequate replacement of thyroid hormone in the form of synthetic levothyroxine should be done in the same way as non pregnant women. Clinical studies have proven that there is an increase in levothyroxine requirement during pregnancy ranging from 25 to 50 %.In an ideal situation dose of levothyroxine should be optimized before pregnancy and dose should be adjusted in such a way that TSH and free T4 remains normal. Frequency of thyroid function tests in pregnancy is 6to 8 weeks[6].If dose is adjusted TFT should be repeated in 4 week time. After delivery woman may sometimes go back to the prepregnant dose of levothyroxine. Iron containing tablets which are frequently used in pregnancy and postpartum can cause malabsorbtion from the gastrointestinal tract, therefore a gap of atleast 2 to 3 hours is advised between these tablets.

Our study is about the maternal and fetal outcome of overt and subclinical hypothyroidism in our hospital.

Aims and Objectives

1) To study the maternal outcome of hypothyroidism in pregnancy
2) To study the fetal outcome of hypothyroidism in pregnancy

Materials and Methods

Study Design; Case control study

Setting of the Study

SAT Hospital, Government Medical College, Thiruvananthapuram

Study Period -1 year

Inclusion criteria

1) All the pregnant patients with hypothyroidism admitted to SAT hospital with high TSH value of > 3mu/l and low free T4 level of <0.86ng/dl detected prior to conception, on thyroxine replacement therapy, irrespective of the duration of hypothyroidism and dose of thyroxine
2) Singleton pregnancy

Exclusion criteria

1) Those with Overt Diabetes.
2) Those with Chronic hypertension.
3) Those with Heart disease.
4) .Those with Asthma.
5) Those with Collagen vascular disease (autoimmune disease), such as lupus, scleroderma and polymyalgia rheumatica.
6) Those receiving anticoagulant therapy.
7) Those with Multiple pregnancy.
8) Those with major fetal anomaly or demise.
9) Those with history of prior caesarean deliveries.

Controls

Euthyroid pregnant women next to the case in the parturition register after excluding the above criteria.

Methodology

A Study was conducted in the SAT Hospital for a period of 1 year. Those singleton pregnancy with high TSH value of >3mu/l and low free T4 level of <0.86ng/dl detected prior to conception, on thyroxine replacement therapy, irrespective of the duration of hypothyroidism and dose of thyroxine admitted in labour room irrespective of the period of gestation after excluding the above criteria were included as cases in the study and the euthyroid patient immediately next to the case in the parturition register satisfying the exclusion

criteria were included as controls in the study. Data was collected by reviewing the existing patient records.

Relevant details like Maternal age, Parity, Socioeconomic status(based on Kuppusamy classification), threatened abortion, Gestational hypertension, Preterm labour, Abruptio placentae, Mode of delivery, Postpartum hemorrhage, maternal death within 1 week of delivery, low birth weight (Birth weight< 2500 grams), Congenital goiter, Congenital external malformation, Neonatal hyperbilirubinemia within 24 hours, Neonatal hypothyroidism, Early neonatal death of the baby within 7 days of delivery, Stillbirths were recorded in a planned proforma.

Statistical Analysis

The data were entered in the master chart and necessary statistical tables were constructed. Diagrams and charts were drawn wherever necessary to supplement statistical tables. In order to test hypothesis statistical tests like Chi-square test and Odd's ratio were used by using the statistical package SPSS.

Observations, Results and Discussion

The study conducted in SAT Hospital, Thiruvananthapuram reflects the results obtained from a tertiary care centre. There are certain limitations in the study as all the cases were diagnosed prior to conception and were started on thyroxine therapy and so foeto maternal outcome of newly diagnosed patients of hypothyroidism in pregnancy could not be studied. However the study has brought about the fetal and maternal outcome of hypothyroidism of those who were on thyroxine in comparison with the euthyroid controls.

