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AOGD BULLETIN

Women's Health to a New Horizon

Theme:
Thyroid Disorders in Pregnancy

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Message from the President

Dear members,

A warm welcome to all of you!

Patient counselling is a key competency element of the healthcare process. The physician must keep in mind that it is his or her responsibility to help patients achieve desired health outcomes. By increasing dialogue and understanding between healthcare provider and patient, we should strive to have a greater impact on improvement on the health services and quality of life. We must seize all opportunities to enhance our communication skills.

The other integral element for increasing access to healthcare is awareness. A holistic approach of health education, awareness and patient support is also critically important to a patient's long-term outcome. With that in mind, we run screening, awareness and counselling programmes, and help empower women with the knowledge to safeguard and manage their own health.

Besides updating knowledge, soft skills acquisition is also a vital aspect of our profession.

Dr Sudha Prasad
President
drsprasad@yahoo.com

Message from the Vice President

Dear Friends,

Seasons' greetings & best wishes from myself and Maulana Azad Medical College team.

It gives me great pleasure in taking over the charge of vice presidentship from the previous team of AOGD. I am thankful to all of you to have shown faith and trust in me to carry out the responsibility.

It was my dream to help women of our country to be empowered physically, mentally and psychologically and help them overcome the adversities of life. This present job, I am sure, can further enhance the opportunities for me and our team to work in this direction. Maternal mortality is still very high in our country and in spite of improved antenatal care in at least cities, the mortality rates have not decreased as desired. All the gynecologists need to work on early detection of diseases in pregnant woman, counseling regarding the need to take treatment, proper follow-up, and timely transportation from periphery to tertiary care centers, so that, critically ill pregnant women can be saved. Focused approach on this matter is essential. We would strive to strengthen these areas by educating the doctors and counseling the patients.

The bulletin is a help academically to many budding gynecologists to keep abreast with the advances in knowledge. Hope you all will like the present format. It would be our endeavor to carry forward the good work done by previous team. Wishing all of you again.

Dr Anjali Tempe
Vice President

From the Secretary's Desk

Dear Members,

Namaskar! Greetings from AOGD Maulana Azad Medical College & Lok Nayak Hospital.

I along with my joint secretaries Dr Poonam Sachdeva, Dr Poonam Kashyap and Dr Niharika Dhiman welcome you all to a happy reading of second issue of the bulletin.

We are focusing on a) increasing awareness about various aspects of health problems among public so that they can seek health care, and b) transferring skills and knowledge among peer groups. A health camp was organised at MCW Centre, Kanchan Puri, Daryaganj on 13th May, 2016. It was attended by more than 100 patients, ASHA workers and ANMs. The antenatal and family planning services were provided. Health talks on various family planning methods, antenatal screening, breast feeding were given by the team. Thalassemia awareness was done in association with Thalassemia Control Cell of Hindu Rao Hospital. Gurukul Classes were conducted on 25th & 26th May, 2016 at Sir Ganga Ram Hospital and students were taught various aspects of the specialty. It is planned to conduct such activities more frequently with the help of members from different areas as well as fields.

I request members / social forum interested to organize or participate in outreach activities or mass education programmes, to coordinate with AOGD secretariat.

I do hope that you must be keeping yourself updated and connected with fellow members by 'facebook' AOGD MAMC, WhatsApp group AOGD 16-17 and website www.aogd.org.

Dr Ashok Kumar
Honorary Secretary
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From the Editor's Pen

Dear friends,

Greetings!

I hope you enjoyed the last issue.

Welcome aboard the June issue of AOGD Bulletin.

Endocrine diseases like thyroid disorders, diabetes and osteoporosis are affecting a significant proportion of women presenting to the obstetrician-gynecologist. In the current issue, we endeavour to bring forth few key and controversial aspects of thyroid disorders in pregnancy. Obstetricians are often the first health-care providers that young women see in adulthood, and thus, have a critical opportunity to identify these women and provide treatment when appropriate.

Yesterday is not ours to recover; but tomorrow is, to win or to lose.

Happy reading!

Dr Sangeeta Gupta
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Monthly Clinical Meeting

Monthly Clinical Meeting will be held at Army Hospital – Research and Referral on 24th June, 2016.

Thyroid Function Tests in Pregnancy

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Introduction

Thyroid function testing during pregnancy is a matter of concern for all the patient, the health care provider and the service provider. The apprehension stems from the diagnosis of hypothyroidism, the overall prevalence being 5.4% in the Indian population and seen more commonly in women.[1]

Some women are known to be either hypothyroid or hyperthyroid and require regular monitoring of their thyroid status to optimize the pregnancy outcome. The need of universal screening for thyroid disorders is a controversial issue with both its merits and pitfalls.

This article will cover the alterations in the physiology of the thyroid gland and its hormones during pregnancy and the factors to be considered while interpreting the thyroid function tests in pregnancy.

Physiological changes in pregnancy and effects on thyroid function

During pregnancy the thyroid gland undergoes various anatomical and physiological changes. Thyroid hormone production increases by 40 to 100 percent to meet maternal and fetal demand. Anatomically it moderately enlarges through glandular hyperplasia and increased vascularity. Physiologically the following changes take place-

1. Thyroxin binding globulin (TBG)

Its levels increase during early pregnancy by 2-3 times and reaches its zenith at about 20 weeks.[2,3]

- Value during the rest of the pregnancy is almost double the baseline in pre-pregnancy period.
- Increased hepatic synthesis due to higher estrogen levels and lower metabolism rates owing to increased TBG sialylation and glycosylation is responsible for the increased levels.
- The elevated TBG binds to tri-iodothyronine (T3) and thyroxine (T4) and increases the total T3 and Total T4 by approximately 1.5 times by the 16th week of gestation[3].

2. Thyroid stimulating hormone (TSH)

- The alpha subunits of TSH and hCG are identical; therefore hCG has intrinsic thyrotropic activity thus causing thyroid stimulation.
- Correlating with the hCG peak by the end of the first trimester there is a transient elevation in free Thyroxine towards the end of the first trimester. This in turn inhibits the TSH levels.
- Thyrotropin levels decrease in more than 80 percent of pregnant women.
- With advancing gestation the hCG decreases reaching a plateau in the last two trimesters which in turn leads to the increase in the TSH levels.[3]
- This may lead to misdiagnosis of subclinical hyperthyroidism or failure to identify women with hypothyroidism.

3. IODIDE

The demand for iodine is also increased in pregnancy on account of various reasons[4].

There is increased production of maternal thyroid hormone and iodide transport across the placenta to the growing fetus. Another theory is of increased renal excretion. Placental deiodination also requires extra thyroid hormone.

Pregnancy is a "stress test" for the thyroid gland where an intact thyroid gland and sufficient iodine supply is essential for maintaining optimum levels of the thyroid hormones both for the mother and the baby.[5]

Patients with insufficient dietary iodine or underlying mild thyroid disease may become hypothyroid. Patients on thyroxine replacement therapy will also require a review of the drug dosages.

Testing in pregnancy

The optimal timing of testing is probably toward the end of the first trimester or before pregnancy in those at high risk.[6]

International thyroid guidelines recommend reference intervals to be based on the 2.5th and 97.5th percentile of the concerned population with adequate iodine intake.[5,6] This is in accordance with the advice of the International Federation of Clinical Chemistry.

Because of the altered thyroid physiology in pregnancy, different range of thyroid function tests is required for the diagnosis. Serum TSH concentration usually is the first clinical indicator of any deviation from the normal functioning of the thyroid gland. As recommended by the American Thyroid Association (ATA) in 2011 thyroid functions in pregnancy should be interpreted on the basis of trimester-specific reference ranges in populations with adequate iodine intake. The gestation specific ranges are as follows[5]

	First trimester	Second trimester	Third trimester
TSH mIU/l	0.1-2.5	0.2-3	0.3-3.5

Uncritical use of Free T4 (FT4) results in pregnancy is not recommended. The American Thyroid Association (ATA) recommended measuring total T4 (TT4) and then calculating the FT4 index (FTI) over FT4 estimation. Likewise the Endocrine Society guidelines also recommend either FTI or TT4 (multiplying the nonpregnant range by 1.5 for the second and third trimesters), whereas the European guidelines suggest either TT4 or FT4 measurement with locally established trimester-specific reference ranges.[3] Screening should be with TSH only and if necessary FT3 and FT4 may be tested.[7]

Thyroid function tests in pregnancy

Hypothyroidism in pregnancy is diagnosed mostly on the basis of blood tests especially an elevated serum TSH level associated with reduced FT4 in "overt hypothyroidism". Various factors are to be kept in mind while interpreting thyroid function tests (TFTs) in pregnancy.

Pre-analytical factors

1. Gestational Age
   As there is a rise and fall in the hCG concentration during the pregnancy the period of gestation has a major effect on the thyroid function. Laboratories not recording the gestational age or who cannot adjust reference intervals for the period of gestation can face practical problems. The TSH falls in the first trimester to reach a nadir at week 10 followed by a progressive increase henceforth[8].
2. Antibody status
   Anti-thyroid peroxidase (ATPO) and anti-thyroglobulin (ATG) antibodies are markers of thyroid autoimmunity. Women with mild, asymptomatic thyroid dysfunction have elevated levels of these antibodies and generally have increased serum TSH levels.[9]
   Positive ATPO antibody status is a risk factor for increased TSH levels specific for the gestational age.[9] Women with subclinical hypothyroidism have significantly higher incidence of positive ATPO antibodies.
3. Iodine Status
   Iodine is required for the synthesis of thyroid hormone and iodine deficiency is the most common cause of hypothyroidism worldwide. To overcome the low dietary intake of iodine consumption of fortified salt is recommended. The daily intake of iodine in pregnancy should be a minimum of 250 µgm to take care of the increased requirement in pregnancy.[10]
4. Multiple Pregnancy
   Since the serum hCG concentrations are higher in multifetal gestation, the TSH levels will be lower.
5. Ethnicity
   Numerous studies have demonstrated the ethnic variation in the levels of thyroid hormones. The relative contribution of hCG concentration, thyroid antibodies, iodine status, genetic factors and maternal age is a matter of discussion. Data from two large studies suggests that compared to white women, the TSH levels in pregnancy are higher in Asian women and lower in the black women.[11]
6. Time of blood collection
   There is significant diurnal variation in serum TSH levels. The TSH concentration is lowest in the afternoon, rising in the evening with a peak in the early half of the night.[12] The difference between the highest and the lowest levels may exceed 100% and is seen less commonly during the daytime.[12] This diurnal variation is also seen during pregnancy in all the trimesters.[13]

Analytical Factors

1. Thyroid Hormones
   Accurate estimation of serum FT4 is essential to differentiate overt hypothyroidism from subclinical hypothyroidism. It is also required to diagnose euthyroid hypothyroxinaemia.

   There may be variations in the FT4 immunoassays affected by the physiological changes in pregnancy-increased serum TBG, decreased albumin and increased free fatty acids. Hence it is recommended by all to be careful with FT4 assays and use method-specific reference interval wherever available.
2. TSH
   TSH levels are not altered by the changes in the binding proteins which increase the concentration

of thyroxine during pregnancy. The natural variation in TSH glycosylation which has the potential to affect its biological activity does not seem to change during pregnancy.[14]

3. Thyroid Antibody

Detection of thyroid autoimmunity requires estimation of both ATPO and ATG antibodies. Two analytical factors are to be considered. Firstly, there may be discordance in the results from different assays i.e., high antibody levels may only be detected on one of the two different assays. Secondly, as pregnancy advances the antibody levels fall hence the proportion of women with autoimmunity is lower at higher gestations.[15,16]

Post-analytical factors

While deriving reference intervals for thyroid function tests in pregnancy ethnicity, gestational age, multiple pregnancy and assay differences should be accounted for.[3] There is an increased risk of underlying thyroid dysfunction in iodine deficiency, goiter or a past history of thyroid disease and positive antibody status. Such subjects should be excluded from a "healthy" reference population.[5] Failure to do so will result in an apparently higher upper limit of normal for TSH.

Conclusion

In pregnant women the standard non-pregnant TSH reference intervals should never be used as many women with subclinical hypothyroidism will be wrongly classified as "normal" in the first trimester. The TSH concentration is lowest at the end of first trimester and the 97.5th percentile of TSH is taken as the cut-off to investigate and treat further.

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Should All Pregnant Women be Screened for Thyroid Disorders?

