

# Selected abstracts from: Diabetes & endocrinology – something for everyone

## PREGNANCY AND THE THYROID

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The management of patients with thyroid disease in pregnancy requires an understanding of complex changes in thyroid hormone economy. There is a reduction in both free T4 and T3 concentrations with time such that reference ranges should be calculated for each trimester. Serum thyroid-stimulating hormone (TSH) concentrations may be low in the first weeks due to the thyrotropic effect of human chorionic gonadotropin (HCG), and temporary hyperthyroidism is most commonly found in patients with hyperemesis. There is an oestrogen-driven doubling in the concentration of the major thyroid hormone carrier protein, thyroid-binding globulin (TBG), with a resultant fall in free T4, largely compensated by the effects of HCG on the thyroid. That compensation is not possible in those with hypothyroidism and an unresponsive gland in whom a mean increase in dose of thyroxine of 50 µg daily is required.<sup>1</sup> Given that the fetal brain cannot use maternal T3 but depends upon the local monodeiodination of maternal T4 for up to 20 weeks, it is essential that this increase in thyroxine dosage is implemented as soon as possible to avoid any potential disadvantage to the neonate in terms of psychomotor or intellectual function.<sup>2</sup> There is no consensus about whether screening for thyroid failure in asymptomatic women before or during pregnancy is warranted.<sup>3</sup>

It is fortunate that both the TSH receptor antibody and antithyroid drugs cross the placenta. It is assumed that fetal thyroid function will reflect that in the mother and the meticulous care of maternal thyroid function with review every 4–6 weeks is essential. Antithyroid drugs are often discontinued some four weeks before delivery. Recurrent hyperthyroidism in the first year is as likely to be due to postpartum thyroiditis as to Graves' disease.

### References

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## HORMONAL MANIPULATION IN INTENSIVE CARE

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Striking alterations within the hypothalamic-anterior-pituitary axes characterise critical illness, and the severity of these hormonal imbalances is associated with risk of morbidity and mortality. Most attempts to treat some of these endocrine abnormalities, however, have shown to be ineffective or harmful. The pathophysiological insight of a biphasic (neuro)endocrine response to critical illness has helped to clarify this controversy.

The acute phase is characterised by an actively secreting pituitary, whereas effective concentrations of most peripheral hormones are low, partly due to the development of target-organ resistance or to altered peripheral metabolism and binding of the target organ hormones. In contrast, in prolonged critical illness, a uniform suppression of the (neuro)endocrine axes, predominantly of hypothalamic origin, contributes to the low serum levels of the respective target-organ hormones.

The adaptations in the acute phase are considered to be beneficial for short-term survival. However, in the chronic phase of intensive care-dependent critical illness, the observed neuroendocrine alterations may contribute to the wasting syndrome of the critically ill and thereby hamper recovery and rehabilitation. With the exception of intensive insulin therapy, and perhaps hydrocortisone administration for a subgroup of patients with septic shock, no hormonal intervention has yet proven to beneficially affect survival. However, the combined administration of hypothalamic-releasing factors holds promise as a safe therapy to reverse the neuroendocrine and metabolic abnormalities of prolonged critical illness by a balanced re-activation of the different anterior-pituitary axes.

### Further reading

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## ADRENAL HORMONES AND THE HEART

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Secreted from the adrenal cortex, corticosteroids activate glucocorticoid and/or mineralocorticoid receptors (MR), which are widely distributed, including in kidneys, peripheral blood vessels and myocardium. Corticosteroids may influence atherogenesis and its complications either indirectly (through effects on blood pressure, blood glucose and lipid profile) or directly (by effects on vascular tone, remodelling and inflammation).

For mineralocorticoids, attention has focused on the beneficial effects of MR antagonists. In the RALES and EPHEBUS studies, these agents substantially improved outcome in patients with heart failure. It remains unclear, however, whether these benefits accrue from diuretic effects of receptor antagonism in the kidney and/or from blockade of MR in the heart and blood vessels. Moreover, it is by no means certain that aldosterone is the ligand which is displaced from MR by receptor antagonists, since in many tissues it is cortisol which occupies MR.

