

### 1.1 Combination endocrine and radiation therapy for locally advanced prostate cancer.

For patients with locally advanced prostate cancer the combination of anti androgen and radiation therapies yields better outcomes than the radiotherapy alone, but until now, combination therapy has not been compared with endocrine therapy alone. 875 Scandinavian men with locally advanced prostate cancer, no affected nodes or distant metastases, were randomized to endocrine treatment of an LHRH agonist followed by an oral non steroidal anti androgen, with or without maximum dose radiotherapy.

After a median follow up of 7.6 years, 8.5% of patients in the combination treatment group had died of prostate cancer vs 18% of patients in the endocrine only group. Between group differences in cancer specific and all cause mortality began to emerge after 4 years of follow up. After 10 years of follow up the cancer specific and all cause mortality difference was even greater. Those who received radiation therapy experienced more genitourinary side effects than those who did not.

**Comment:** Although this trial was not blinded, both authors and accompanying Editorialists agree that combination therapy of long term endocrine therapy + radiotherapy, should be the new standard of care for locally advanced prostate cancer.

**Ref:** Widmark A et al Lancet 2009 Jan 24; 373: 301.  
Tan A and Parker C IBID : 274.

### 1.2 Hysterectomy (H) after endometrial ablation (EA) is less likely in older women.

EA has been promulgated as a reasonable alternative to Hysterectomy when medical treatment for abnormal uterine bleeding fails. A retrospective analysis of more than 3,600 women (age 25 – 60) who underwent EA during a 6 year period was conducted in California.

The probability of hysterectomy at 8 yrs after ablation was 26% , with most surgeries occurring within 3 years of ablation. Age was the most important predictor of subsequent H , with likelihood of subsequent H exceeding 40% in women who were younger than 40 at the time of ablation. These findings were independent of the presence of uterine fibroids.

**Comment:** In women with abnormal uterine bleeding, EA is far more likely to alleviate symptoms and to eliminate the need for subsequent H as women approach menopause than in younger women.

**Ref:** Longinotti M.K. et al Obstet Gynaecol 2008 Dec; 112: 1214.

### 1.3 What is the mortality risk following osteoporotic fractures (OF)?

OF, particularly of the hip and spine are associated with premature mortality. 4,005 Australians age > 60 were enrolled. During the next 18yrs (1989 – 2007), 1,295 participants experienced fractures.

The mortality rate for participants with fractures were roughly double that of participants without fractures. Relative mortality rose further after subsequent fractures (double for women, triple for men). Elevated mortality risk continued for 5 years after fractures, persisting for 5 – 10

yr for hip fractures. The main clinical factors associated with excess mortality were older age, subsequent fracture, weak quadriceps strength, smoking in women and low physical activity in men.

**Comment:** These results demonstrate that, not only is OF associated with excess mortality, but that this risk persists for several years after any fracture and as long as 10 yrs after hip fracture.

**Ref:** Bliuc D. et al JAMA 2009 Feb 4; 301:513.

#### 1.4 Treatment of jetlag or sleep disturbance due to shift work – Melatonin Receptor agonists (MRA)

The circadian sleep wake cycle is mediated by endogenous melatonin from the pineal gland. Although the MRA **Ramelteon** is FDA approved for use in patients with chronic insomnia, the drug's efficacy for that indication appears to be modest. A newer MRA – **Tasimelteon** (T) appears useful in coping with acute changes in the sleep cycle as in jet lag or shift work. The drug is given 30 mts before bed time and was given for 3 consecutive days and was compared with placebo in 39 volunteers. Placebo recipients on the first treatment day had a 113 minute decline in total sleep time whereas T recipients had a mean 9 mt decline in sleep efficiency.

In a separate study the same researchers randomized 412 volunteers to either T or placebo 5 hours before their normal bed time. Those who took any dose of T had significantly greater sleep time and sleep efficiency, significantly shorter latency to sleep onset and to persistent sleep and significantly less wake time after sleep onset. There were no short term adverse effects.