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Introduction

Maternal thyroxine is vital for the normal neurodevelopment of the fetus. Pregnancy is a stress test for the thyroid gland. It must produce 50% more thyroid hormone to maintain euthyroidism and provide enough thyroid hormone for the developing fetus. Fetal thyroid gland starts thyroid hormone synthesis at about 12 weeks of gestation. Women with pre-existing hypothyroidism often need a higher dose of levothyroxine during pregnancy to maintain euthyroidism. Research in the past two decades has lead to a better understanding of the interaction between the thyroid gland and pregnancy, and its impact on adverse events in the mother and fetus leading to advocacy for screening for thyroid dysfunction in pregnancy.[1,2]

Thyroid disorders in pregnancy

Thyroid dysfunction is one of the common endocrine disorders to affect women of reproductive age. There is a broad clinical spectrum ranging from myxedema, end-organ effects and multisystem failure to an asymptomatic, subclinical condition. Broadly these are classified as overt hypothyroidism, overt hyperthyroidism, subclinical hypothyroidism and subclinical hyperthyroidism.

- ***Overt Hyperthyroidism*** occurs in 0.2% of pregnancies. Inadequately treated maternal thyrotoxicosis is associated with a greater risk of severe preeclampsia and maternal heart failure than treated cases.
- ***Subclinical hyperthyroidism*** has been reported in 1.7% of pregnant women. It is not associated with adverse pregnancy outcomes.
- ***Overt hypothyroidism*** affects up to 1% of all pregnancies. Untreated overt hypothyroid is associated with adverse pregnancy outcomes like gestational hypertension, preeclampsia, spontaneous abortion, IUGR, low birth weight and fetal death. It can lead to subsequent childhood neuropsychologic and cognitive impairment and cretinism in the child.
- ***Subclinical hypothyroidism*** affects 3% -15% of pregnancies and thus accounts for the largest proportion of thyroid dysfunction. It is essentially a biochemical diagnosis based on raised serum thyroid stimulating hormone (TSH) levels in presence of normal serum thyroxine (T4) levels. There are conflicting reports regarding functional relevance of subclinical hypothyroidism in pregnancy. This has lead to much controversy regarding whether to screen all pregnant women for thyroid disorders or to screen only those with symptoms and risk factors.

The rationale for screening

The rationale for screening for any disease is based on following factors:

(a) The disease should be prevalent and be an important health problem.

(b) The disease should have adverse affect and should be treatable with beneficial results.

(c) The screening test should be reliable, acceptable, easy to administer and affordable

Diagnosis and Prevalence of thyroid disease

The prevalence of any disease can only be estimated if there are well defined diagnostic criteria. Thyroid dysfunctions are diagnosed on the basis of serum TSH and T4, T3 levels. The cut offs for the upper limit of TSH during pregnancy have been much debated. The cutoff promoted by the western literature is TSH > 2.5 mIU/L.[3,4] However some experts recommend that 4.5mIU/L be kept as the cutoff as there is a lack of evidence of adverse outcome between serum TSH of 2.6 to 4.5 mIU/L. There are regional variations in the TSH levels in pregnancy. Indian data demonstrated a significantly higher TSH reference range for each trimester (Table-1).[5] Thus ideally local guidelines should determine the normal TSH range for the three trimesters of pregnancy.

Several studies from all over the world, including India, have reported on prevalence of thyroid disorders in pregnancy.[6-11] Subclinical hypothyroidism is the most common thyroid disorder during pregnancy. Using a cut off of 4.5 mIU/L, a study of 1000 pregnant women

conducted at our institution reported that 13.5% of them had subclinical hypothyroidism while only 0.7% and 0.3% had overt hypothyroidism and overt hyperthyroidism respectively.[12] It is obvious that a lower TSH (>2.5 mIU/L) cut off would exaggerate the prevalence rates of subclinical hypothyroidism.

Table-1: Indian data on TSH levels in three trimesters of pregnancy

	1st trimester	2nd trimester	3rd trimester
TSH (mIU/L): 5th-95th percentile Marwaha et al, 2008	0.6-5.0	0.44-5.78	0.74-5.7
TSH (mIU/L): normal range Endocrine Society, 2012	0.1–2.5	0.2-3.0	0.3–3.0

Impact of abnormal thyroid functions on pregnancy outcomes and treatment outcomes

Untreated overt hypothyroid is harmful for a woman and her fetus. It is associated with gestational hypertension, preeclampsia, spontaneous abortion, IUGR, low birth weight, fetal death and cretinism in the child. Since subclinical hypothyroidism is the most common thyroid disorder in pregnancy, it is important to know about the clinical impact of subclinical hypothyroidism on the pregnancy outcome and the potential benefits of its treatment. The association between adverse pregnancy outcome and possible subsequent childhood neuropsychologic and cognitive impairment in mothers with overt hypothyroidism is not questioned. However data regarding impact of subclinical hypothyroidism is limited and conflicting. While many studies document its association with adverse maternal outcome and impaired neuropsychological development of the baby, some well designed studies have found no link between subclinical hypothyroidism and adverse pregnancy outcomes. An RCT of 21,800 pregnant women with subclinical hypothyroidism found no effect of treatment on cognitive function of children at age 3. The treatment was started at around 14th week of pregnancy.[13] Presently, The Endocrine Society and Thyroid Association guidelines recommend treatment.[3,4] However the American College of Obstetricians and Gynecologists (ACOG) does not recommend treatment for subclinical hypothyroidism.[14]

Screening test and its cost efficacy

The screening for thyroid dysfunction is done by serum TSH estimation. This test is widely available and can be easily administered along with other blood screening tests during pregnancy requiring no extra visit or needle prick. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole. Studies have used decision analysis model to measure incremental cost per quality-adjusted life-year (QALY) gained with universal versus high risk screening.[15,16] They concluded that risk-based screening and universal screening were both cost-effective relative to no screening. Universal screening was cost-effective compared with risk-based screening.

Opinion of professional bodies regarding universal screening for thyroid dysfunction in pregnancy

Most of the professional bodies recommend against universal screening for thyroid dysfunction in pregnancy (Table-2). The main unresolved point is the lack of an agreed policy on whether to treat subclinical hypothyroidism. The ACOG states that "Association between subclinical hypothyroidism and impaired neurodevelopment in offspring are just that, an association".[14] There are mixed results about associations between subclinical hypothyroidism and adverse pregnancy outcomes like preterm delivery, preeclampsia and gestational diabetes. The ACOG and The Society for Maternal-Fetal Medicine oppose universal screening for thyroid disease in pregnancy (Level A recommendation).[14,17]

The American Thyroid Association and the American Association of Clinical Endocrinologists are also proponents of selective but not universal screening.[3,18] There was a lack of unanimity within the 2012 Endocrine Society guidelines with a majority of experts advocating selective screening and a minority opinion recommending universal screening.[4] Cochrane review on the subject states that universal screening for thyroid dysfunction in pregnancy does not clearly impact (benefit or harm) maternal and infant outcomes.[19] However, a few other scientific societies are beginning to recommend universal screening, such as the Spanish Society of Endocrinology and Nutrition.[20]

Alternative to universal screening

It has been proposed that pregnant women should be screened on the basis of their medical history, physical exam, or prior biochemical data:[4]

- All women >30 years old
- Clinical symptoms suggestive of thyroid hypofunction-cold sensitivity, fatigue, dry skin
- Family history of thyroid disease or autoimmune disorders,

Table-2: Recommendations of various professional bodies regarding universal screening for thyroid dysfunction in pregnancy

Professional source	Recommendation
American Thyroid Association[3], 2011	There is **insufficient evidence to recommend for or against universal TSH** screening at the first trimester visit. Level I-USPSTF
The Endocrine Society[4], 2012	**The committee could not reach agreement** with regard to screening recommendations for all newly pregnant women. Two versions are therefore presented. 1. Some members recommended screening of all pregnant women for serum TSH abnormalities by the ninth week or at the time of their first visit. USPSTF recommendation level: C; 2. Some members recommended neither for nor against universal screening of all pregnant women for TSH abnormalities at the time of their first visit. These members strongly support aggressive case finding to identify and test high-risk women.
Society for Maternal-Fetal Medicine[17], 2014	**Routine thyroid screening in pregnancy is not recommended.** Thyroid testing in pregnancy should be conducted for women "at risk," including known thyroid disease, symptoms of overt thyroid disease, suspected goiter, autoimmune medical disorders such as Type 1 diabetes mellitus
ACOG[14], 2015	**Universal screening for thyroid disease in pregnancy is not recommended** because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved neurocognitive function in offspring. Indicated testing of thyroid function should be performed in women with a personal history of thyroid disease or symptoms of thyroid disease.
COCHRANE Review[19], 2015	Though universal screening for thyroid dysfunction in pregnancy increases the number of women diagnosed with hypothyroidism who can be subsequently treated, **it does not clearly impact (benefit or harm) maternal and infant outcomes. More evidence is needed** to assess the benefits or harms of different screening methods for thyroid dysfunction in pregnancy, on maternal, infant and child health outcomes.

- History of infertility, previous miscarriage, preterm delivery, type 1 DM, an autoimmune disorder, goiter, or thyroid nodule.
- Any woman with known antithyroid peroxidase antibodies, previous thyroid surgery
- A history of radiation to head and neck region

Case finding strategy, however, has limitations as it will miss 33% to 81% of pregnant women with hypothyroidism and a large number of risk factors need to be evaluated, which is time consuming.[21,22] Even the risk factors that need to be included in a case finding strategy are controversial. Several symptoms like weight gain, exhaustion and constipation mimic common pregnancy related symptoms.

Conclusion

- There is a low prevalence of overt hypothyroidism and overt hyperthyroidism in pregnancy. Subclinical hypothyroidism affects 3% -15% of pregnancies but its impact on pregnancy and beneficial effects of its treatment are debated. Without the inclusion of subclinical thyroid dysfunction, the low prevalence of undetected overt hypothyroidism or overt hyperthyroidism in pregnancy does not justify routine screening.
- Proponents of universal screening in the first trimester argue that risk factors for thyroid disease are common and case finding as a strategy for identifying women with thyroid disease during pregnancy has limitations. They believe that benefits to pregnant women with overt disease make routine screening worthwhile to justify universal screening for thyroid disease even if it does not strictly fulfill all criteria for an ideal screening test. Currently pregnant women and neonates are screened for conditions with lower incidence rates. Overt hypothyroidism is as common and sometimes more frequent than many pregnancy-related conditions detected by routine monitoring.
- Current evidence, however, does not support universal screening for thyroid dysfunction in pregnancy. Lower TSH (>2.5 μU/L) cut off have been promoted which exaggerate prevalence rates of subclinical hypothyroidism. Indian studies showed higher values for each trimester. There is no conclusive evidence that treatment of subclinical hypothyroidism improves pregnancy outcomes. Thus universal screening does not clearly impact maternal and infant outcomes. **The ACOG- recommends –"Do not do universal screening for thyroid disease in pregnancy" (Level A recommendation).**
- A prerequisite for offering screening for thyroid deficiency during pregnancy is to develop gestational age-specific normative data especially for the 1st and 2nd trimesters. More evidence is

needed to assess the benefits or harms of different screening methods for thyroid dysfunction in pregnancy, on maternal, infant and child health outcomes. Ongoing randomized prospective trials are evaluating the impact of levothyroxine therapy in women with subclinical hypothyroidism and will provide crucial data for future guidelines.

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Subclinical Hypothyroidism in Pregnancy

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Background

Hypothyroidism in pregnancy is not rare but because the symptoms of hypothyroidism (fatigue, cold intolerance, constipation and weight gain) are most of the times attributed to pregnancy, diagnosis may be missed. On the other hand subclinical hypothyroidism is common and usually aymptomatic and may not be diagnosed till the thyroid tests are done. Hypothyroidism requires treatment with levothyroxine, however, there remains a controversy about whether to treat subclinical hypothyroidism (SCH). This write up provides a comprehensive review of the evidence and recommendations on this subject.

Thyroid physiology

Due to increasing demands of pregnancy, there are physiological changes in thyroid hormones[1].

Under the influence of increased estrogens during pregnancy, there is increased production of thyroid binding globulin (TBG). It in turn results in increase in TBG bound T3 and T4 and therefore increase in total T3 and T4[2].

Another change is increased concentration of human chorionic gonadotrophin (HCG). TSH and HCG are glycoproteins, which are formed by alpha and beta subunits. Both the hormones share alpha subunit and there is some resemblance in beta subunit also. Therefore HCG acts on the TSH receptors and increases synthesis of T3 and T4. It is estimated that 1 µU of HCG is equivalent to 0.0013µU of TSH. There is increase in concentration of free T3 and T4, however, the levels remain within the normal range and TSH concentration is less as compared to non-pregnant state[3,4].

