Thyroid Disorders in Pregnancy

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Introduction

- Prior to 12 weeks' gestation maternal thyroxine (but not fT3) crosses the placenta.
- Following binding to receptors in fetal brain cells, thyroxine is converted intracellularly to fT3, a process thought to be important for normal fetal brain development.

- From 12 weeks onwards, placental changes prevent significant passage of maternal thyroxine and fetal thyroid function is controlled independently of the mother, provided that her iodine intake is adequate.
- In pregnancy, Well-designed, isolated, term placental studies show passage to the fetal side of only 0.008% of maternal thyroxine in normal circumstances

Changes in pregnancy

- The half-life of thyroxine binding globulin extends from 15 minutes to 3 days and its concentration triples by 20 weeks of gestation, as the result of estrogen-driven glycosylation.
- Total thyroid hormone levels increase and, therefore, measurements of total T4 and total T3 are not reliable in pregnancy.

Changes in pregnancy

- fT4 and fT3 remain relatively constant and are the tests of choice in pregnancy: they should be interpreted in relation to pregnancy-specific reference ranges.

Changes in pregnancy

- Human chorionic gonadotrophin(hCG) and thyroid stimulating hormone (TSH) have similarities, in first trimester, a hormone spillover syndrome can occur in which hCG stimulates the TSH receptor and gives a biochemical picture of hyperthyroidism. This is particularly common in multiple pregnancy, trophoblastic disease and hyperemesist gravidarum, where concentrations of both total hCG and thyrotropic subtypes can be greater .

Changes in pregnancy

- Increased glomerular filtration and greater uptake of iodine into the thyroid gland driven by increased total thyroxine concentration can deplete iodine and cause or worsen iodine deficiency.
- Transplacental transfer can also exacerbate this but when there is severe maternal iodine deficiency, maternal iodine trapping overrides fetal needs, resulting in cretinism.

Changes in pregnancy

- Three deiodinase hormones control metabolism of T4 to the more active T3 and their breakdown to inactive compounds. The concentration of deiodinase III increases in the placenta with gestation, releasing iodine where it is required for transport to the fetus and, possibly, contributing to reduced thyroxine transfer.

Hypothyroidism

- Hypothyroidism occurs in around 1% of pregnant women. Its management in pregnancy remains surprisingly contentious and complicated.

Situation 1

- Untreated hypothyroidism (low fT4, high TSH, often symptomatic) who require urgent initiation of treatment with thyroxine.

Situation 2

- Previously diagnosed hypothyroidism who may be on optimal therapy (normal fT4 and TSH) at conception or who may not (low fT4, high TSH); in the latter, rapid achievement of euthyroidism is important, particularly in the 1st trimester.

Situation 3

- Subclinical hypothyroidism (normal fT4, raised TSH, asymptomatic) in whom the place of thyroxine therapy is debatable.

Situation 4

- Hypothyroxinaemia (low T4, normal TSH).

Therapy

- From a maternal perspective, biochemical euthyroidism remains the goal, as it is outside of pregnancy.
- Adjustment of thyroxine dose on the basis of clinical signs and symptoms is particularly challenging in pregnancy.
- Both excess and deficient thyroid hormone levels cause problems that are difficult to distinguish from those of normal pregnancy. This results in an increased dependence upon biochemical results and pregnancy-specific reference ranges.
- Some suggest an association between treated hypothyroidism and adverse pregnancy outcomes, including miscarriage, pre-eclampsia, placental abruption and prematurity.

Factors that could influence thyroxine dosage during pregnancy

- Reduced absorption in the First trimester related to nausea and vomiting.
- Malabsorption resulting from binding of thyroxine to newly-commenced iron and calcium supplements.
- Suboptimal control prior to conception.
- Altered compliance, with either an improvement, resulting in an apparent need to reduce the dosage, or a deterioration (perhaps from false concerns of safety), resulting in apparent need to increase the dosage.
- Normal variation in thyroxine dosage.

- The therapeutic window of thyroxine is broad, with doss adjustments usually of 25 or 50 micrograms, i.e. by approximately 25%. Few individuals are on a tightrope of therapeutic control. Although in pregnancy increased concentrations of thyroxine binding proteins occur that result in an increased total thyroid hormone pool, it is likely that, for many women, this will not in itself necessitate dose adjustment.
- In addition, deiodinase II, the enzyme responsible for peripheral activation of T4 to T3 in the brain, increases m concentration with advancing gestation (when fT4 is low). This may help to explain why thyroxine. increases are not routinely required, despite the physiological changes explained above.

