The role of the placenta in thyroid hormone delivery to the fetus

Chan SY, Vasilopoulou E and Kilby MD

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All clinicians in the field of obstetric medicine are aware of the important role of maternal thyroid hormone in fetal neurodevelopment and placentation. Even mild hypothyroidism in early pregnancy is thought to be significant and there has been a growing call for prepregnancy, or at least early pregnancy, screening for hypothyroidism. What remains hotly debated is the correct target level for thyroid hormone replacement therapy or suppression of hyperthyroidism.

In the past, the human placenta was thought to be impermeable to maternal thyroid hormone, but this is clearly not the case. In this elegant and thorough review, Chan *et al.* have described all aspects of fetal and materno-fetal thyroid physiology. This includes the uptake and metabolism of maternal thyroid hormone by the fetus, including specific data about fetal tissue uptake in various organs during embryogenesis. Transplacental supply of thyroid hormones to the fetus is primarily determined by the maternal concentration of circulating thyroid hormones. Other mechanisms modulate this process, particularly a family of thyroid hormone transporters, degradation by a variety of enzymes as well as binding of thyroid hormones to proteins within trophoblast cells themselves. An inability to modify these processes during early pregnancy in women with pre-existing thyroid disease may explain some of the fetal effects of thyroid disease.

The review concludes: 'As the placenta is unable to alter transplacental thyroid hormone supply to compensate for abnormalities in maternal and fetal concentrations of circulating thyroid hormones, maintaining normal maternal thyroid status is likely to be the primary factor in ensuring adequate transplacental thyroid hormone passage and appropriate iodide supply to the fetus ... A better understanding of these mechanisms would also permit us to refine the timing and dosage of the increase in levothyroxine therapy in hypothyroid pregnant women and to establish whether thyroxine on its own is indeed the best form of thyroid hormone replacement in pregnancy.'

It is likely that clinical decisions regarding the dose and type of thyroid hormone replacement in the future will be based on these aspects of physiology rather than clinical trials.'

Should we lower the dose of iron when treating anaemia in pregnancy? A randomized dose-response trial

Zhou SJ, Gibson RA, Crowther CA and Makrides M

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Setting up and running a randomized clinical trial is an enormous task. Performing such studies for pharmacological treatments in pregnancy is even more difficult because of

the additional risks and ethical implications. This group from South Australia has an excellent reputation for similar studies often involving multiple centres. In this small, randomized study they asked a very simple question: what is the optimal dose to achieve correction of iron deficiency in pregnancy?

A number of preparations are used for the treatment of iron deficiency containing various iron conjugates at different doses. All are associated with gastrointestinal side-effects. In non-pregnant subjects, low doses (18–30 mg elemental iron/day) have been shown to be as effective as higher dose supplements. Hence the rationale for this trial comparing 20, 40 and 80 mg elemental iron/day given as ferrous sulphate for the treatment of anaemia (haemoglobin [Hb] <110 g/L) in mid-pregnancy. The primary outcome measures were incidence of Hb <110 and gastrointestinal side-effects. Secondary outcomes were based on the measurement of iron status by various parameters. The iron status was not determined prior to treatment and women were excluded if they were already taking supplemental iron, possibly biasing the results to a subgroup of women who may have been avoiding iron for some reason. The design, performance and analysis of the trial were well documented.

Approximately 60 women were included in each group and they were well matched including for dietary iron based on a validated iron checklist. The compliance with therapy in this study setting was around 80%, perhaps better than what might be expected in the real world. The results demonstrated a clear dose-response relationship between iron dose and change in Hb. The mean Hb after therapy with 20, 40 and 80 mg elemental iron/day for eight weeks was 111, 114 and 119 g/L, respectively. This dose-response relationship was also reflected in the percentage of women with Hb >130 g/L after eight weeks treatment, a surrogate marker for haemoconcentration. However, in terms of increase of Hb per gram of elemental iron, the greatest change was seen in the 20 mg group (0.4 ± 0.6 g/L) compared with 0.2 ± 0.1 g/L in the 80 mg group. The proportion of women with Hb <110 after treatment was greatest in the 20 mg group (38%) compared with the 40 mg (26%) and 80 mg (24%) groups. The incidence of side-effects was significantly greater in the high dose versus the lowest dose groups, predominantly nausea, stomach pain and vomiting, although the incidence of constipation was similar at each dose level.