Normal levels of thyroid hormones

Because of physiological changes of pregnancy, the normal limits of TSH differ. The American Thyroid Assosician (ATA), based on the 2.5 to 97.5th percentile value of TSH in first trimester, has proposed reference ranges for TSH according to the trimester of pregnancy (Table 1)[5].

The concentration of total T3 and T4 is 1.5 times the normal values in non pregnant state. The concentration of free T4 depends on the method used and the assay kits provide trimester specific reference range[5].

Table 1: Normal serum TSH range during pregnancy

Trimester	Serum TSH, mU/L
1st	0.1 to 2.5
2nd	0.2 to 3.0
3rd	0.3 to 3.0

Definition

When only concetration of TSH is raised above the normal limits and the free T3 and free T4 concentrations are within the range the condition is termed as the subclinical hypothyroidism(SCH)[5].

During pregnancy, hypothyroidism is diagnosed when serum TSH is above the reference range specific for the trimester and concentration of free T4 is below the reference range (Table 2). Subclinical hypothyroidism (SCH) is defined when TSH value is more than the reference range but T4 is within normal limits. SCH has been further subdivided into mild-SCH when TSH levels are ≤ 10 mU/L and severe-SCH when TSH is >10 mU/L[6].

Table 2: Definitions of hypothyroid disorders during pregnancy

Hypothyroidism	Serum TSH above reference range specific for the trimester and concentration of free T4 below reference range
Subclinical Hypothyroidism • Mild • Severe	Serum TSH more than the reference range but T4 within normal limits Serum TSH ≤ 10 mU/L Serum TSH >10 mU/L

Incidence

Incidence of overt hypothyroidism in pregnancy is reported to be 0.3 to 0.5%, however incidence of subclinical hypothyroidism is more and has been reported to be 2 to 2.5% in a study from USA[7]. Reasons for lower incidence of overt hypothyroidism during pregnancy is probably because it causes ovulatory dysfunction leading to infertility and also associated with first trimester miscarriage[2-4].

Indian scenario

In a study from southern West Bengal on 510 pregnant women, Mandal et al found high prevalence of SCH. The prevalence was 33% (TSH>2.5 m/u/ml) and 14% subjects had TSH >4.5 mU/L. TPO Ab was present in

34% women with SCH whereas it was present in only 1.5% of normal subjects[8].

Clinical implications

Effect on pregnancy

Women with hypothyroidism are at risk of complications – preeclampsia and gestational hypertension, preterm delivery, nonreassuring fetal heart rate, risk of cesarean section, PPH and cognitive impairment[9].

Studies have reported that SCH has adverse effects on the pregnancy. There is risk of miscarriage and preterm birth[5,10]. In a study involving 3315 pregnant women, the risk of fetal loss was higher in women with high TSH (5.2 to 10 mU/L) as compared to women who had normal TSH (risk of fetal loss 7.2% vs 2.2%). This risk was highest in women who were anti TPO antibody positive (15.2%)[11]. Another study reported higher pregnancy loss rate in women who had TSH 2.5 to 5 mU/L as compared to those having TSH of below 2.5 mU/L (6.1 vs. 3.6%)[12].

However the First and Second Trimester Evaluation of Risk (FASTER) trial did not find any significant increase in adverse effects in women with subclinical hypothyroidism[13].

Cognitive impairement

Observational studies suggest that subclinical hypothyroidism is associated with impaired cognition in the children[14]. However randomized studies do not support it. In an RCT, 21,846 healthy pregnant women at 15 weeks were randomized to control and study group. All participants had samples drawn for TSH and free T4. Only study group samples were tested immediately and the control samples were tested after birth. Women who had TSH >3.65mU/L and free T4 below 2.5th centile were treated with levothyroxine to achieve serum TSH level of 0.1 to 1.0mU/L. There was no difference in the IQ of children at 3 years of age[15].

There is suggestion that preterm birth may be responsible for cognitive impairement but an interesting study in which maternal thyroid function was done in women with preterm birth at less than 34 weeks and neurodevelopment was assessed in children at 5.5 years of age indicated that cognitive impairement is associated with high levels of TSH. It was found that there was significant decrease in the general cognition, verbal and perceptual performance for each unit increase in TSH[16].

Therefore we still need more evidence to say with certainty that subclinical hypothyroidism during pregnancy affect the cognitive function of the offsprings.

Screening for thyroid disease

It is not recommended to universally screen all pregnant women for hypothyroidism (ACOG, level A recommendation)[5,17]. However a targeted approach is practiced. TSH is tested in women with a history of recurrent miscarriage, infertility, past or family history of hypothyroidism, positive thyroid peroxidase antibodies, morbid obesity or type 1 diabetes. These women are tested for serum TSH during first trimester of pregnancy[5].

TPO antibodies are present in cases of autoimmune thyroiditis also known as Hashimoto's thyroiditis. Even euthyroid women with positive TPO are at risk of developing hypothyroidism[5]. Anti TPO antibodies are not tested routinely, but may be useful in guiding the start of treatment and monitoring of treatment in women with SCH[5].

Treatment

Evidence

Maraka et al in an observational study on 82 women with SCH found that treatment with levothyroxine (LT4) reduces the risk of low birth weight and low APGAR scores[18].

Yang et al performed a trial involving 2042 women with subclinical hypothyroidism and concluded that treatment with thyroxine in early pregnancy reduces complications in women with SCH[19].

However in a systematic review and meta analysis, Maraka et al concluded that beneficial effect of levo-thyroxine therapy in women with SCH during pregnancy remains uncertain[20].

Recommendations

Though we do not have strong evidence of benefit of treatment of SCH, however, since euthyroidism may be potentially needed for normal fetal development, many authors suggest to give levothyroxine irrespective of anti TPO antibody status so as to achieve TSH levels within the reference rangs for the gestation as well as the normal free T4 levels.

American Thyroid association (ATA) recommend to start levothyroxine if the TSH level is more than trimester specific range the woman if TPO antibody positive but do not recommended in subclinical hypothyroidism with TPO antibody negative women[5].

Endocrine Society for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum suggests that levothyroxine should be started in all

women with SCH irrespective of the anti-TPO status[21].

ACOG recommends treatment of hypothyroidism with levothyroxine in sufficient doses to return TSH to normal levels however does not state anything about SCH(.).

Therefore, it needs to be discussed with the woman regarding the potential benefit of treatment of subclinical hypothyroidism with negative TPO antibodies and accordingly take the decision.

Conclusion

Levothyroxine should be started in SCH when serum TSH level is above 10 mU/l. However below this level if woman is TPO-AB positive treatment can be started. If she is negative for TPO-AB then she needs to be counselled regarding the doubtful potential benefit of treatment and if woman opts for treatmentthen it can be started.

Women with severe SCH should be started in therapeutic dose 1.6 µg/kg of body weight daily empty stomach, preferably one hour before the breakfast. At TSH level<10, lower dose 1µg/kg of body wt daily can be started[24]. Then TSH is repeated every 4 weeks and dose is monitored to achieve TSH level of within range for the gestation. Increments can be done in doses of 12 to 25 µg daily.

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Thyroid Emergencies: Problem recognition before it becomes a catastrophe

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Care should not start at the emergency room!

So is the case with any emergency in pregnancy. Medical and surgical emergencies in pregnancy are very challenging. The symptoms of thyroid emergencies in pregnancy can be misleading and be confused with normal pregnancy as the vital signs are normally altered in pregnancy, physical examination is often more difficult, lab values are difficult to interpret and imaging algorithms for pregnant patients are very complicated. In addition, outcomes are generally worse in pregnant women with thyroid emergencies than non-pregnant patients. These pregnant women due to either excess or deficiency of thyroid hormones, may land up in catastrophe with high maternal and fetal morbidity and mortality. The two thyroid emergencies which an obstetrician can face are *thyroid storm* and *myxedema coma*.

Thyroid Storm

Thyroid storm is a rare, life-threatening endocrinal emergency due to excess of thyroid hormones. It can lead to cardiac arrest and death. A total of 20% to 30% of all cases are fatal.[1] Grave's disease is a common cause of thyroid storm.

Incidence in pregnancy: The incidence in pregnancy is not well reported. Only about 1% - 2% of women with hyperthyroidism, who receive thionamide, experience thyroid storm. However, it is a devastating complication.[2] Maternal & fetal mortality is as high as 20-30%.

Clinical Features

Thyroid storm is a hypermetabolic complication of hyperthyroidism. The characteristic features of thyroid storm are hyperthermia, widened pulse pressure, tachycardia out of proportion to the fever, arrhythmias, cardiac failure, diarrhea, restlessness, nervousness, changed mental status, confusion, and seizures[3] Thyroid storm is a clinical diagnosis, and treatment should be initiated before confirmatory test results are available. Thyroid storm is usually seen in patients with poorly controlled hyperthyroidism and can be precipitated by surgery, infection, trauma, or labor and delivery. Other features in pregnancy are nausea, abdominal pain, vomiting, severe agitation, diaphoresis, dehydration, congestive heart failure, confusion, cardiovascular collapse and malignant exopthalmos.

Investigations

Laboratory investigations should include baseline electrolyte, blood glucose, renal and liver function testing, and coagulation profile. It reveals leukocytosis, elevated hepatic enzymes, and occasionally hypercalcemia. If patient is unconscious or has focal CNS signs, it may be helpful to do a CT scan or MRI of the brain. Thyroid function test results are consistent with hyperthyroidism (elevated FT4/FT3 and depressed TSH). An ECG and continuous cardiac monitoring is essential. An echocardiogram is helpful for management in cases where cardiac decompensation is suspected. Pulse oximetry should be used to monitor peripheral arterial oxygen saturation, and blood gas analysis will help acid-base balance assessment.

Table 1: ACOG Guidelines for Diagnosing Thyroid Storm in Pregnancy, 2002

- Diagnosis is based on a combination of signs and symptoms: fever, tachycardia out of proportion to the fever, altered mental status (nervousness, restlessness, confusion, seizures), vomiting, diarrhea, and cardiac arrhythmia.
- An inciting event (e.g., surgery, infection, labor, delivery) may be identified.
- Serum-free triiodothyronine (FT_3), FT_4, and TSH levels help confirm the diagnosis, but treatment should not be delayed for test results.

Management

Management of thyroid storm is best accomplished in an obstetric intensive care unit (ICU), or an ICU that has continuous fetal monitoring and can handle an emergent delivery.

Table 2: Aims of therapy in thyroid storm

Therapy is designed to:
- Reduce the synthesis and release of thyroid hormone;
- Remove thyroid hormone from the circulation and increase the concentration of TBG;
- Block the peripheral conversion of T4 to T3;
- Block the peripheral actions of thyroid hormone;
- Treat the complications of thyroid storm and provide support;
- Identify and treat potential precipitating conditions.

Medical Management

Medication to reduce synthesis of thyroid hormones are: thionamides (propylthiouracil (PTU) and methimazole); iodide and glucocorticoids. These drugs should be started as soon as diagnosis of thyroid storm is made. PTU and methimazole inhibit iodination of tyrosine - leading to reduce synthesis of thyroid hormones and block peripheral conversion of T4 to T3.[4] These drugs alone can reduce the T3 concentration by 75%. Iodide can be in the form of Lugol's iodine, SSKI (Strong Solution of Potassium Iodide), sodium iodide, orografin, or lithium carbonate (for use in patients allergic to iodine). These drugs function by inhibiting proteolysis of thyroglobulin and thereby blocking the release of stored hormone (wolff chaikoff effect). Because one of the side effects of Iodide is an initial increase in production of thyroid hormone, it is therefore very important to start PTU before you give iodides. Glucocorticoids block release of stored hormone (as do iodides), and peripheral conversion of T4 to T3 (as do thionamides). They may also bolster adrenal function, and prevent adrenal insufficiency, although data in support of this particular benefit are few.[5]

Other Therapies

Plasmapheresis or peritoneal dialysis can be reserved to remove circulating thyroid hormone for patients who do not respond to conventional therapy. Anticoagulants may be prescribed, if appropriate. If conventional therapy is unsuccessful, subtotal thyroidectomy (during second-trimester pregnancy) or radioactive iodine (postpartum) may be required.

