CONFERENCE REPORT

Endocrine Disorders in Pregnancy: Selected Highlights from the Medical Complications in Pregnancy, 31st October - 2nd November 2011, London, UK.

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Abstract

This course has been run annually for the past seventeen years. It encompasses reviews and updates in the management of medical problems that obstetric physicians and obstetricians can encounter in their practice. There were 120 delegates to this course from different countries around the world. Over three days, internationally renowned experts in obstetric medicine considered a wide range of topics such as thyroid disease and other endocrine disorders, connective tissue disorders, diabetes, sickle cell disease, asthma, neurology disorders, renal diseases and heart diseases. We chose to reflect on some of the endocrine- related topics to present a brief summary rather than go through the full curriculum.

Key words: Pregnancy, Obstetric Medicine, Thyroid, Pituitary,

Introduction

Medical disorders in pregnant women are particularly seriously viewed by both obstetricians and physicians. This lead to the development of a highly specialized medical subspecialty namely "Obstetric Medicine". Practitioners in this field are required to have a good base of general medicine in addition good in-depth knowledge of the limits of physiological changes during pregnancy. This course is run annually for the past seventeen years in The Royal College of Physicians in London. It encompasses review and updates in the management of medical problems that obstetric physicians and obstetricians can encounter in their practice. This course is an intensive three day course which includes lectures by internationally recognized speakers, like Professor Raymond Powrie, Professor Catherine Nelson-Piercy, Professor Scott Nelson, Professor Catherine Williamson, Professor Steve Robson, Professor Ian Greer and many more well known experts in obstetric medicine mainly from England.

There were 120 delegates to this course from different countries around the world. The audience was mainly made

up of obstetricians but also a good number of physicians and anesthetists. In addition to the lectures there were discussions with the audience on interesting cases, in the form of case presentation followed by suggestions on management from the audience and the views of the experts in these fields.

Wide range of topics were covered which included thyroid disease and other endocrine disorders, connective tissue disorders, diabetes, sickle cell disease, asthma, neurology disorders, renal diseases and heart diseases. We have chosen some of the endocrine-related topics to present a brief summary rather than go through the full curriculum.

Thyroid Disease and Pregnancy

Physiology

Professor Scott Nelson started his lecture with a concise overview of managing thyroid disease in pregnancy with special reference to American Thyroid Association recommendations (1). The circulating thyroid hormone levels fluctuate during pregnancy as shown in the gestatation-specific nomogram given in Figure 1. Therefore the American Thyroid Association recommends a gestation-specific reference range for TSH (Table 1). Serum TSH is a more accurate indicator of thyroid status in pregnancy than other alternative methods.

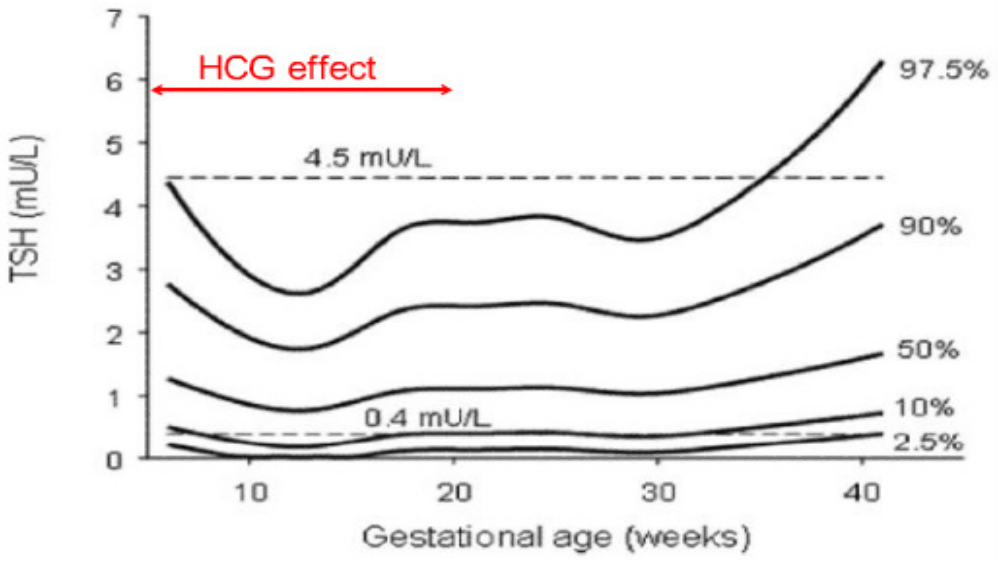

Figure 1. Thyriod hormones fluctuate during pregnancy as shown in the gestation-specific nomogram (ref 2).