Although the study was small, there was no difference in pregnancy outcomes between groups. The paper refers to previous studies suggesting adverse pregnancy and paediatric outcomes following iron supplementation.

In conclusion, although the 80 mg/day iron dose resulted in the highest Hb levels, even a 40 mg daily dose will allow most women to increase their Hb to >110 after eight weeks therapy with less side-effects. In this study, more iron improved the Hb result but doubt remains about the real target in this setting. Is it always necessary to achieve an Hb >110 and <130 and iron repletion based on iron studies, or does future research need to concentrate on the optimal iron status for the best functional outcome for both mother and baby?

First evidence of a possible association between gastric acid suppression during pregnancy and childhood asthma: a population-based register study

Dehlink E, Yen E, Leichtner AM, Hait EJ and Fiebiger E
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Having not followed the rodent literature that closely, I was surprised to discover in the introduction to this paper that acid-suppressive medications during rat pregnancy may predispose the offspring to allergy. This follows on from human studies that have implicated acid-suppressive drugs in allergic sensitization, possibly by preventing destruction of allergic epitopes in the stomach. These allergens are then preserved, absorbed and may be recognized by the immune system. In this study, the authors have taken advantage of the extensive and thorough Swedish Health Registries to perform a population-based observational cohort study of acid-suppression therapy in pregnancy and its association with allergic disease in the offspring.

By matching data from the Swedish Medical Birth Register and the Swedish Prescribed Drug Register, the authors identified all babies who were born to women who were dispensed acid-suppression therapy during pregnancy. This did not include over-the-counter medications or drugs used in hospital. Children were defined as allergic if they had ever been hospitalized for an allergic disease or received two or more prescriptions for allergy medications, including asthma medications, antihistamines, steroid ointments or epinephrine pens.

As would be expected in such studies, the numbers were huge: 860,215 children were born in the 10-year period of the study, of which 29,490 were subsequently diagnosed with allergy (5.03%). If one accepts that having been dispensed an acid-suppressing drug in pregnancy equates to fetal exposure, then such exposure was associated with a 43% increased risk of developing allergic disease in the offspring (odds ratio 1.43, 95% confidence interval 1.29–1.59). Similar results were seen in subgroup analysis for different types of acid-suppressing drugs, timing of exposure and irrespective of the maternal history of allergic disease. The allergic history of the mothers might be relevant if acid-suppressive drugs were being prescribed to women because of asthma exacerbations related to gastroesophageal reflux. In particular, exposure to acid-suppressing drugs increased the risk of asthma but not other allergic diseases in the offspring.

Data linkage studies can only report associations which then must be interpreted in the light of potential biological explanation. The authors go on to describe possible explanations for their findings based predominantly on similar animal

studies. The study failed to take into account paternal factors that may have influenced these results and there is an extensive discussion about the limitations of data linkage studies in general.

Although the use of medication in pregnancy is generally discouraged, there are few clinicians who fail to recommend drug therapy when pregnant women complain about indigestion and gastroesophageal reflux. This is an important conceptual paper to remind us of the potential dangers in prescribing. The problem remains that very few drugs have been adequately studied in terms of either their fetal or long-term effects, meaning that we continue to prescribe to the best of our abilities in an environment of ignorance.

Primary hyperparathyroidism in pregnancy: a case series and review

Truong MT, Lalakea ML, Robbins P and Friduss M
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Many of the conditions encountered in obstetric medicine are relatively rare and may or may not impact on the pregnancy. In caring for such women, case series are often the only available source of 'research' to guide management. Within any one institution, it may take many years to gather a significant number of cases, particularly when they are cared for by a variety of clinicians. One of the advantages of the dedicated obstetric physician is the ability to accumulate this experience more rapidly. Even small case series can be helpful as demonstrated in this article.

As the authors state, the incidence of primary hyperparathyroidism in women of child-bearing age is 8/10,000. In each of their cases, surgery was performed during pregnancy because of worsening maternal symptoms. Interestingly, in two of the cases surgical management was planned when the patients were not pregnant, but before this could be performed the patients became pregnant. Despite this, their recommendations for treatment fail to mention the importance of appropriate contraceptive advice.

The paper concisely reviews the potential maternal and fetal consequences of hypercalcaemia, and stresses the relative benefits and safety of surgical versus medical management during pregnancy.

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