Adverse effects of anti-thyroid medications

Adverse effects of PTU include fever, rash, urticaria, arthralgias, and leucopenia. A rare adverse effect, agranulocytosis, usually manifested by fever and sore throat may be manifested. If fever and sore throat occur, a complete blood cell count should be done, and if agranulocytosis is diagnosed, treatment with thiopropyluracil should be stopped PTU may cause liver failure especially in pregnancy.[7] Methimazole therapy may be associated with aplasia cutis in fetus (a localized lesion in the parietal area of the scalp, characterized by congenital absence of the skin, punched-out "ulcer" lesions).[8]

Table 4: Supportive therapy in thyroid storm

- IV fluids and electrolytes;
- Cardiac monitoring;
- Consideration of pulmonary artery catheterization (central hemodynamic monitoring to guide beta-blocker therapy during hyperdynamic cardiac failure);
- Cooling measures: blanket, sponge bath, acetaminophen, avoid salicylates (risk of increased T4). Acetaminophen is the drug of choice;
- Oxygen therapy (consider arterial line to follow serial blood gases);
- Nasogastric tube if patient is unable to swallow (may be only avenue for propylthiouracil administration).

Obstetric management

Because of the hypermetabolic state of thyroid storm, medications are metabolized faster than normal. Therefore, higher and more frequent doses may be required to control the thyrotoxicosis. During this period, careful monitoring of the fetus is also a critical element of management. Current recommendations are to avoid delivery during thyroid storm unless the condition of the fetus demands prompt delivery.

Maternal and fetal outcome

This extreme hypermetabolic state is associated with a high risk of maternal heart failure. It may also lead to various other complications like severe uncontrolled hypertension and eventual high morbidity and mortality.[9] Associated fetal complications are low birth weight, intrauterine growth restriction and preterm delivery. The stimulating thyroid antibodies when

Table 3: Drugs used in Treatment of Thyroid Storm

Thionamides	Propylthiouracil (PTU) Methimazole	PTU orally or via nasogastric tube, 300-800 mg loading dose followed by 150-300 mg every 6 hours
Iodide	Lugol's iodine SSKI (strong solution of potassium iodide) Sodium iodide, Orografin Lithium carbonate	One hour after instituting PTU, Sodium iodide, 500 mg every 8-12 hours or oral Lugol's solution, 30-60 drops daily in divided doses can be given. Iodides may be discontinued after initial improvement.
Glucocorticoids	Hydrocortisone Dexamethasone Prednisone	Adrenal glucocorticoids are administered to inhibit peripheral conversion of T4 to T3. Following options can be used: • Hydrocortisone, 100 mg IV every 8 hour, or • Prednisone, 60 mg PO every day, or • Dexamethasone, 8 mg PO every day
Beta blocker	Propanalol	Propranolol can be used to control autonomic symptoms (especially tachycardia).[6]

Table 5: Algorithm for Management of Thyroid Storm

• Stabilize the patient (Airway, Breathing, Circulation)
• Give Propylthiouracil (PTU) 600-800 mo orally followed by 150 mg every 4 - 6 hrs (Methimazole is an alternative if PTU administration is not possible)
• 1 -2 hours after administering PTU, Administer potassium iodide, 2-5 drops orally every 8 hours or Lugols solution, 8 drops every 6 hours, or Sodium Iodide 0.5 – 1 gm intravenously (IV) every 8 hours
• Immediately administer dexamethasone 2 mg IV or IM 6 hours for 24 hours (4 doses)
• Immediately initiate Propranalol 20- 80 mg orally every 4-6 hours, or 1-2 mg IV every 5 minutes, until a total of 6 mg, then 1-10 mg IV every 4 hours.
• Give Phenobarbital, 30 – 60 mg orally every 6-8 hours, as needed for agitation and restlessness
• Supportive therapy goes side by side
Obstetric Management: Strict Maternal and Fetal monitoring Avoid delivery during thyroid storm unless the condition of the fetus demands prompt delivery

cross the placental barrier are capable of stimulating the fetal thyroid gland and causing fetal or neonatal hyperthyroidism.[10] Fetal and maternal mortality may be as high as 20-30%.

Myxedema Coma

Myxedema coma, occasionally called myxedema crisis, is a rare life-threatening clinical condition that represents severe hypothyroidism. Myxedema crisis is a potentially fatal complication of uncontrolled hypothyroidism manifesting as progressive mental deterioration like lethargy, stupor, delirium, or coma and multiple organ abnormalities. Diagnosis of this rare phenomenon is hampered by its insidious onset. It usually occurs when precipitating factors like infection, illness, drugs, labour and delivery etc weaken the compensatory responses. The condition usually occurs in patients with long-standing, undiagnosed hypothyroidism.

Incidence in pregnancy: Myxedema coma is rare entity among pregnant women with fewer than 40 cases reported.[11]

Physical Findings

Clinical features can be:

- Hypothermia, hypotension, bradycardia, decreased respiratory rate
- Periorbital puffiness, macroglossia, pleural effusion, pericardial effusion, abdominal distension due to ascites
- Diminished or absent bowel sounds due to ileus, abdominal distension
- Cold extremities, non-pitting edema of the upper and lower extremities, pale, dry, scaly, and thickened skin, ecchymoses, purpura, dry and brittle nails, coarse or thinning of hair
- Confusion, stupor, slow speech, delayed reflexes and seizures
- Complications like respiratory failure, coma, heart failure, myocardial infarction, sepsis and gastrointestinal bleeding can occur.

There can be accumulation of fluid rich in mucopolysaccharides within the pericardial sac leading to pericardial effusion. Neurologically, there can be altered consciousness. There can be hypoventilation, leading to decreased responsiveness to hypoxia and hypercapnia. Fluid accumulation may cause pleural effusions and decreased diffusion capacity. It may cause malabsorption, gastric atony, impaired peristalsis, paralytic ileus. Hematologically, there are higher risk of bleeding caused by coagulopathy related to an acquired von Willebrand syndrome (type 1) and decreases in factors V, VII, VIII, IX, and X. In the kidneys there can be reduced glomerular filtration rate because of low cardiac output and peripheral vasoconstriction. Hyponatremia is common in patients with myxedema coma and is caused by increased serum antidiuretic hormone and impaired water excretion.

Investigations

- Thyroid function tests
  - TSH is elevated in most patients indicating a primary thyroid disorder
  - Free T4 and free T3 levels are low
  - A low or normal TSH level with low levels of free T4 and free T3 may indicate that the disorder is due to pituitary or hypothalamic dysfunction.
- Hypoglycemia and hyponatremia should be evaluated and adrenal function should be checked with either serum cortisol or ACTH stimulation.
- Chest X-ray may show signs of cardiomegaly, pericardial effusion, congestive heart failure, or pleural effusion.
- Electrocardiography reveals sinus bradycardia, low-amplitude QRS complexes, a prolonged QT interval, flattened or inverted T waves, or arrhythmias.

Management

Airway management: Maintenance of adequate airway is crucial, since most patients have depressed mental status along with respiratory failure

Thyroid hormone replacement: Some clinicians favor the administration of levothyroxine (T4), while others prefer a combination of T4 and liothyronine (T3).

The American Thyroid Association recommends combination therapy with T4 and T3. Intravenous thyroid hormone therapy is advised. Measurement of thyroid hormones every 1-2 days is suggested. Failure of TSH to decrease or of thyroid hormone levels to increase suggests the need to increase doses of T4 and/or add T3.

Glucocorticoid therapy: Hydrocortisone at a dose of 50-100 mg every 8 hours is administered. Alternatively, dexamethasone at a dose of 2-4 mg every 12 hours can be administered. Dexamethasone does not affect the serum cortisol concentration and can be used immediately without affecting the results of the ACTH stimulation test, which can be performed at any time. If the test is normal, corticosteroids can be stopped without tapering.

Supportive measures: Hypothermia should be treated with passive rewarming using ordinary blankets and a warm room. Associated infection needs treatment. Severe hyponatremia needs correction with saline and free water restriction. Hypoglycemia also requires correction with intravenous dextrose.

Surgical Care: Patients with myxedema coma should be stabilized before surgery as they are at high risk for complications of anaesthesia as well as intraoperative and postoperative complications.

Follow up

If primary hypothyroidism was diagnosed, TSH levels are assessed every 4-6 weeks, and the dose of T4 is adjusted accordingly. If hypothyroidism is secondary to pituitary dysfunction, free T4 levels are monitored. TSH level is not an accurate measure of thyroid function in this setting.

Maternal and Fetal Outcomes

If the condition is not promptly diagnosed and treated, the mortality rate can be more than 50%.[11] Myxedema crisis in pregnancy can cause preeclampsia, abruptio placentae, anemia, postpartum hemorrhage, cardiac ventricular dysfunction, increased risk of spontaneous abortions, low birth weight. And the fetuses can have complications such as premature birth, low birth weight and increased neonatal respiratory distress. Fetal distress and even demise may occur. Newborn may be affected with impaired cognitive development and cretinism.

Table 5: Poor predictors of outcome in myxedema coma

Presence of the following is associated with poor prognosis:
• Bradycardia
• Persistent hypothermia
• Altered level of consciousness
• High APACHE II score at presentation
• Hypotension
• Need for mechanical ventilation

Conclusion

Thyroid Storm and Myxedema coma are life threatening medical emergencies and if acted upon promptly can prevent morbidity and mortality of the mother and the fetus. We have managed a case of myxedema coma in labor and reported the case.[11] Prompt diagnosis and management lead to good maternal and fetal outcome. Proper counselling of the family regarding poor prognosis of the condition should be carried out. Prompt diagnosis and timely administration of therapy is crucial to prevent catastrophe. Multi-disciplinary approach should be adopted.

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Events Held

- Monthly clinical meeting was held in the Auditorium of Indraprastha Apollo Hospital on 29th April. Interesting cases were discussed.
- Managing Committee Meeting of the FOGSI held in Gurgaon on 30th April-1st May 2016.
- CME on 'The Use of Gonadotrophins in IUI' was organized by Infertility Committee of FOGSI and AOGD on 4th April 2016
- Awareness Program on 'Thalassemia Screening and Diagnosis' was organized by Thalassemia Control Cell & Department of Obstetrics &Gynaecology, Hindu Rao Hospital on 04.05.2016
- CME on the 'Current Concepts in the Management of Pre-term Labour : search for New Molecule (Atosiban)' was organized by The Forum of Obstetricians and Gynaecologists of South Delhi (FOGSD) on 7th May 2016.
- Meeting of Chairpersons of Sub Committees, AOGD was held at MAMC on 6th May 2016.
- 'Insight AUB-Indian Perspective 2016' was organized by FOGSI on 8th May 2016
- A health camp was organised by AOGD MAMC at MCW Centre, Kanchan Puri, Daryaganj on 13 May 2016. It was attended by more than 100 patients, ASHA workers and ANMs. Thalassemia awareness was done in association with Thalassemia Control Cell of Hindu Rao Hospital.
- 26th biannual FOGSI certified course in basic and advanced laparoscopy was conducted at Jeewan Mala Hospital from 16th to 21 May,2016
- CME on Stress Urinary Incontinence was organized by North Delhi Forum on 19 May, 2016.
- Gurukul Classes on 25th & 26th May 2016 was conducted by Institute of Obstetrics & Gynaecology, Sir Ganga Ram Hospital
- CME under aegis of Reproductive Endocrinology subcommittee AOGD and DGF North was held on 24th May 2016, at Fortis Hospital, Shalimar Bagh.
- Lunch CME was organized by South Delhi Forum on 26th May 2016.
- Monthly Clinical Meeting was held in Dr Ram Manohar Lohia Hospital on 27th May. Interesting cases were discussed.