**Comment:** By resetting the circadian clock, MRAs might be more physiological treatment for acute sleep cycle changes and might cause fewer adverse effects than do traditional hypnotics such as Benzodiazepines.

**Ref:** Rajaratnam S.M.W. et al Lancet 2009 Feb 7 ; 373: 482.

#### 1.5 Recent advances in diabetic retinopathy (DR)

Laser treatment remains the mainstay of treatment for proliferative DR and maculopathy (M). A particular issue is the problem of chronic macular oedema that is not responding to laser treatment. The selective proteinkinase C beta inhibitor **Ruboxistaurin** (R) taken orally has been shown to reduce retinal vascular leakage in patients with diabetic M and to reduce the rate of sustained moderate visual loss in those with moderate to very severe non proliferative DR.

Intra vitreal levels of vascular endothelial growth factor (VEGF), a major proangiogenic and permeability factor in the eye, are high in proliferative DR. Intra vitreal triamcinolone inhibits angiogenesis and expression of VEGF, reduces vascular permeability and inhibits the migration and activation of inflammatory cells. It has been used to reduce macular oedema but unfortunately cataracts and glaucoma occur in about 40%. It has also been used as an adjunct to laser treatment for diabetic M.

**Pegaptanib** sodium binds and blocks the activity of VEGF –A. It is given **intravitreally** every 6 weeks for 2 years. It delays the deterioration and improves the vision in proliferative DR and diabetic M. It also caused the regression of neovascularization.

**Ranibizumab** is a monoclonal antibody that binds and inhibits the action of VEGF – A. It is given by intravitreal injection every 4 weeks over 2 years. It is mainly used in diabetic M . Long term results are awaited.

**Bevacizumab** is an antibody acting against VEGF. It is used iv in the treatment of bowel cancer but is used intraocularly in M.

The draw backs of all VEGF inhibitors is that it may lead to a loss of neuroprotection and prevent the maintenance of normal retinal vasculature. Theoretically intra vitreal anti VEGF treatment could increase the risk of systemic thromboembolic events, as small amounts of drug do reach the systemic circulation from the eye.

**Ref:** Bailey C RCP Lond 2008; Horizons in Medicine 20: 249 – 254.

## 1.6 Diabetes, depression and pregnancy

Attention to depression during and after pregnancy and its relation to diabetes has increased in recent times. A retrospective analysis between diabetes and depression in pregnant women was undertaken, 6 months before and 12 months after giving birth in 11,000 women.

Risk for perinatal depression in women who had pre pregnancy or gestational diabetes was 15% , compared with 8% in non diabetics. Risk for perinatal depression was about 80% higher in patients who had diabetes than those who did not. In women with diabetes, but no evidence of prenatal depression, the risk of post partum depression was 69% higher than in women without diabetes or prenatal depression.

**Comment:** Diabetic pregnant women should be monitored for prenatal and post natal depression.

**Ref:** Kozhimannil K.B. et al JAMA 2009 Feb 25; 301: 842.

## 1.7 Are overweight and obesity risk factors for congenital anomalies – a meta analysis?

During pregnancy, being overweight (BMI 25 – 30) or obese (BMI > 30) confers substantial risk for both mother and child for several conditions, including gestational diabetes, hypertension, operative delivery, macrosomia and birth trauma. Are there specific risks for congenital anomalies?. A meta analysis of 18 studies was undertaken.

Compared with women with normal weight women, obese women delivered infants with higher risk for several congenital anomalies including spina bifida (OR 2.24) , neural tube defects (OR 1.87), hydrocephaly (OR 1.68), anorectal atresia (OR 1.48), limb reduction anomalies (OR 1.34), cardiovascular anomalies (OR 1.30) and cleft palate (OR 1.23).

The ORs associated with overweight mothers were somewhat smaller but still significantly elevated for neural tube defects (1.20) and cardiovascular anomalies (1.17).

**Comment:** Several potential mechanisms for this excess risk are proposed, including insulin resistance and hyperglycaemia and particularly to folic acid deficiency. Obesity is known to be associated with reduced folate levels. The risk for marked structural anomaly in all pregnancies is roughly 3%. So, the odd ratios in obese and overweight mothers is not clinically unimportant. This is one more reason to prevent obesity or to treat it in women before they become pregnant.