Hyperthyroidism

Hyperthyroidism is diagnosed by low TSH (<0.01) and high free T4 is seen in 0.2% of pregnancies. Thyrotoxicosis has been implicated in infertility, miscarriage, still birth, pre- term delivery, IUGR and pre eclampsia. Neonatal thyrotoxicosis occurs in 1%. Antithyroid drugs in excess can cause fetal goitre and decreased IQ. Fetal hypo or hyperthyroidism can occur depending on the antibodies and drugs.

The use of Propylthiouracil (PTU) is preferred in the first trimester. Carbimazole crosses the placenta more readily than PTU and is associated with aplasia cutis, choanal atresia and omphalocoel. After the first trimester, it is recommended to consider switching over to carbimazole as PTU can cause hepatotoxicity. Monitor thyroid function every 4 weeks with the aim to keep FT4 at or above the normal reference range. Measurement of Thyroid Receptor Antibody (TR-Ab) at 24-26 weeks is recommended. Fetal surveillance with ultrasound should be performed if there is uncontrolled hyperthyroidism or high TR-Ab levels more than three time greater than the upper end of the normal range. Both Carbimazole in doses less 20mg/day and Propylthiouracil less than 300mg/day can be used safely in lactating mothers. Radioactive iodine is absolutely contraindicated due to fetal transfer. There is no role for blockade-replacement therapy during pregnancy. Thyroidectomy, if indicated such as for non responsive thyrotoxicosis, stridor, dysphasia and carcinoma, should be performed optimally during the second trimester when risk of pregnancy loss is minimal. Subclinical hyperthyroidism has no effect on pregnancy outcome or neonatal outcome. Generally; antithyroid drugs are not recommended for the management of gestational hyperthyroidism

Table 1. The American Thyroid Association's recommended gestation-specific reference range for serum TSH.			
Pregnancy Phase (Trimester)	First Trimester	Second Trimester	Third Trimester
Serum TSH (mIU /L)	0.1 – 2.5	0.2 – 3.0	0.3 – 3.0

Table 2. Widely accepted recommendations for screening for thyroid functions in pregnancy.	
History of thyroid dysfunction or prior thyroid surgery	Age >30 years
Symptoms of thyroid dysfunction or presence of goiter	TPO Antibody positivity
Type 1 diabetes or other autoimmune disorders	History of miscarriage or preterm delivery
History of head or neck radiation	Family history of thyroid dysfunction
Morbid obesity (BMI >40 kg/m^2)	Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
Infertility	Residing in an area of known moderate to severe iodine sufficiency

Hypothyroidism

Hypothyroidism affects 0.3-0.5 % of pregnancies. Diagnosis is confirmed when TSH is above 2.5 mIU/L with low serum T4 or TSH greater than 10mIU/L irrespective of FT4. Fetus is dependent on maternal production in the first 12 weeks. Overt hypothyroidism should be treated as it is associated with increased rates of miscarriage, anaemia, fetal loss, preeclampsia, low birth weight infants and reduced IQ in infants. Subclinical hypothyroidism, defined as normal FT4 associated with high serum TSH above 97th centile, has been associated with adverse maternal and fetal outcomes. There is insufficient evidence to recommend for or against universal Levothyroxine treatment in Tr-Ab negative pregnant women. However, TPO Ab positive women should be treated. The goal of Levothyroxine treatment is to normalize maternal serum TSH values within the trimester specific range. Non-treated subclinical hypothyroidism should be monitored with measurements of serum TSH and FT4 every 4 weeks until 16-20 weeks of gestation and once between 26 and 32 weeks gestation.

A practical recommendation was made that pregnant women with treated hypothyroidism should increase Levothyroxine from once daily dosing to a total of nine doses per week when pregnancy is diagnosed (thus making a 29% increase in the dose). Maternal serum TSH should be monitored approximately every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation. Postpartum Levothyroxine should be reduced to the patient's preconception dose. TSH testing should be performed at approximately 6 weeks postpartum. In women with adequately treated Hashimoto's thyroiditis, no other maternal or fetal thyroid testing is recommended beyond measurement of maternal thyroid function. The

CAT (Controlled Antenatal Thyroid Screening) study is an ongoing prospective randomized controlled trials comparing "screening plus treating" versus "no screening". There was no difference in average IQ but those who were treated had better IQ score > 85.

There is insufficient evidence for universal screening. However screening is recommended in high risk groups (Table 2) (2).

Postpartum Thyroiditis

Postpartum thyroiditis (PPT) is caused by destructive autoimmune lymphocytic thyroiditis and is associated with TPO (thyroid perioxidase) positive antibodies. If TPO antibodies are present, the risk of thyroiditis is 50-80% of pregnancies. Recurrence risk is about 70 % in future pregnancy. Most patients do recover spontaneously.