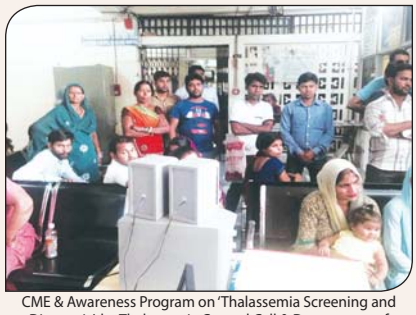


Monthly Clinical Meeting at Apollo Hospital on 29th April, 2016

Managing Committee Meeting of FOGSI 30th April -1st May, 2016

CME on 'The Use of Gonadotrophins in IUI' - organized by Infertility Committee of FOGSI & AOGD on 4th May 2016


CME & Awareness Program on 'Thalassemia Screening and Diagnosis' by Thalassemia Control Cell & Department of Obstetrics & Gynaecology, Hindu Rao Hospital on 4th May, 2016



CME & Awareness Program on 'Thalassemia Screening and Diagnosis' by Thalassemia Control Cell & Department of Obstetrics & Gynaecology, Hindu Rao Hospital on 4th May, 2016

CME on the 'Current Concepts in the Management of Pre-term Labour: search for New Molecule (Atosiban)' by Dr PC Mahapatra -The Forum of Obstetricians & Gynaecologists of South Delhi (FOGSD) on the eve of Mother's Day 7th May, 2016


CME on the 'Current Concepts in the Management of Pre-term Labour: search for New Molecule (Atosiban)' by Dr PC Mahapatra -The Forum of Obstetricians & Gynaecologists of South Delhi (FOGSD) on the eve of Mother's Day 7th May, 2016

Health camp at MCW Centre, Kanchan Puri, Daryaganj on 13th May, 2016



Health Camp at MCW Centre, Kanchan Puri, Daryaganj on 13th May, 2016

Health Camp at MCW Centre, Kanchan Puri, Daryaganj on 13th May, 2016

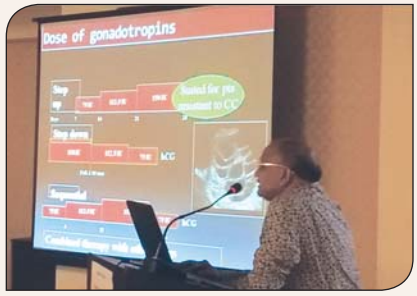

26th Biannual FOGSI certified course in basic and Advanced Laparoscopy under aegis of AOGD at Jeewan Mala Hospital from 16th to 21st May, 2016

CME on Stress Urinary Incontinence was organized by North Delhi Forum 19th May, 2016.

CME under aegis of Reproductive Endocrinology subcommittee AOGD and DGF North on 24th May 2016, at Fortis Hospital, Shalimar Bagh

CME under aegis of Reproductive Endocrinology subcommittee AOGD and DGF North on 24th May 2016, at Fortis Hospital, Shalimar Bagh

Gurukul Classes by Institute of Obstetrics & Gynaecology, Sir Ganga Ram Hospital on 25th & 26th May 2016



Lunch CME was organized by South Delhi Forum on 26th May, 2016

Lunch CME was organized by South Delhi Forum on 26th May, 2016

Monthly Clinical Meeting at Dr RML Hospital on 27th May, 2016

19th Post-graduate
Practical Course & CME

Organized by Department of Obstetrics & Gynecology
Maulana Azad Medical College, New Delhi

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Venue: **Auditorium, MAMC, New Delhi**

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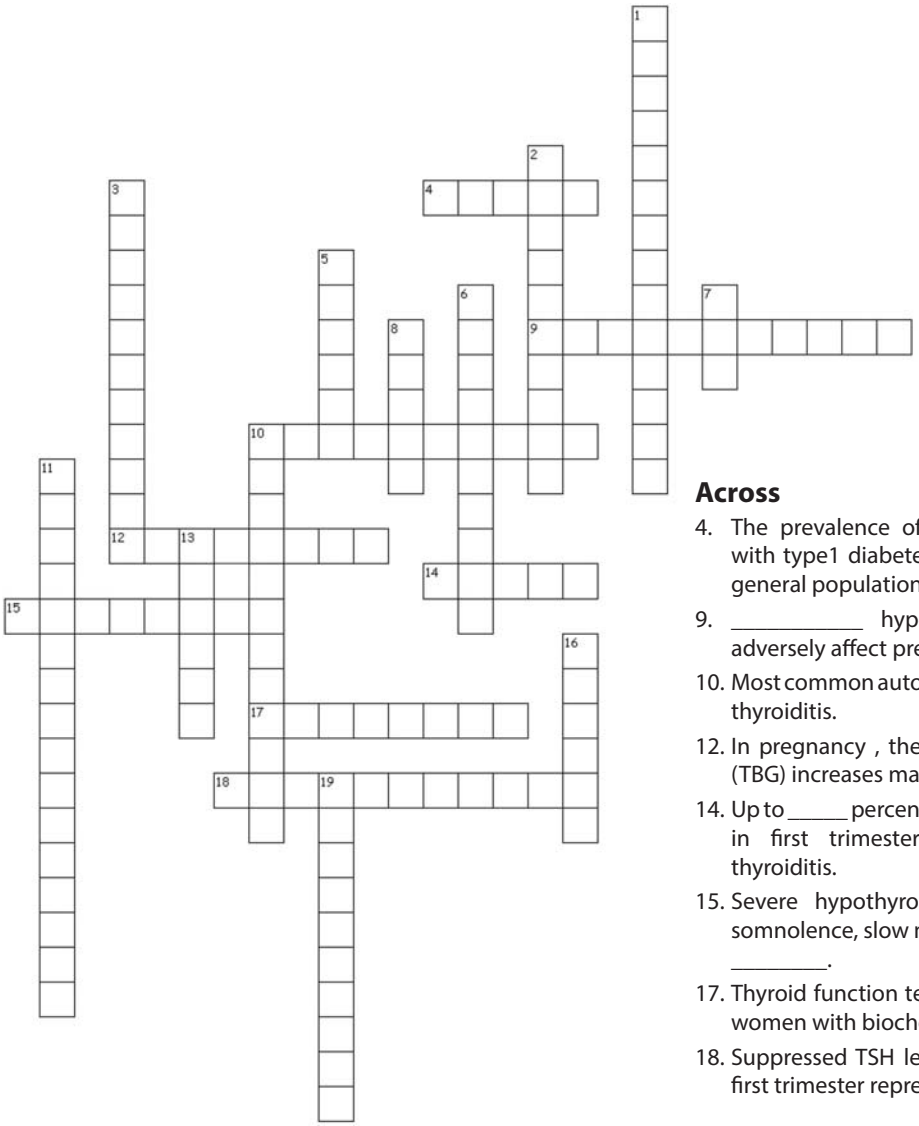
Contact: Dr Devender Kumar 9968604407 (devender123@gmail.com)
Dr Pushpa Mishra 9873617596 (pushpamishra81@yahoo.in)

Crossword - Thyroid disorders

Compiled and designed by Meenakshi Goel[1], Sangeeta Gupta[2]
[1]Resident, [2]Professor, Obstetrics & Gynecology, Maulana Azad Medical College, New Delhi, India



Across

4. The prevalence of post partum thyroiditis in females with type1 diabetes mellitus is _____ fold greater than general population.
9. _____ hyperthyroidism has not been shown to adversely affect pregnancy.
10. Most common autoimmune thyroid disorder is _____ thyroiditis.
12. In pregnancy , the levels of thyroxine binding globulin (TBG) increases mainly under the effect of _____.
14. Up to _____ percent females with thyroid auto-antibodies in first trimester are predisposed to postpartum thyroiditis.
15. Severe hypothyroidism characterized by puffy skin, somnolence, slow mentation and hoarseness is known as _____.
17. Thyroid function tests normalize by _____ weeks in women with biochemical thyrotoxicosis.
18. Suppressed TSH levels with slightly elevated free T4 in first trimester represent _____ thyrotoxicosis.

Down

1. _____ due to excessive hcg production is seen in molar pregnancy.
2. Females with post partum thyroiditis are at increased risk of developing post partum _____.
3. Aplasia cutis of scalp and choanal atresia are reported with _____ therapy for hyperthyroidism in first trimester.
5. Most common cause of pre-existing hyperthyroidism in pregnancy is _____ disease.
6. Transient _____ is seen in ten percent pregnant females on antithyroid drugs.
7. Females should avoid pregnancy for at least ___ months after radio-ablative therapy for safety reasons.
8. Maternal thyroxine is important for normal fetal _____ development, even before development of fetal thyroid.
10. Iatrogenic electrolyte disturbance due to thyroidectomy is _____.
11. _____ is recommended first line drug for treatment of hyperthyroidism in pregnancy.
13. Embryogenesis of fetal thyroid gland is complete and begins synthesizing thyroid hormone by _____ weeks of gestation.
16. _____syndrome ,also called as multiple endocrine neoplasia type II (MEN-II) is characterized by phaeochromocytoma and medullary thyroid carcinoma.
19. Besides thyroxine, _____ is secreted by thyroid gland involved in bone metabolism.

(..... answers to crossword on page 41)

Does Obstetric Management need to be Modified in Thyroid Disorders?

Reva Tripathi[1], Sarita Shah[2]
[1]Director professor, [2]Senior Resident, Department of Obstetrics & Gynecology, Maulana Azad Medical College & Lok Nayak Hospital, New Delhi

Thyroid disease is the second most common endocrine problem encountered during pregnancy as most diseases of thyroid affect young females. Most thyroid conditions can be diagnosed, problems can be anticipated, and effective treatment is available.

Though universal screening for thyroid disease in pregnancy leads to increase in diagnosis and subsequent treatment, studies have not shown any clear differences in maternal or fetal outcomes like abortion, pre-eclampsia, preterm birth and fetal or neonatal death.[1] The outcome is almost always a healthy one, for both the mother and her baby.[2]

Most of the studies and trials have been on screening and treatment of thyroid dysfunction and there is paucity of literature on obstetric management in thyroid disorders. This is applicable to both monitoring for obstetric problems during antenatal period and also to timing and mode of delivery.

Hyperthyroidism

The risk of miscarriage and stillbirth is increased if thyrotoxicosis goes untreated. Thyroid-stimulating autoantibodies can cross the placenta and activate the fetal thyroid gland. Fetal monitoring during pregnancy is essential as *neonatal hyperthyroidism* may occur, especially if TSH receptor antibody (TRAb) levels are high.[3] Fetal thyrotoxicosis can be suspected when the fetal heart rate is more than 160 bpm. In such cases serial fetal ultrasonography for fetal growth restriction, hydrops fetalis, advanced fetal bone age, goitre, tachycardia and heart failure is advised as anyone or more of these complications could occur.

Hyperthyroid pregnant women with elevated levels of TRAbs, thyroid-stimulating immunoglobulin, or those being treated with anti-thyroid drugs (ATDs) should be screened for *fetal hypothyroidism*. Ultrasonography is the mainstay of monitoring fetal hypothyroidism while treating maternal hyperthyroidism. Presence of a fetal goitre on ultrasonography is highly suggestive of fetal hypothyroidism. If a fetal goitre is present, ATDs should be reduced or discontinued as the risks due to maternal hyperthyroidism in pregnancy are much less than of the fetal hypothyroidism, particularly with regard to growth and development of the fetus and the neonate.[4] Rarely umbilical cord blood sampling may be considered if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical and sonographic data and the information gained would change the treatment.[5]

Clear guidelines on antepartum fetal surveillance for hyperthyroid women in the absence of associated comorbidity are not available. However, poorly controlled hyperthyroidism during pregnancy is associated with pregnancy-induced hypertension, preeclampsia, fetal growth restriction, low birth-weight and stillbirth. Antepartum fetal surveillance is advisable in such patients.[6]

Iodine- 131 (I^{131}) should not be given to a woman who is or may be pregnant. There are no data for or against recommending termination of pregnancy after I^{131}exposure (USPSTF recommendation level: I; evidence, poor)[5].

No guideline is available for induction of labour in women with hyperthyroidism. According to the Endocrine Society, 2012 early delivery may need to be considered in the case of *fetal thyroid dysfunction*, in women with hyperthyroidism depending on the gestation at diagnosis and the severity of fetal signs.[5]

Subclinical hyperthyroidism

Subclinical hyperthyroidism and gestational diabetes are considered to be associated due to presence of insulin resistance in both overt and subclinical hyperthyroidism.[7,8] However, Tudela et al reported a protective effect of hyperthyroidism in relation to gestational diabetes.[9] In view of conflicting data on this issue it is suggested that decision for screening or testing for gestational diabetes should not be based on thyroid function tests but considered independently depending on the prevailing clinical situation. There is no consensus for fetal surveillance or induction of labour in women with subclinical hyperthyroidism.

Women can continue taking ATDs while breastfeeding. According to current knowledge both propylthiouracil

(PTU) and methimazole are likely to be safe for the infants. Careful monitoring of both mother and infant is still advisable, including evaluation of serum T_4 and thyrotropin levels at least 3 to 4 weeks after initiation of breastfeeding.[10] Taking PTU right after nursing the baby and waiting for 3 to 4 hours before nursing again should minimize the amount of drug transferred to the infant.