Hypothyroidism was detected in 71.8% of cases <30 years and the mean age was 24.88 years, median was 27 years, age group varied from 20 to 30 years in controls. This shows that hypothyroidism is being detected at an earlier age nowadays because of its diverse presentation. Religion wise distribution of the cases and controls follow the same trend with no statistical difference between the two. Hence, Religion wise both were comparable. The proportion of Christians is slightly more in the study group.57.7% of the primigravidae, 29.5% of PI, 7.7% of P2 and 5.1% of P3 had hypothyroidism and the distribution was same as the controls making no statistical difference the two. Hence cases and controls were comparable. Primigravidae constituted the maximum number of cases. This may be due to the diagnosis of thyroid disorders at an earlier age in view of the awareness of the effects of the same[7].Cases and controls among the high, middle and low socioeconomic class were similarly distributed bringing no statistical difference between the two. Hence socioeconomic class wise both were comparable. However, majority of the cases belonged to middle socioeconomic class. Socioeconomic status does not influence the occurrence of hypothyroidism as the main etiology is autoimmunity. Ranjith singh et al from Uttarpradesh has showed that hypothyroidism due to infectious etiology(DeQuervain's thyroiditis) is more common among low socioeconomic class[8].Threatened abortion was seen in 23.1 of cases and 7.7% of controls and this difference statistically proved to have significant association. Those with hypothyroidism had 3.6 times the risk of developing threatened abortion during pregnancy. Miscarriage rates have been higher among untreated hypothyroid patients but recurrent miscarriage was unaffected by their thyroid antibody status and hence thyroid function tests are not routinely recommended in recurrent pregnancy loss unless the patient is symptomatic[9]. Several studies have suggested that hypothyroid-dism is associated with pregnancy loss but the results in women with subclinical or mild hypothyroidism have been somewhat conflicting. Studies of women during pregnancy have suggested the TSH normal range is not the same as for non-pregnant individuals but the exact range had not been clearly identified[10]. The incidence of preterm labour is more in the study

group (25.6%) than in the control group (20.5%). But the observed difference was not statistically significant though the probability of developing preterm labour was more in those with hypothyroidism than those without. In a study conducted by Kesavan P et al[11]same relationship has been observed. A study published in 2005 in the Indian journal hypothyroid pregnant women gave birth early, compared to women who delivered their babies after 37 weeks of pregnancy. The authors of the study found that women with high levels of TSH—indicating either subclinical or overt hypothyroidism-were much more likely have a very preterm delivery. This suggests that hypothyroidism is a risk factor for very early delivery of the baby, which can have serious and long-term implications to the baby[4-1].35.9% of the cases as against 12.8% of the controls had gestational hypertension making the difference statistically significant thus implicating that gestational hypertension is an associated outcome and the cases had 3.8 times the higher risk of developing gestational hypertension. A 1993 study investigated the potential link between hypothyroidism and high blood pressure during pregnancy by studying two groups of women. This suggests that hypothyroidism in either its overt or subclinical form may increase the risk for pregnant women to develop both high blood pressure and the associated, potentially serious, condition of pre-eclampsia[12] Postpartum hemorrhage complicated 12.8% of the cases and 3.8% of the controls and this difference when analyzed was found to be statistically significant and thus PPH had a significant association with hypothyroidism. Post-partum hemorrhage occur through uterus hypotony and through coagulation disorders (problem of the plaque adhesiveness). The causes of the hypotony and hypo contractions in hypothyroidism are multiple; amongthem there are the endogen intoxications,the change of muscular tissue, the myxedema impregnation, the hypovitaminosis (B1 vitamin), affecting the transmission of the nervous influx, affecting the endocrine metabolism, water-electrolytic change which leads to the change of the functional biometrical schemes and to the change of the interaction between actin and myosin: the K and the intracellular Mg decrease due to the metabolic acidosis and therefore the contraction is more difficult. Ca decreases and the equilibrium of P, bicarbonate and H ions is disturbed; on the other hand, the metabolic acidosis also modifies the extracellular distribution of Na, Ca, Mg and K and has a negative influence on the contractions through the decrease of the membrane contraction[15].Statistically significant difference was not observed between the cases and controls with regard to the occurrence of abruptio placentae. Venu et al in 2005 has shown a higher incidence of abruption which may be probably due to higher incidences of gestational hypertension. Caesarean section was done in 51.3% of cases and 28.2% of controls and this difference statistically proved to have no significant association though the incidence is slightly higher in the study group. During hypothyroid pregnancy, cephalopelvic dispropor-tions can also occur with the vitiated pelvis (limit pelvis). There are a lot of intricate mechanisms (direct and indirect effects of the thyroid hormones) since the very beginning of the pre-gestation period, which can affect the pelvic bones (lower bone density, even osteoporosis), of the spine (multiple deformations), problems of the articulations through the specific infiltration, various arthropathies, inflammatory or non-inflammatory, polyarthritis, arthrosis. Excessive deposits of mucopolysaccharides and glucose in the tissues, affecting protein synthesis, diminution of the insulin like growth factor, can lead to various muscles and skeleton symptoms. A clear mechanism is not established, but a decrease in the proliferation of the cartilage cells and bone tissue and chondrocalcinosis (depositing the hydrates crystals and the calcium pyrophosphates. In the group with pregnant women who had premature delivery, the percentage of the caesarean operations is high and known as an existing situation at present time, both on the