Anti-inflammatory glucocorticoids are among the most commonly prescribed medicines. Pharmaco-epidemiological studies reveal an association of glucocorticoid therapy with an excess of cardiovascular events, notably heart failure. This association appears over and above any cardiovascular risk of the underlying inflammatory disease for which glucocorticoids are being prescribed. In patients with glucocorticoid deficiency (e.g. Addison's disease or hypopituitarism), there is evidence that a subtle excess of glucocorticoid replacement therapy contributes to cardiovascular risk. These observations reinforce advice to minimise glucocorticoid therapy.

Manipulating corticosteroid hormone action may provide new opportunities to prevent and treat cardiovascular disease. However, systemic manipulations are probably too indiscriminate and research is now focussed on selective manipulations within relevant tissues.

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**Declaration of interests** Prof. Walker consults extensively to the pharmaceutical industry on pre-clinical and early clinical development of 11-HSDI inhibitors and is an inventor on relevant patents owned by the University of Edinburgh.

## THYROID RECEPTOR MODULATORS

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Thyroid hormones have diverse actions, some of which are beneficial and others harmful. Thyrotoxicosis results in increased energy expenditure, weight loss and favourable effects on serum cholesterol and lipids. Although these effects would be beneficial for cardiovascular risk, they come at the expense of important deleterious responses that include tachyarrhythmia, cardiac failure, bone loss, fatigue and neuropsychological disturbance.

Thyroid hormone action is mediated by the nuclear receptors TR $\alpha$  and TR $\beta$ , and a key aim in the field is to develop selective ligands that favour activation of one isoform relative to the other. Such selective drugs might harness the beneficial actions of thyroid hormones without eliciting detrimental side effects. TR $\alpha$  and TR $\beta$  are expressed in tissue-specific patterns and mediate selective responses to thyroid hormones. TR $\alpha$  is the major isoform expressed in the heart, skeleton and brain, whereas TR $\beta$  predominates in the liver and pituitary gland. TR $\beta$  has been proposed to mediate the lipid and cholesterol lowering effects of thyroid hormones, while TR $\alpha$  is suggested to mediate detrimental responses in the skeleton and central nervous system. It is unclear whether effects on energy expenditure, weight loss and skeletal muscle are selective responses to either isoform.

This presentation will consider potential therapeutic benefits of TR $\beta$ -selective agonists in the treatment of metabolic syndrome by reviewing their actions in animal studies and discussing emerging results from a recent clinical trial in humans.

Conclusions from these studies suggest promise for TR $\beta$  thymimetics as a novel strategy for treatment of dyslipidemia and obesity.

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## CONTROVERSIES IN TREATING HYPERPROLACTINAEMIA

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Hyperprolactinaemia is common and found in 20% of women with secondary amenorrhoea. Early assessment should exclude pregnancy and primary hypothyroidism. Many drugs cause hyperprolactinaemia, particularly those that antagonise or deplete hypothalamic dopamine.<sup>1</sup> Well over 50% of patients on first-generation antipsychotics have hyperprolactinaemia, although this is a lesser problem with atypical antipsychotics such as quetiapine. The consequences of chronic hyperprolactinaemia in these patients are poorly researched.<sup>2</sup> Appropriate treatment may include sex-hormone replacement or prolactin (PRL) lowering therapy.

Prolactinoma is an important cause of hyperprolactinaemia; primary medical therapy with a dopamine agonist (most commonly cabergoline) is now standard practice for all tumour sizes.<sup>3,4</sup> The majority of patients experience significant symptom relief, PRL lowering and tumour shrinkage. After prolonged treatment some prolactinomas go into remission – this occurs with about 30% of small prolactinomas. It has recently been demonstrated that larger tumours may also remit, particularly those with marked PRL lowering and tumour shrinkage.<sup>5</sup> In patients with persistent prolactinoma, cabergoline can often be reduced to a low maintenance dose. Recent studies have reported the occurrence of fibrotic valvular heart disease in some Parkinsonian patients exposed to high doses of dopamine agonists with 5HT<sub>2B</sub>-receptor activity (especially pergolide and cabergoline). However, preliminary studies of endocrine patients treated with much lower doses of cabergoline (only about 5% of those used in Parkinson's treatment) have been reassuring; no patient with significant valvulopathy has been described.<sup>6</sup> Cabergoline therapy is usually well tolerated although rare adverse events – due to dopamine agonist induced changes within a prolactinoma – include CSF rhinorrhoea, traction ophthalmopathy and apoplexy.