Transient gestational hyperthyroidism

Gestational hyperthyroidism is a transient condition which occurs early in pregnancy and is not due to intrinsic thyroid disease. It is known by different names like *transient non-autoimmune hyperthyroidism of early pregnancy, gestational transient thyrotoxicosis* and *thyrotoxicosis of pregnancy*. It is considered here as it is associated with hyperemesis which requires treatment.

Gestational thyrotoxicosis has a prevalence of 2-3% in Europe but is much higher in South Asians.[11] It occurs from high levels of hCG which stimulate the TSH receptor. Diagnosis is established based on elevated thyroid hormone levels, absence of hyperthyroid features on physical examination and absence of thyroid autoantibody, in a previously euthyroid women. TSH concentration is suppressed. In most cases, the symptoms are mild, mainly nausea and sometimes vomiting both resolving spontaneously by 20 weeks of gestation. The most severe form of gestational thyrotoxicosis is hyperemesis gravidarum, known as *transient hyperthyroidism of hyperemesis gravidarum*.[12] Management is symptomatic with intravenous rehydration, electrolyte correction and antiemetic medication. Treatment with an anti-thyroid drug is not indicated because the symptoms subside spontaneously with progression of pregnancy as hCG levels falls, with normalization of T4 levels by 14 to 20 weeks of gestation. Rarely women with worsened or prolonged symptoms, not responding to routine management may require anti-thyroid agents such as short term propylthiuracil.

Hypothyroidism

Endemic iodine deficiency accounts for most cases of hypothyroidism in pregnant women worldwide while chronic autoimmune thyroiditis is the most common cause of hypothyroidism in iodine sufficient parts of the world.[13,14] While the importance of iodine cannot be understated, excessive iodine can paradoxically cause fetal hypothyroidism and has been linked to development or aggravation of autoimmune hypothyroidism.[15]

There are no studies comparing pregnancy outcomes in iodine deficiency hypothyroidism and autoimmune thyroid dysfunction, so it is open to debate whether these two entities require different line of management. It is likely that autoimmune hypothyroidism would fare worse in relation to pregnancy outcomes when compared to that due to iodine deficiency and therefore patients with autoimmunity may warrant certain extra obstetric monitoring and interventions.

Women with uncontrolled hypothyroidism are at higher risk of preeclampsia, miscarriage, low birth weight and stillbirth. There is 22% risk of gestational hypertension in pregnant women with overt hypothyroidism, higher in comparison to euthyroid women or those with subclinical hypothyroidism.[16] According to Idris et al maternal hypothyroidism in the third trimester may increase the risk of low birth weight and the likelihood for caesarean section. The latter observation was not due to a higher rate of emergency caesarean section nor to a lower threshold for performing elective caesarean section. They also recommended larger studies with adjustments made for the various confounders to confirm this observation as no definite explanation for this finding was available.[17]

Antepartum fetal surveillance is not routinely recommended for hypothyroid women except for other reasons such as concurrent diabetes mellitus or hypertension.[18] According to some authors, antenatal fetal surveillance *may be* beneficial.[19] There are no guidelines on termination of pregnancy in hypothyroid women. Delivery should be considered at term. For well controlled hypothyroid women and no associated co-morbidity, there is no indication to terminate at expected date of delivery or earlier and she may be allowed for spontaneous onset of labor up to 41 weeks. However, in hypothyroid women who have been diagnosed late in pregnancy and are not well controlled, individualization of case may be practised to select time of induction. The clinician should analyse the risk benefit ratio of higher risk of caesarean section in the induction group with uncontrolled hypothyroidism versus risk of continuing pregnancy beyond term.

Thyroid hormones stimulate erythropoiesis and therefore hypothyroidism has been associated with maternal anaemia which may be normocytic, hypochromic-microcytic or macrocytic. Treatment of anaemia often requires correction of thyroid status and similarly haematological status should be carefully monitored during management of thyroid diseases.[20] However, in India where anaemia in pregnancy is ubiquitous this pathophysiology is likely to be applicable to a very small fraction of pregnant females.

Subclinical hypothyroidism

There is no evidence for fetal surveillance and early termination of pregnancy in women with subclinical hypothyroidism.

Thyroid nodule

All thyroid nodules should be evaluated even during pregnancy as up to 40 percent are found to be malignant. FNAC can easily be done and will clinch the diagnosis. The report can be utilised to plan subsequent management. Thyroid cancer is treated with thyroidectomy and radiation (i.e. I^{131}). Thyroidectomy can be performed, preferably during the second trimester, but radiation therapy should not be administered until after the pregnancy. Management options for thyroid cancer during pregnancy range from termination of the pregnancy followed by full treatment, treatment during pregnancy to induced preterm or term delivery followed by full treatment. Gestational age and tumour characteristics affect the management choice.

For a benign solitary nodule obstetric management should be according to the thyroid function status.

Thyroid storm

It is a medical emergency and it is usually seen in patients with poorly controlled hyperthyroidism complicated by additional physiological stressors, such as infection, surgery, thromboembolism, preeclampsia, and parturition.[21] As many as 20% to 30% of cases can end in maternal and fetal mortality.[22] It requires prompt recognition, antithyroid drugs and supportive management. Management should be in an obstetric ICU with *continuous fetal monitoring*. Delivery should be for fetal indication. According to ACOG 2002, depending on gestational age, fetal status should be evaluated with ultrasound examination, non-stress testing, or a biophysical profile. Unless deemed necessary, delivery during thyroid storm should be avoided.[23] It is also important to note that even if fetal status is not reassuring in the acute setting of thyroid storm, that status may improve as maternal status is stabilized.[24] Even after crisis is over the delivery should be for fetal indication only.

Myxoedema coma

Myxoedema coma is a life threatening form of decompensated hypothyroidism. The extremely high mortality rate (25-60%) makes it necessary for early recognition and treatment. Precipitating factors are hypothermia, infections and septicaemia, surgery, cerebrovascular accidents, CHF, gastrointestinal bleeding, trauma and fractures, drugs (anaesthetics, sedatives, tranquilizers, narcotics, amiodarone, and lithium) and withdrawal of thyroid supplements.[25] Continuous fetal monitoring should be instituted and termination of pregnancy should be reserved only for fetal indication. The management should be in an obstetric ICU and be targeted to treatment of any precipitating factors and thyroxine replacement to reverse the decompensation. Once the acute crisis is over, obstetric management is similar to other cases of hypothyroidism.

Conclusion

There is paucity of literature on obstetric management of thyroid disorders in pregnancy as most literature has targeted evaluation of thresholds, frequency of testing and dosage of replacement therapy. Most of the standard recommending authorities (RCOG, ACOG, SOGC, etc.) are silent on obstetric management. In light of this, it is difficult to suggest a specific line of management. However, instituting fetal monitoring or considering termination of pregnancy must be cautiously viewed as there are no grade A recommendations. It is likely that patients who have an auto-immune basis for thyroid dysfunction could be considered candidates for some obstetric intervention depending on the clinical situation, but the more frequently seen cases of simple (non- autoimmune) thyroid dysfunction- whether overt or subclinical are unlikely to require either fetal monitoring or induction of labour. These should be reserved for patients with co-morbidities where the indication for the intervention would be these associated conditions rather than only thyroid dysfunction.

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Forthcoming Events

- AOGD Fetal Medicine and Genetics Subcommittee is planning to hold a half day workshop on ''Intrapartum CTG - interpretation and action' at Asian Hospital, Faridabad on 2nd June, 2016 (Thursday) from 1.00pm to 5.00pm.
- Monthly Clinical Meeting will be held at R & R Army Hospital on 24th June, 2016 from 4.00pm-5.00pm.
- Multi Discplinary Committee of AOGD is organising a workshop on ABC of Critical Care Obstetrics in Collaboration with the Department of Obstetrics & Gynaecology, Department of Pulmonary & Critical Care Medicine and Department of Anaesthesia & Intensive Care, VMMC & Safdarjung Hospital, on Saturday, 9th July, 2016, 9.00am-5.00pm, at Gynae LT, Safdarjung Hospital. Only 40 seats on first come basis. Registration fee Rs 1000/. For further details please contact Dr Jyotsna Suri, 9810858358; Dr Rekha Bharti, 9871394999
- Sunrise Hospital, Delhi will be organizing – Workshop on Gynae Laparoscopic Surgery on 16th and 17th July, 2016.
- Quiz on 'Contraception', on 23rd July, 2016, 1.00pm-2.00pm at Maulana Azad Medical College, New Delhi. For details, contact Dr Rachna Sharma 09873617586.
- CME on "Preventive Gynae Oncology & Beyond ..." on 10th & 11th September, 2016, 8.30am at Auditorium, Sant Parmanand Hospital, Delhi is being organized by the Department of Obstetrics & Gynaecology, Sant Parmanand Hospital, in association with ISCCP & Oncology Committee of AOGD.
- 19th Post-Graduate Practical Course and CME will be conducted from 14th to 16th October, 2016 in MAMC Auditorium, New Delhi. Details at http://www.mamc.ac.in/

Postpartum Thyroiditis

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Create a life that feels good on the inside, not one that just looks good on the outside.

Postpartum period is a very dynamic period with lot of physical, mental and emotional changes occurring in the mother. Many times trivial symptoms go unnoticed. Postpartum thyroiditis (PPT) is an auto-immune condition, affecting women, two to four months after delivery. Most of the patients present with vague physiological changes and stresses of motherhood. It resolves mostly, by the end of one year, many a times with no treatment at all. Most of the patients present with hyperthyroidism followed by hypothyroidism and rest with either of them.[1, 2] These minor symptoms do not get much attention and are left unattended and undiagnosed. Therefore, such complaints must be evaluated for postpartum thyroiditis.

Prevalence

The prevalence of postpartum thyroiditis is 5 to 10 % in postpartum women.[2] Different studies from different regions of world report the prevalence to be varying between 3 to 6%. It is three times more common in patients with Diabetes Mellitus Type 1. Prevalence is higher in Iodine deficient population, eg. the sub-himalayan region according to some studies, however, few studies refute this statement and report that the prevalence does not depend on iodine deficient state of the population.[3] Zargar et al reported the prevalence of 8% in the Kashmir valley.[3] However, exact prevalence is unknown due to under-reporting and faltered diagnosis.

As many as 30-50% women with antithyroid antibodies in first trimester will develop postpartum thyroiditis.

Etiology

The etiology is not well-understood. There is usually a strong family history of auto immune thyroid disorder. Most probable cause is dynamic immune system of the mother in postpartum period. It is suggested that subclinical auto-immune condition of the mother and flare up in postpartum period results in the cell mediated auto-immune inflammation of the thyroid gland. This causes destruction of the gland and increased release of the T3 and T4 hormones. It is related with the level of the antibodies - thyroglobulin (TgAb) and thyroid peroxidise (TPOAb). The higher the values of these antibodies, the severe the symptoms are. PPT resembles Hashimoto's thyroiditis and in fact, it is not possible to differentiate between the two. Some studies have shown an association of HLA-BRB, -DR4, -DR5 with postpartum thyroiditis.

Risk Factors

The risk factors of PPT are:

- Patients with increased levels of auto antibodies i.e. TgAb, TPOAb, in the early pregnancy or in the postpartum period.[1,4]
- Presence of other autoimmune conditions like DM Type 1
- Family history of auto immune thyroid disease
- History of PPT in previous pregnancies
- Prior history of thyroid disease in patient

Patho-physiology

Its histopathology is indistinguishable from the Hashimoto's thyroiditis so it is considered as a variant of Hashimoto's disease. It is characterized by the extensive and diffuse, destructive lymphocytic infiltration of the thyroid gland.[1] In few women, with sub-clinical Graves disease, recurrent postpartum hyperthyroidism may occur. It is proposed as suppressor T cell defect which is tissue specific to thyroid antigens. Thyroid destruction leads to increased release of T3 and T4 hormones in the circulation, therefore, decreasing the TSH (thyroid stimulating hormone) level in the circulation, resulting in thyrotoxicosis. Thyroid gland enlargement can also be there.

Clinical Presentation

Postpartum thyroiditis presents 2 to 4 months after delivery in different phases, as mentioned below. These phases are in sequential form in approximately 80% cases.[4] However, onset can be sudden in few cases.

- Phase of hyperthyroidism (2 to 6 months)
- Phase of hypothyroidism (3 to 12 months)

- Phase of resolution (12 to 18 months)
- In approximately 20 to 25 % cases, either hypo or hyperthyroidism persists

Hyperthyroidism presents with palpitations, anxiety, sweating, warm skin, heat intolerance, nervousness, loss of concentration, muscle weakness, tremors, goitre etc. Hypothyroidism presents with fatigue, dry skin, cold intolerance, weight gain, hair loss, loss of appetite, body aches and pains, goitre etc. Patient can be asymptomatic during the transit phase, from hyper to hypothyroidism. Mood disorders are associated with PPT.[5]

Women suffering from PPT, more commonly present with hypothyroidism 4-8 months after delivery and it may last upto 9-12 months.