- This is reflected in the reference ranges for thyroid function, which are broad. Some state that thyroxine doses should be increased such that TSH falls into the lower hall of the range.
- Some feel this would be detrimental.
- Others feel that individuals have their own narrow normal range, outside which they may develop symptoms or be at increased risk of the longterm consequences of hypothyroidism (cardiac failure) or hyperthyroidism (atrial fibrillation or osteoporosis).
- a In pregnancy these questions remain unanswered, as does whether it is the circulating fT4 or TSH that is a better marker of euthyroidism from the mother's or baby's perspective.

- Thyroid function can he influenced by hyperemesis gravidarum in the first trimester.
- Reference ranges for thyroid hormones are / different in pregnancy (especially in the third trimester, when there is a move towards the hypothyroid end of the spectrum).
- Trimester specific reference ranges should be used in the management of thyroid disease in pregnancy.

Conclusions

- Women with under or untreated hypothyroidism, optimal replacement doses should, ideally, be reached prior to conception or early in 1st trimester.
- Women with established hypothyroidism need to increase their dose of thyroxin during pregnancy to maintain euthyroidism according to trimester-specific ranges.
- Only first trimester control influences fetal wellbeing.
- Hypothyroidism itself does not influence pregnancy outcome or complications.
- For women with hypothyroidism who intend to become pregnant and who are on the correct dose of thyroxin, thyroid testing is needed only prepregnancy, early in the 1st trimester and again later in the 2nd or 3rd trimester.
- The majority of their antenatal care can be midwifery-led unless risk factor dictate otherwise.

Hyperthyroidism

- Autoimmune thyrotoxicosis or Garrives' disease affects around 2 per 1000 pregnancies.
- Management is more complex but less controversial than that of hypothyroidism.
- The main tenet is to ensure euthyroidism is achieved as early as possible in pregnancy, preferably prior to conception, as this minimizes the likelihood of maternal or fetal complications.

Complications

- Maternal; PET, Congestive heart failure, thyroid storm.
- Fetal; IUGR Prematurity, stillbirth.

Therapy

- B-blockade, usually with propranolol hydrochloride, should be used in pregnancy, if required, to control tachycardia, tremor or anxiety. Concerns about fetal growth restriction are vastly outweighed by the maternal and fetal benefits.
- Euthyroidism is achieved using the antithyroid agents carbimazole or propylthiouracil. These block thyroid hormone synthesis and have an immunosuppressive effect, reducing the titer of TSH receptor stimulating antibodies and, thereby, directly influencing the course of the disease.

Both cross the placenta in similar amounts.

- Difficult to distinguish clinically between the signs and symptoms of hyperthyroidism and pregnancy, reliance is placed on serial biochemical measurement.

- Failure to gain weight, despite a good appetite, and tachycardia greater than 100 beats per minute that fails to slow with Valsalva manoeuvre and onycholysis (elevation of the distal nail bed) are good indicators of thyrotoxicosis.
- Eye signs and pretibial myxoedema do not reflect disease activity.

- Clinical disease activity follows the titre of TSH receptor stimulating antibodies, which rises in the first trimester and puerperium and falls in the second and third trimesters.
- Thyroid function should be measured monthly when control is good and more frequently when the diagnosis is new or there is a relapse.
- Antithyroid medication is titrated against the results: Most women can reduce their dose and almost one-third of women can stop treatment during pregnancy, which helps prevent fetal hypothyroidism. Most women will need to restart of increase their dose in the puerperium to avoid a relapse.

Propylthiouracil (PTU) or Carbimazole?

- Propylthiouracil is more heavily protein-bound than carbimazole; studies using isolated perfused human placental lobules show similar placental transfer kinetics for both drugs.
- No differences in fetal thyroid function measured using cord sera were found in 77 babies whose mothers were taking one or other of the agents.

Propylthiouracil (PTU) or Carbimazole?

- Previously: carbimazole causes aplasia cutis congenita of the scalp in the infant, a rare congenital defect affecting 0.03% of the general population.
- More extensive and recent work indicates, however, that this association is either spurious or, at most, extremely rare and should not influence the choice of drug in pregnancy.
- No other teratogenesis has been linked with antithyroid drugs.
- Pregnancies in which there is poor control in the first trimester are more likely to be complicated by fetal anomaly than those in which drug therapy is successfully used to achieve control.