global level as well as in our country[14].Among the 21.2% total low birth weight babies, the incidence of low birth weight was more in the study group (28.2%) than in the control group(19.2%). But the observed difference was not statistically significant though more number of cases gave birth to babies <2.5 kg. In hypothyroidism, the cardiac debit is not adequate and the uterus-placenta circulation becomes insufficient, which induces a moderate and chronic fetal hypoxia, fetal bradycardia, fetal hypotrophy, diminution of fetal movements and an insufficient tolerance of the delivery by the fetus. The intrauterine chronic hypoxia of the newborn can be met in the literature at variable percentages between 14%-22% of pregnant women with hypothyroidism[14]. There were two babies among the study group and only one baby among the control group had congenital goitre, however no statistical significance had been observed. Transplacental passage of excessive amounts of iodide appears to depress hormone synthesis by the fetal thyroid gland. Goitrous enlargement results from the consequent increased pituitary thyrotropic secretion (TSH). Congenital goitre have also been reported in the' offspring of euthyroid mothers who received iodide therapy for asthma or other illnesses during their pregnancies (Parmelee et al.,1990;).Congenital malformation were found in 7.7% of cases and 5.1% of controls and this difference statistically proved to have no significant association though the incidence is slightly higher in the study group. David et al in 2009 has shown that typically, the problems tended to most often affect the heart, but other defects, such as kidney and nervous system problems, cleft foot and cleft palate, were more common in women who were hypothyroid during pregnancy[8]. Statistically significant difference was not observed between the cases and controls with regard to the occurrence of congenital hyperbilirubinemia. Hence, cases and controls were comparable. The distribution of congenital hypothyroidism was more in the study group than in the control group.. But the observed difference was not statistically significant.[15]In greater than 95% of newborn infants with Congenital hypothyroidism, there are no symptoms or signs of Congenital hypothyroidism when the diagnosis is suspected by newborn screening.

Approximately 15 to 20% of affected infants with Congenital hypothyroidism have one of several inherited forms of Congenital hypothyroidism collectively known as Familial Thyroid Dyshormonogenesis. These diseases are caused by mutations in the enzymes that are required for thyroid hormone synthesis, metabolism and end organ responsiveness, and are inherited as autosomal recessive traits. With similar inheritance patterns the mutations in genes for the synthesis of hypothalamic-pituitary hormones and their receptors infrequently cause congenital hypothyroidism. There are very rare mutations in genes that regulate thyroid and pituitary gland embryogenesis. The mode of inheritance is unknown. Though not a cause of congenital hypothyroidism, Thyroxine Binding Globulin (TBG) deficiency is caused by mutations in the gene that is required for the synthesis of this major plasma binding protein for T4. Among the 7 babies which died in the early neonatal period 4 were cases and 3 were controls bringing no statistically significance and hence both were comparable. Cases had a higher incidence of stillbirth compared to the controls but the difference was statistically insignificant. Anomalies of fetus cardiac rhythm (FCR) - fetal suffering: alterations of the basic cardiac rhythm (tachycardia, bradycardia), of heart rate variability (diminution until their loss or periodical variations of heart rate in relation with the uterine contractions, a type of belated slow-ups) in pregnant women who continued to be hypothyroid until the due term.

Conclusion

Hypothyroidism was detected in 71.8% of cases <30 years and the mean age was 26.29 years, median was 25.5 years, age group varied froml8 to 33 years. Mean age was 24.88 years, median

was 27 years and the age group varied from 20 to 34 years among the controls. Religion wise, socioeconomic class wise and parity wise cases and controls were comparable. Cases had 3.6 the risk of developing threatened abortion, 3.8 times the risk of developing gestational hypertension, 3.6 times the risk of getting postpartum hemorrhage. 25.6% of cases and 20.5% of the controls developed preterm labour.5.1% of cases and 2.6% of controls had abruption with a higher risk among the cases. Caesarean section was done in 51.3% of cases and 28.2% of the controls.

Congenital goiter was seen in 2.6% of cases and 1.3% of controls. Congenital malformations were observed in 7.7% of cases and 5.1% of controls. Congenital hyperbilirubinemia was seen in 6.4% of cases and 2.6% of controls. Congenital hypothyroidism was observed in 5.1% of cases and 2.1% of controls. Early neonatal deaths were seen in 5.1% of cases and 3.8% of controls. Stillbirths were observed in 6.4% of cases and 5.1% of the controls.

Recommendations

Women who have overt thyroid disease should be treated. Women who are diagnosed and treated hypothyroidism will probably need an increased dosage of thyroid medication during pregnancy, and should be periodically tested and treated. Women with thyroid conditions require the care of a high-risk obstetrician. Women who are hypothyroid should give birth at a hospital that is experienced in' the postnatal care of babies. Women should use prenatal vitamins containing iodine, which is essential for thyroid function.

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