Most women return to the normal thyroid state within 12-18 months of onset of symptoms.

The three common courses of postpartum thyroiditis are:

- A hyperthyroid phase followed by return to a normal function
- A hypothyroid phase alone
- A hyperthyroid phase followed by a hypothyroid phase

Diagnosis

Only suspicion of the condition can make a clinician to advice a TSH level for the patient. It is very important, not to snub her symptoms as maternal stress of rearing a baby. The following laboratory values may aid in diagnosis of PPT.

- Hyperthyroidism - Increased level of serum T3 and T4, decreased level of serum TSH (< 0.5)
- Hypothyroidism - Decrease level of serum T3 and T4, increased level of serum TSH
- ***An elevated T4: T3 ratio is very much suggestive of PPT***
- Antibodies levels (TgAb, TPOAb) should be done in addition to above tests
- In the presence of goitre, sonography of the thyroid gland should be done to rule out any toxic nodule.
- FNAC should be done in the presence of suspicious nodule
- CBC, liver function test, serum calcium level and magnesium level should be done for the supportive therapy of the patient

Differential Diagnosis

Hashimoto's disease is a differential diagnosis of PPT. Grave's disease is also a differential diagnosis. To differentate Grave's disease from PPT, a radioactive iodine uptake test can be performed. Iodine is secreted in breast milk, hence, women undergoing this test should stop breastfeeding for 3 to 5 days. Alternatively, the procedure can be delayed.

Management

Counselling and explanation of the disease to the patient and relatives are of foremost importance, especially with minimal symptoms. In transit phase, usually no treatment is required. Endocrinologists should be involved in management of these women.

In hyperthyroid phase, beta blockers preferably propranolol (does not secrete in the milk) is used for the symptomatic relief. Usually other anti-thyroid medications are not required.[6] Methimazole is safer in low doses (20 to 30 mg /day) for the lactating mother and infant. Propylthiouracil, if required, patient should be assessed for liver toxicity. In hypothyroid phase, L-thyroxin, 25 to 75 mcg, is to be given according to level of the hormones. Mood disorders are associated with PPT, so psychiatrist should be consulted for the same.

Follow-up

10 to 20% cases of PPT remain hypothyroid and never recover. One third of them, develop thyroid problems later in life. After recovery, patients with high risk factors, should be advised regular monitoring with TSH level, once a year. Approximately 50% patients, positive for peroxidase antibodies develop hypothyroidism after 6 to 7 years.

Screening of women for postpartum thyroiditis

The value of screening for postpartum thyroiditis and the best test to use for screening are unclear. There is no consensus on whom to screen and when to screen. Some physicians prefer screening all patients for PPT. However, considering the cost constraints, this is not a feasible option in India. However, screening should be done in high risk women i.e. presence of other autoimmune conditions like DM Type 1, family history of auto immune thyroid disease, history of PPT in previous pregnancies and women with goiter.

Conclusion

Postpartum thyroiditis is a relatively common disorder that has previously been unrecognised and untreated.

The symptoms are temporary and mild. Women who are diagnosed with the condition are infact, relieved with the fact that they have some organic problem and its 'not in their heads'. It is an unanswered question, whether to screen all women, when to screen and how to screen. It is time to answer all these questions, to unravel the mysteries of postpartum thyroiditis.

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3. Zargar AH, Shah IH, Masoodi Sr, LAway BA, Salahuddin M, Bhat IA. Postpartum thyroiditis in India: prevalence of postpartum thyroiditis Kashmir valley of Indian sub-continent. Exp Clin Endocrinol Diabetes. 2002; 110(4): 171-5.
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5. Pearce EN, Monitoring and effects of iodine deficiency in pregnancy still a unsolved problem? European journal Clin Nutr. 2013; 67(5): 481.
6. Lucas A, Pizarro E, Granada ML. Postpartum thyroid dysfunction and depression: Are they two linked disorders? Clinical Endocrinol. 2001; 55: 809.

Calendar of Monthly Clinical Meetings 2016-17

Months	Name of the Institute
June, 2016	Army Hospital-Referral & Research
July, 2016	VMMC & Safdarjung Hospital
August, 2016	AIIMS
September, 2016	Fortis Hospital
October, 2016	Sir Ganga Ram Hospital
November, 2016	MAMC & LN Hospital
December, 2016	Hindu Rao Hospital
January, 2017	LHMC
February, 2017	ESI Hospital
March, 2017	UCMS & GTB Hospital
April, 2017	Apollo Hospital

Case Summaries for AOGD Bulletin may be sent by email to the editor/CD may be handed over on the day of the meeting.

-Dr Sangeeta Gupta

Journal Scan

Deepti Goswami
Professor, Department of Obstetrics & Gynaecology, Maulana Azad Medical College & Lok Nayak Hospital, New Delhi

Abstract of the research articles are available free at the journal websites and on PubMed (http://www.ncbi.nlm.nih.gov/pubmed). A summary of the articles has been provided so as to put the findings of the articles into perspective for current clinical practice.

Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study

Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, Peeters RP.

Citation: Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, Peeters RP. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol. 2016 Jan; 4(1): 35-43.

Study Question: Is there an association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology?

Methods

- A population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands).
- Subjects included the women living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. Women with available serum samples who presented in early pregnancy (<18 weeks) were included.
- Data were obtain for:
  - Maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at 9-18 weeks of pregnancy)
  - Child IQ- assessed by non-verbal intelligence tests at a median of 6.0 years of age [95% range 5.6 – 7.9 years].
  - Brain morphology- assessed on brain MRI scans done at a median of 8.0 years of age [6.2-10.0].
- Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.

Results

- Data for child IQ were available for 3839 mother-child pairs, and MRI scans were available from 646 children.
- Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (P = 0.0044), child grey matter volume (P = 0.0062), and cortex volume (P = 0.0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1.4-3.8 points reduction in mean child IQ.
- Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology.
- All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).

Conclusion

Both low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume.

The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.

Perspective

Thyroid dysfunctions are prevalent in pregnant women. However, most of these women have subclinical hypothyroidism (13.5%) and very few (0.7%) have overt hypothyroidism (Dhanwal DK et al. Indian J Endocrinol Metab. 2013; 17:281-4). Issues like - cut offs for normal (or abnormal) thyroid function during

pregnancy, universal screening for thyroid functions and treatment of subclinical hypothyroidism are much debated.

This study involved a large number of mother-child pairs and a long term follow up of 6-10 years. Both functional aspects (child IQ) and morphological aspects (grey matter volume, cortex volume on MRI) of children's neurodevelopment were studied. The analysis of the results showed that both high and low free thyroxine (fT4) concentrations during pregnancy are detrimental to child's neurodevelopment. Hence one should exercise caution when administering levothyroxine to pregnant women, particularly those with subclinical hypothyroidism. A high maternal free thyroxine concentration might be as bad as a low free thyroxine concentration for child's neurodevelopment.

Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss or live birth.

Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, Galai N, DeCherney AH, Mumford SL.

Citation: Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, Galai N, DeCherney AH, Mumford SL. Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss or live birth. J Clin Endocrinol Metab. 2016 Mar 29:jc20161049. [Epub ahead of print] PubMed PMID: 27023447.

Study Question: Is there an association of pre-pregnancy TSH concentrations and thyroid autoimmunity with time to pregnancy (TTP), pregnancy loss, and live birth?

Methods

A prospective cohort study from a large, randomized controlled trial (Effects of Aspirin in Gestation and Reproduction trial), conducted in four medical centers in the United States. Participants were 1193 healthy women, ages 18-40, who were actively attempting to conceive and had one or two prior pregnancy losses and no history of infertility. The subjects were recruited during the period 2007-2011.

Preconception TSH, fT4, thyroid globulin antibody (anti-TG), and thyroid peroxidase antibody (anti-TPO) levels were measured. Participants were followed until completion of six cycles attempting pregnancy and also throughout pregnancy if they conceived. The primary outcomes were time to hCG pregnancy (in cycles), pregnancy losses (both biochemical and clinical) and live birth.

They categorized participants into two groups based on TSH level: TSH < 2.5 or ≥ 2.5 mIU/L. Additionally, women were evaluated based on presence or absence of anti-TG and anti-TPO antibodies (positive = anti-TG $\geq$ 115 IU/mL or anti-TPO ≥ 35 IU/mL; negative = anti-TG $<$ 115 IU/mL and anti-TPO < 35 IU/mL).

Results

Women with TSH ≥ 2.5 did not have an increased risk of pregnancy loss (risk ratio [RR] 1.07, 95% confidence interval [CI] 0.81, 1.41) or a decrease in live birth rate (RR 0.97, 95% CI 0.88, 1.07) or TTP (fecundability odds ratio [FOR] 1.09, 95% CI 0.90, 1.31) compared to women with TSH < 2.5 mIU/L after adjustment for age and body mass index. Similar findings were observed for women with thyroid autoimmunity and after additional adjustment for treatment assignment.

Conclusion

Among healthy fecund women with a history pregnancy loss, TSH levels ≥ 2.5, or the presence of anti-thyroid antibodies, were not associated with fecundity, pregnancy loss or live birth. Thus, women with subclinical hypothyroidism or thyroid autoimmunity can be reassured that their chances of conceiving and achieving a live birth are likely unaffected by marginal thyroid dysfunction.

Perspective

Overt hypothyroidisms as well as hyperthyroidism interfere with conception and maintenance of pregnancy. However, the studies on effect of subclinical hypothyroidism on reproduction report mixed results. Subclinical hypothyroidism is essentially a biochemical diagnosis based on raised serum TSH levels in presence of normal serum thyroxine levels.

This study provides useful information on functional relevance of subclinical hypothyroidism and thyroid autoimmunity in women trying to conceive. The subjects were recruited preconception and the study captured early pregnancy losses. The results showed no association between preconception subclinical hypothyroidism and time to pregnancy, pregnancy loss and live birth among healthy fertile women attempting to conceive. The results showed no relationships between thyroid autoimmunity and pregnancy loss or live birth.

The Grandeur History of a Gland

Nilanchali Singh
Assistant Professor, Obstetrics & Gynecology, Maulana Azad Medical College & Lok Nayak Hospital, New Delhi, India

Greetings everyone!! I received scores of positive feedback for my previous article on 'history of forceps' in the preceding issue. It gives me immense pleasure to bring forth to you, another enthralling historical perspective, pertaining to theme of current issue, thyroid disorders. The word 'thyroid' itself is derived from Greek word 'Thyros", meaning warriors' shield, due to its shape. As grand is the name, so is the history. To write this article, I went through a lot of articles and it seemed like, I am time-travelling in the past.

The 'Grandeur Past' of a Gland!

Thyroid swellings dwell in tales of historic travelers.. to paintings of historic painters;
It resides in the aesthetics of iconic beauties... to the minds of great thinkers!!

Visible outgrowths of front of neck have been a subject of curiosity and study since ancient times. Goiter has been observed since ancient times, when nothing was known about any other gland. It would not be a hyperbole if 'Thyroid Gland' is labelled as the first endocrine gland to attract attention of humans in ancient times. While going through the history of thyroid gland, it surprised me to the core, how a little gland can evoke so much interest in atavistic civilizations, that too, without being aware of its actual function!! I hope you will enjoy this grandeur history of a quintessential gland.

Perception of Thyroid in Ancient Times

Enlarged thyroid glands have been reported in ancient Chinese Paintings dating back to 2700 BC. Ancient Egyptian writings often emphasize the size of the thyroid gland in women. There is a relief found in ancient Egypt, showing Cleopatra with enlarged thyroid, which was considered to be a beauty symbol. The God Bes of ancient Egypt is usually depicted as a dwarf but it has not been conclusively determined whether he suffered from myxoedema or achondroplasia.

Figure 1: Cleopatra, the Egyptian beauty icon of ancient era, had enlarged thyroid gland!! It surprised me that enlarged thyroid was considered a "beauty symbol"..

Figure 2: God Bes of ancient Egypt had features of Myxedema, though the disease per se, was an unknown entity then.

'Galaganda' of ancient Indian medicine

In the Ancient Indian medicine of Ayurveda, which came into existence in around 1400 BC, goiters are mentioned by the designation galaganda and are described in detail, both in writings and paintings.