Propylthiouracil(PTU) or Carbimazole?

- Both drugs cause agranulocytosis and pregnant women should be reminded to report a sore throat immediately.
- This reaction is unpredictable and is a reason not to change agent routinely during pregnancy.

- Lactation is the period when there is some difference between the drugs.
- Studies of radiolabeled drugs show that 0.077% of propylthiouracil and 0.47% of carbimazole reaches breast milk. Small numbers of babies, however, whose mothers have taken antithyroid medication have had thyroid function monitored in the first weeks of life and adverse effects have not been found.
- There are concerns that high doses, especially of carbimazole, could cause neonatal hypothyroidism. Doses should be split through the day, with feeding to occur before a dose where possible, monitoring of neonatal thyroid function and regular consideration given to switching to propylthiouracil.

Surgery or Radioactive iodine?

- Thyroid surgery can be carried out in pregnancy if required, most usually in the second trimester.
- Indications include: compression from a large goiter, suspicion of malignancy and failed antithyroid therapy.
- Surgery: pregnancy associated increase in the vascularity of the thyroid and so should only be undertaken by an experienced thyroid surgeon.
- Radioactive iodine crosses the placenta and binds to and destroys the fetal thyroid. It is totally contraindicated in pregnancy. Lactation should be stopped (preferably 4 weeks if it is given in the puerperium.

Fetal & Neonatal consequences of thyrotoxicosis

- Fetal or neonatal problems relating to well controlled Graves' disease are rare.
- TSH receptor stimulating antibodies cross the placenta and the risk of fetal Graves' disease after 20 weeks (the gestational age at which the fetal thyroid can respond to these antibodies) is directly proportional to their titre (although even at the highest titres the risk is very low).
- It is very important that women who have had Graves' disease in the past treated by surgery or radioactive iodine, as well as those actively being treated for the condition during pregnancy, have this antibody measured. Women with positive results should be monitored for signs of fetal thyrotoxicosis, including tachycardia, excessive movements, fetal growth restriction, oligohydramnios and goitre.
- Fetal Graves' disease can cause premature delivery in untreated women.

Fetal & Neonatal consequences of thyrotoxicosis

- Craniosynostosis and associated intellectual impairment.
- Hydrops fetalis.
- Intrauterine death.
- Polyhydramnios related to oesophageal pressure.
- Obstructed labour from neck extension related to goitre.

Fetal & Neonatal consequences of thyrotoxicosis

- Management is usually based on delivery if the gestational age is sufficiently advanced.
- It this is not appropriate, high doses of propylthiouracil or carbimazole should be given to the mother and the response titrated against the fetal heart rate; the pregnant woman can take thyroxine if she becomes clinically hypothyroid and this will not cross the placenta. Although fetal reference ranges for thyroid function are known, fetal blood sampling is not routinely needed unless the diagnosis is in doubt.

Fetal & Neonatal consequences of thyrotoxicosis

- At delivery, thyroid function should be measured using cord blood. Rarely, hypothyroidism is reported secondary to transplacental passage of antithyroid drugs, this is usually self-limiting.
- Hyperthyroidism is also occasionally detected, although this more typically presents 7-10 days postnatally, since the half-life of maternally-derived antithyroid drugs is shorter than that at TSH receptor antibodies.
- Parents should be warned to look for changes in their baby, such as weight loss or poor feeding.
- Neonatal treatment, when required, rarely lasts for more than a few months.

Hyperemesis Gravidarum

- Hyperemesis gravidarum is the term for vomiting in the first half of pregnancy that is sufficiently severe to cause dehydration requiting intravenous fluids, weight loss and/ or abnormalities in liver function (secondary to starvation) or thyroid function tests.
- This, usually transient, hyperthyroidism (suppressed TSH and high or very high fT4) occurs in over 60% of pregnancies with sever hyperemesis and is caused by the TSH-like effect of the beta subunits of hCG.
- Some pregnancies, either the total concentration of hCG is increased (in multiple or molar pregnancies) or the beta subunits of hCG have a greater ability to bind to TSH receptors.
- This biochemical hyperthyroidism must he differentiated from the rare, first trimester presentation of Graves' disease with vomiting, by taking a detailed history and by ensuring a return to biochemical normality as the hyperemesis resolves.