Finally, it was stressed that thyroid disorders are associated with adverse pregnancy outcomes if untreated. But if diagnosed early and treated adequately, the outcome is good and unaffected by the disease process.

Other Endocrine Disorders

Professor Catherine Williamson, covered collectively a number of endocrine disorders under the title other endocrine disorders. The following three topics were covered.

Vitamin D Deficiency

There is an increase in incidence of vitamin D deficiency among pregnant women. The presented data showed that half of non European ethnic group had vitamin D levels less than 20nmol/L in a study from Cardiff (3) . Similar data from a Dutch study (n=358) where 59% of non western pregnant women had Vitamin D levels below 25 nmol/L (4). Maternal vitamin D deficiency has implications on the women and her fetus. The classic maternal consequences are bone loss, mild hypocalcaemia, secondary hyperparathyroidism and in severe cases osteomalacia and myopathy. There is evidence from the literature regarding association of vitamin D deficiency with increased risk of pre-eclampsia, impaired glucose homeostasis and gestational diabetes (5). With regards to the fetal consequences bone effects are noted with reduced fetal femoral growth, neonatal cord calcium levels, skeletal mineralization and bone mass, increase rate of craniotabes (22%). From animal and epidemiological studies there are other adverse neonatal outcomes from fetal vitamin D deficiency with increased risk of learning difficulties, memory disorders, type1 diabetes and asthma. In view of these consequences, vitamin D supplementation is essential in pregnancy and the UK Endocrine society's latest guideline 2011 states that pregnant and lactating women require at least 600 IU vitamin D per day, to maintain a blood level over 30nmol/L at least 1500-2000 IU vitamin D supplementation per day is required and for breast milk fed infants the mother requires at least 4000-6000IU of vitamin D a day (6). There are no adverse outcomes associated with supplementation of vitamin D at a dose of 400-4000 IU per day as reported from a recent randomised control trial with 494 pregnant women . Most studies showing the teratogenicity of vitamin D deficiency are from animal studies and the 2 human studies are in the context of treatment of hyperparathyroidism where the average dose of vitamin D was 100,000 IU a day (8). Prof. Williamson advised to supplement all pregnant women with 400-800 IU per day, and recommended to recheck serum calcium and vitamin D if deficient to consider higher doses like 20,000 IU per week for 4 weeks (9).

Parathyroid disease

There are physiological changes in pregnancy that decrease the effect hypercalcemia in women with hyperparathyroidism. These changes include an increase urinary excretion of calcium, hypoalbunimia, and transfer to the uteroplacental unit hence most pregnant women with hyperparathyroidism are asymptomatic. Some women do present with nephrolithiasis but the most common feature encountered in pregnancy is hypertension, hence young women in the reproductive age with unexplained hypertension should be screened for hyperparathyroidism. There is 40-50% perinatal complication rate associated with hyperparathyroidism in pregnancy. Fetal loss and neonatal tetany are the commonest of these perinatal complication from a single centre study (9). Parathyroidectomy is the treatment of choice for most cases with hypercalcemia, as fetal loss is seen in all levels of hypercalcemia. Timing of surgery should be in the second trimester . Parathyroidectomy may be challenging in pregnancy when medastinal exploration maybe required which is not recommended in pregnancy. Increase of fluid intake to 3L per day may be an option to decrease the calcium levels in patient with moderate level (10). A study from Sweden has shown that women with parathyroid adenomas are at higher risk of pre eclampsia (11). It is also important to consider family history in women with primary hyperparathyroidism therefore need to screen for multiple endocrine neoplasia type 1 and type 2 (MEN1 and MEN2 respectively), familial hyperparathyroidism and jaw tumours.

Pituitary tumours

In pregnancy there is an increase in the prolactin secretion

therefore measuring serum prolactin levels in pregnancy has no value in monitoring prolactinomas (12,13). Studies have shown that is acceptable to stop dopamine agonist with review in each trimester in women with microadenomas as it has been noted that microprolactinoma enlargement in only 2.5% of cases while macroprolactinoma 29.6% enlarge. In contrast with macroadenomas when continuing of treatment and carefully monitoring for signs of tumour expansion is advisable . Both bromocriptine and cabergoline are safe to use in pregnancy from various studies despite the theoretical risk of cardiac fibrosis with cabergoline that was seen with high doses in the treatment of Parkinson disease (14,15). Newer drugs like quinagolide has a 5% fetal risk of malformation. During breast feeding cabergoline and bromocriptine must be stopped and to reassure women that breast feeding does not increase the size of pituitary tumours (16-17).

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