The controversy of hippocratic writings

There is much controversy as to whether goiter is mentioned in any writings of ancient Greece. In his History and Iconography of Endemic Goiter and Cretinism, Frank Merk states that there is no reference to goiter in Hippocrates' writings or of anyone else of the period.

However, in his book De Glandulis, Hippocrates (460-337 BC) states in relation to the glands: ...*when glands of the neck become diseased themselves, they become tubercular and produce struma*....

Hippocratic writings of the 4th century BC, also use the term '*choiron*' and '*gongroma*' for goiter. During the epoch of the Alexandrian School (331- 156 BC), the Hippocratics failed to differentiate between the thyroid and the cervical glands.

Dirty waters cause goiter: Only men and swine can have it!!

Gaius Plinius Secundus of Pliny (23 BC-79 AD) believed that goiter was caused by dirty water. Aurelius Celsus (25 BC-50 AD) was among the first to differentiate between the various forms of tumor of the neck. He defined the enlargement of the neck as bronchocele, describing it as a tumor under the skin and the larynx, which may contain honey-like substance.

First Surgeries for thyroid- Rendering the patients "Mute" and "Semi-Mute"

Gallen (130-200 AD) was the most important physician of the Greco-Roman period. He described operations on two boys by ignorant physicians who removed 'tubercular' nodes with their fingernails, rendering one boy mute and the other semi-mute. Gallen believed that the secretions of the thyroid lubricated the larynx and the cartilage and that the aphonia was provoked by cutting the laryngeal nerves.

History of surgeries in thyroid disease

First successful thyroidectomy was performed for the treatment of toxic goiter in 1884. In Europe, Theodore Kocher (1841-1917), a Swiss surgeon, performed over 2,000 thyroidectomies with a mortality rate of 5%, while in the United States, Charles Horace Mayo was an authority in thyroid surgery.

Parathyroid glands were also removed inadvertently during the surgery with multiple consequences. Gley, in 1891, was the first one to differentiate the functions of thyroid from those of parathyroid glands.

The thyroid gland: First Depiction.. First Disease.. First function!!

Leonardo Da Vinci drew what is the first depiction of thyroid in 1500s. One of the first references to the thyroid gland in Western medicine is in 1656, when it was thought that the main function of the thyroid gland was to lubricate the trachea. In the early 1800s, the thyroid was thought to be a vascular shunt to divert the blood flow from the brain. Cancer of the thyroid was the first disease of the thyroid to be described in 1811.

Thyroid disorders unveiled: One by one..

Parry was the first one to note association between an enlarged thyroid gland and the characteristic clinical features of hyperthyroidism in 1786. He did not publish them until almost 40 years later. This publication was followed by the classic descriptions of Graves Disease in 1835. Cretinism was described in 1871. In 1874, Gull noted the clinical changes associated with atrophy of the thyroid gland and 4 years later, Ord coined the term myxedema because he felt that excessive mucus formation and deposition under the skin were responsible for the characteristic thickening of the subcutaneous tissue.

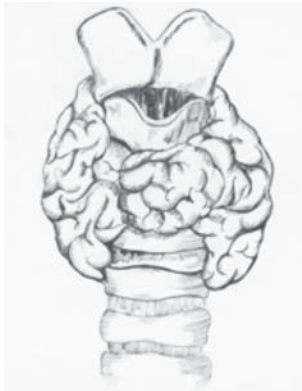

Figure 3: Replica of first depiction of thyroid gland by Leonardo Da Vinci in 1500s. I wonder how accurate he was!!

Origin of thyroid hormones

In 1891, Murray obtained a good clinical response in patients with hypothyroidism by injecting them with thyroid extracts. Shortly afterward, Howitz, Mackenzie, and Fox independently found that thyroid extracts were effective when administered orally.

Thyroid and woman: Some superstitions.. Some interpretations..

Rush reported in 1820 that the thyroid gland is larger in women because it is "necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex."

The Glorious Past of Indian Medicine!

The history of Indian Medicine is so grandiose, that, meandering through it makes me proud. According to Ayurvedic medicine, which originated in the 1400 BC, goiters are called 'galaganda'. It classifies thyroid diseases into three types; Vataja (hyperthyroidism), Kaphaja (hypothyroidism) and Medaja (thyroidal cyst). The symptoms of these diseases are described in detail in the Ayurvedic medicine. They correlate with those described by the modern medicine.

Conclusion

We saw how enthralling, the history of thyroid was. Not only it has amazed humans of varied genre but also, led to various interesting theories pertaining to it, some right and some wrong! Indians had so much knowledge of this gland and its disorder in 1400 BC that the Europeans could not even attain that in 19th century. Such is the rich Indian past we have. As I have mentioned earlier that 'History makes us to look back at the way our ancestors lived', we Indians certainly need to take pride on the advances in medicine, our ancestors have generated. And not only take pride but also, strive to bring forth the same old glory of the past!!

Where there is no temptation, there is no glory! Now we have a temptation..so where is the glory!!

Suggested Reading

1. *V. Leoutsakos. A short history of the thyroid gland. Hormones 2004, 3(4):268-271*
2. *Asfandyar Khan Niazi, Sanjay Kalra, Awais Irfan, Aliya Islam. Thyroidology over the ages. Indian J Endocrinol Metab. 2011 Jul; 15(Suppl2): S121–S126.*

Proceedings of the AOGD Monthly Clinical Meeting, PGIMER Dr RML Hospital, New Delhi, 27th May, 2016

Case 1

Adnexal cyst torsion as a rare cause of acute abdominal pain in an adolescent

Sonal Gupta, Veena G Malla, P Yadav, R Malik

Torsion of ovarian masses is quite common. However, twisted para-ovarian cyst is rare. Isolated fallopian tube torsion has also been reported in the literature as an extremely rare complication. We present a case of a 16 year old girl, who presented in our OPD, with acute lower abdominal pain and vomiting. Ultrasound showed a 9x7 cm cyst in vicinity of left ovary without any impeded Doppler flow. A laparoscopy was done which revealed a large gangrenous para-ovarian cyst on left side along with torsion of distal end of fallopian tube and fimbria stretched over the cyst. Bilateral ovaries were normal. Laparoscopic cystectomy was done and the histopathology reported it to be, an infracted cyst without ovarian stroma. Though benign in nature, rarely paraovarian cyst can undergo torsion, causing acute pain and rarely compromising fertility. Physicians need to maintain a high index of suspicion for this uncommon and often difficult to diagnose cause of abdominal pain in adolescents. Early intervention helps in preserving the functional integrity of the adnexa.

Case 2

A case of postmenopausal bleeding

Parul Sharma, Priyanka Arya, Bani, Majhi, Alka, Batra

Abstract: A case of 60 yr postmenopausal with complaint of heaviness, lump per abdomen and a short history of post menopausal bleeding. On examination, uterus was enlarged to 20 week gravid uterus size, firm, mobile and non tender. USG & CECT revealed large fibroid, thickened endometrium and intrauterine fluid collection. 2.6l of intrauterine altered blood was drained over 3 days. Serial USGs showed intrauterine fluid (persistent hematometra). Endometrial sampling confirmed adenocarcinoma uterus for which exploratory laparotomy with TAH with BSO with peritoneal fluid cytology with pelvic lymphadenectomy was done. Histopathology showed Endometrioid adenocarcinoma stage 1b and peritoneal cytology was also positive for malignancy. Patient was referred to higher centre for chemo-radiation.

Case 3

Short long bones- a cause of worry for obstetricians!

Manisha V Ramani, Anshu Dhar, Pushpa Singh, Sushma Rani, Upma Saxena, Kamna Datta

Short long bones on antenatal scans should make an obstetrician alert. Case 1 is a 32 year old female with all first trimester scans and investigations normal. She had a level 2 scan revealing short long bones and heart defects. Second trimester abortion was done. On autopsy chromosomal analysis for 13,18,2,22 and X Y chromosomes was normal. The diagnosis however could not be confirmed as the attendants declined further investigations.

Second case is a 32 year old female with IVF conception. All antenatal investigations were normal. Antenatal scans had a lag of 2-3 weeks in femur length. The baby delivered by LSCS in view of breech pregnancy at 37weeks was diagnosed to be suffering from skeletal dysplasia and died 11 hours after birth. Spectrum of babies delivered after antenatal diagnosis of short long bones can range from completely healthy to syndromic babies, to babies who other than having a short stature are capable of leading perfectly healthy lives. Therefore these cases need to be thoroughly investigated; diagnosed and timely intervention should be done.

Tickle the Funny Bone

Compiled by Nilanchali Singh[1], Sangeeta Gupta[2]
[1]Assistant Professor, [2]Professor, , Department of Obstetrics & Gynecology, Maulana Azad Medical College, New Delhi, India

Laughter is strong medicine for mind and body.

Drive to Maternity Hospital

A woman gets into a taxi and asks:

- To maternity hospital, please..

After a while she asks the driver:

- Do not drive so fast, please, I'm simply working there.

Not a good doctor

Wife returns from the clinics and tells her husband:
- The doctor recommended me to spend one month at the sea, two weeks in the countryside and go for one week abroad. Where will you take me first?
- To another doctor...

Hug Harder.

Laugh Louder..

Smile bigger…

Love longer….

Answers: Crossword - Thyroid disorders

Across			Down			
4. Three	12. Estrogen	17. Eighteen	1. Thyrotoxicosis	5. Grave's	8. Brain	13. Twelve
9. Subclinical	14. Fifty	18. Biochemical	2. Depression	6. Leucopenia	10. Hypocalcemia	16. Sipple
10. Hashimoto's	15. Myxedema		3. Methimazole	7. Six	11. Propylthiouracil	19. Calcitonin

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Announcing next course

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Important Dates

- Last date for registration **31 July 2016**
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- Online classrooms start **11 September 2016- 8 January 2017**
- **MRCOG Part 2 Revision Course (written) January 2017 (duration 3 days-Dates to be announced later) in New Delhi -**Includes examination tips and techniques to answer exam questions, MCQs. EMQs and SAQs.(There will be separate registration formality and fees to be payable for this course at a later date)

Course Fee: Rs 35,000 (Thirty Five Thousand Only)

UK Course Organizer & Convener - Dr Sanjeev Sharma

India Conveners and Contacts for details - Dr Puneet Kochhar (drpuneet.k20@gmail.com/9953001628)
- Dr Sweta Gupta (swetagupta06@yahoo.com/8130140007)

Registration Guidelines (Online registration available on website)

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- Member, Educational Committee, IFFS
- Member, International Scientific Exchange Committee – Federation of Obstetric and Gynaecological Societies.
- Editor In-chief: "Fertility Science & Research", official Journal of IFS

OUR MILESTONES

- First IVF conception, February 2000
- First ICSI conception, March 2000
- First PESA/TESA conception, October 2000
- First Blastocyst conception, March 2003
- Introduced vitrification, February 2005
- Started IUI training programmes in 2004
- Introduced one year fellowship programme in clinical ART in 2015
- Introduced one year fellowship in clinical embryology in 2016
- Introduced short term training programmes in endoscopic surgery in 2016
- Started USG training courses in 2016
- Established academy of Reproductive Medicine 2014.

OUR USP

- ICSI results at par with best in the world.
- Acceptable results even in patients with repeated failures and difficult cases (up to 25%)
- Avoid 3rd party reproduction even in azoospermia (no sperm), poor ovarian reserve (low AMH), cavity with adhesions (Asherman's grade- 3,4)
- Hallmark is simplified procedures as we consider pregnancy by simpler route our greater achievement.
- Difficult endoscopic surgeries- fibroid, septum, adhesions removal and tubal reopening are skillfully done
- We offer a legal solution for all infertility problems

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Dr. Hafeez Rahman
Gynae Laparoscopic Surgeon

Dr. Nikita Trehan
Gynae Laparoscopic Surgeon

Dr. Ajay Aggarwal
Gynae Laparoscopic Surgeon

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Early Bird Registration:
Upto 20th May, 2016:- 4500/-
After 20th May, 2016:- 6000/-
Spot Registration:- 7000/-
Accompanying Persons:- Same as above
For PG Students: - 4000/-

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Account Name: Trinity Sunrise Healthcare Pvt. Ltd.
Account No.: 910020001999044
Bank Name: Axis Bank
Branch: Nehru Place, New Delhi
IFSC Code: UTIB0000049
Account Type: Current

*For registration please contact: Dr. Shuchita Singh:- +91 70600 50225

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