Hyperemesis Gravidarum

- By 19 weeks' gestation, one series reported that fT4 levels had fallen to normal and TSH had escaped full suppression in all women.
- Typically, in women with hyperemesis gravidarum, the symptoms clearly postdate the pregnancy, the woman is washed out, deflated and tired, there are no eye signs or goitre and tachycardia responds to intravenous rehydration. The absence of thyroid autoantibodies is helpful in supporting hyperemesis.

Hyperemesis Gravidarum

- Therapy; correcting the metabolic insults of prolonged vomiting and minimizing further vomiting.
- There is usually no place for antithyroid medication, as there is no intrinsic increase in thyroid activity, the duration of hyperemesis gravidarum is usually relatively short and the antithyroid medication crosses the placenta and has the potential to make the fetus hypothyroid.
- When hCG-related thyrotoxicosis IS treated, antithyroid medication is either ineffective or very high doses are needed.

Iodine Deficiency

- The WHO: worldwide, 2 billion people are iodine deficient and more than 20 million have adverse neurological sequelae secondary to in utero iodine deprivation.
- Worldwide, neurological cretinism is the leading preventable cause of mental handicap. It affects 2-10% of people in iodine deficient areas and causes mild mental handicap in a further 10-50%. (significant negative impact on the economy of afflicted regions).

Iodine Deficiency

- The developing cochlea, cerebral neocortex and basal ganglia are most sensitive to iodine deficiency, especially in the second trimester, resulting in deaf-mutism, intellectual deficiency and spastic motor disorder.
- Less severe maternal iodine deprivation spares hearing, speech and motor function but causes mental handicap (myxoedematous cretinism), presumably because the mother is able to transfer enough T4 and iodine and the fetus is subsequently able to make enough T3 to protect these functions.

Iodine Deficiency

- In areas of endemic iodine deficiency, pregnant women usually have low or very low T4 and normal T3, with raised TSH levels and a compensatory goitre. This supports the physiological pathways but that maternal T3 is not enough to protect the fetal brain, which needs intracellular T3 (derived from circulating T4). In these circumstances, there is not enough maternal T4 to be transferred, even if deiodinase II is suppressed, nor enough iodine to allow fetal production of T4.
- Changes in renal clearance of iodine and increased thyroxine binding globulin exacerbate the level of iodine deficiency in susceptible populations.
- Iodine administration prior to conception or up to the second trimester can protect the fetal brain and, when given early enough, reduce miscarriage and later pregnancy losses.
- Programmes to deliver annual boluses of iodine to susceptible women are difficult to sustain and, unfortunately, national programmes to iodinate flour, salt or water continue to flounder.

Thyroid Storm

- Thyroid storm requires prompt recognition, aggressive reversal of thyroidotoxins with antithyroid drugs (ATDs), and supportive management of signs and symptoms. Antithyroid agents are propylthiouracil and methimazole.

- The standard practice is to give an initial loading dose of 300mg to 600mg propylthiouracil enterally and then 150mg to 300mg every 6 hours.
- 1f a patient cannot take the solution by mouth, propylthiouracil can be administered via the nasogastric tube or can be compounded by the pharmacy and given as a rectal suppository. Iodides are commonly given because they rapidly inhibit the release of thyroid hormones. Iodides are administered several hours alter propylthiouracil therapy is initiated to avoid the buildup of hormones stored in the thyroid gland.

- A saturated solution of potassium iodide is given orally in dosages of 2 to 5 drops every 8 hours, or sodium iodide is given intravenously in dosages of 0.5 to l g every 8 hours.
- Beta blockers such as propranolol should be given to help decrease some of the thyrotoxic effects on the cardiovascular system.
- Additional supportive measures: administration of intravenous fluids for dehydration, antipyretics to control of hyperthermia (a cooling blanket may be necessary), nutritional support, correction of possible electrolyte imbalances, and use of glucocorticoids, which also inhibit conversion of T4 to T3 and prevent adrenal insufficiency.

- If sedation is required, barbiturates are most often used because they lower the levels of thyroid hormones by increasing the catabolism of the hormones.
- Oxygen should be used as needed for possible increased oxygen demands.
- Because of the hypermetabolic state of thyroid storm, medication are metabolized faster than normal. Therefore, higher and more frequent doses may be required to control the thyrotoxicosis.
- Patients in thyroid crisis require close assessment and monitoring of cardiovascular status, including continuous cardiac monitoring and frequent monitoring of vital signs. Significant changes should be reported immediately.
- 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.

Many Thanks