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## MANAGING THE BENIGN THYROID NODULE

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Three recent guidelines include recommendations on the approach to be taken with a thyroid nodule.

The main concern is to exclude malignancy; fine needle aspiration biopsy is mandatory, but the use of ultrasound is controversial. This latter technique can identify the features and size of a nodule and any additional non-palpable nodules, and detect cervical lymphadenopathy. However, many thyroid nodules are impalpable, yet their discovery by ultrasound poses a dilemma since the majority will be benign. There is no definitive ultrasonographic feature which will identify a nodule as malignant. British guidelines do not recommend calcitonin measurement in patients with a thyroid nodule. Thyroid function must be established prior to fine needle aspiration biopsy. Urgent referral (the two-week cancer waiting time rule) is required in those with unexplained hoarseness or voice change, presentation of thyroid nodule in a child, palpable cervical lymphadenopathy and a rapidly enlarging painless mass over a period of weeks. Same-day referral is required in any patient presenting with a stridor and a thyroid nodule. The accuracy of fine needle aspiration biopsy is increased by taking multiple samples and in general two non-neoplastic results from fine needle aspiration, three to six months apart, are advisable to exclude malignancy. A patient who has a multinodular goitre has the same risk of malignancy as a patient with a solitary nodule. Fine needle biopsy should be directed to the dominant (largest or recently enlarged) nodule, although recent evidence suggests that it may be prudent to consider fine needle aspiration biopsy in adjacent nodules.

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*Declaration of interests* Prof. Weetman has received lecture fees from Merck in the past.

## MODERN PARATHYROID SURGERY

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The treatment of primary hyperparathyroidism (HPT) includes more liberal indications for surgery than previously.<sup>1-3</sup> Approximately 50% of patients with primary hyperparathyroidism are suitable for less than a traditional, gold standard four-gland neck exploration – unilateral, small incision, video-assisted surgery. Preoperative localisation studies – prior to first time (ultrasound and MIBI scans) and reoperative surgery (CT/MRI/PET/selective venous and arterial catheterisation) – facilitate and are essential for a minimally invasive approach.

Confirmation of biochemical cure with intra-operative parathyroid hormone measurement is neither necessary nor cost-effective at the first intervention but is very helpful in reoperative cases.

An experienced parathyroid surgeon is still required to achieve the expected cure rates of above 95% in patients with primary HPT.

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## DIABETES, DRIVING AND EMPLOYMENT

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In people with insulin-treated diabetes, hypoglycaemia is the principal problem that can affect employment and driving. Hypoglycaemia impairs cognitive function and can interfere with work and driving performance. Employment may also be affected by poor glycaemic control and diabetic complications; unemployment is more common in people with diabetes. Although hypoglycaemia in the workplace is relatively infrequent, the potential risk disbars people with insulin-treated diabetes from some occupational areas such as commercial aviation, the armed forces and vocational driving. Working in dangerous areas is restricted by employers, and not through legislation. An assessment of potential employees for potentially hazardous jobs should use recommended criteria; unfair limitation on employment through discrimination by employers should be avoided.

Diabetes is designated as a prospective disability for medical fitness to drive. Hypoglycaemia interferes with driving performance and can cause road traffic accidents. Impaired awareness of hypoglycaemia and a history of recurrent severe hypoglycaemia during waking hours are major risks for driving, and may cause revocation of the driving licence. In the UK, people treated with insulin are required to inform the licensing authority, the Driver and Vehicle Licensing Agency (DVLA), and are issued with period-restricted driving licences of up to three years' duration. Those treated with insulin are disbarred from holding Group 2 (vocational) licences, including large goods vehicles (LGV) and public service vehicles (PSV). Recommendations for avoiding hypoglycaemia while driving, and for its effective treatment if it occurs, should be available to all drivers with diabetes. Unfortunately, unsafe practices in relation to driving are common.

### Further reading

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