**Ref:** Stothard K.J. et al JAMA 2009 Feb 11; 301: 636.

## 1.8 Does weight loss improve mild sleep apnoea?

Observational studies indicate that weight loss has salutary effects on obstructive sleep apnoea (OSA). Researchers from Finland have now conducted a randomized trial to examine the effect of weight loss on mild OSA.

The trial involved 81 overweight adults (BMI 28 – 40) with mild OSA (apnoea – hypopnoea index, (AHI) 5-15 events / hour). The intervention group received individualized very low calorie diet (600 – 800 cal/d) with life style counseling for 12 weeks. This was followed by a less stringent low fat diet. The controlled group received only general dietary information.

At 12 months, mean weight loss was significantly greater in the intervention group (10.7 Kg vs 2.4 Kg). The mean AHI declined from 10 events per hour at base line to 6.0 in the intervention group and 9.6 in the controlled group – a significant difference. The AHI dropped into the normal range (< 5 events/hour) in 63% of intervention patients vs 35% of controls. Various subjective outcome trends ( eg: quality of life, snoring, day time sleepiness) , consistently favoured the intervention group.

**Comment:** This is the first randomized trial in which researchers examined the effects of weight reduction and life style intervention on mild OSA. Weight reduction is a reasonable option compared to continuous positive airway pressure and mandibular advancement devices. Maintaining weight loss is the critical problem.

**Ref:** Tuomilehto H.P.I et al Am. J. Respir. Crit. Care Med 2009 Feb 15; 179: 320.

## 1.9 A rare cause of precocious puberty (PP) – Rathke Cleft Cyst (RCC)

PP has been associated with different types of brain masses including gliomas, germinomas and hamartomas. Gliomas cause PP through the secretion of neuroactive substances including transforming growth factor Alpha and fibroblast growth factor, which stimulate the release of GnRH. Germ cell tumours produce Beta HCG, which stimulates testosterone secretion by the Leydig cells of the testes. Hamartomas cause PP by producing GnRH ectopically.

RCCs are cystic sellar and supra sellar lesions that arise from remnants of the Rathke pouch and are usually lined by a layer of ciliated, cuboidal and columnar epithelium. They are non neoplastic and are often not detected unless incidentally discovered during neuroimaging or autopsy. At autopsy, 13 – 22% of pituitary glands have been found to harbour RCC. Affected patients are usually asymptomatic but they can present with symptoms attributable to the cyst mass or to specific endocrine abnormalities. The most common initial manifestation in children is growth failure. Other symptoms include headache, visual disturbances, hypopituitarism, diabetes insipidus, hyperprolactinaemia and amenorrhoea. The mechanism for PP in RCC is unknown but it may be due to interruption of the normal inhibitory mechanisms for gonadotrophin release.

**Ref:** Acharya S.V et al Endocrine Practice 2008 March; 15(2): 134 – 137.

## 1.10 Can the ACTH stimulation test for Addison's disease be performed and be valid while on high dose glucocorticoid therapy?

In a study of 8 patients, it was found that the validity of this test remained during the first 72 hours after initiation of empiric glucocorticoid therapy. An inadequate response of serum cortisol to ACTH stimulation may be indicative of adrenal insufficiency.

**Ref:** Villabona C.V. et al Endocrine Practice 2008 March; 15 (2): 122 – 127.

### **1.11 A new cause for thyrotoxicosis – Epoprostenol (PGI<sub>2</sub>)**

The usual drugs that can affect thyroid functional status by an increase of T<sub>3</sub> and T<sub>4</sub> are Iodide, Amiodarone and rarely Lithium. Cytokines such as Interferon Gamma, Interleukin 2 and Granulocyte macrophage colony stimulating factor are also associated with hyperthyroidism. Hyperthyroidism has also been found in 4 cases of pulmonary arterial hypertension (PAH), in whom the PAH improved after achievement of a Euthyroid state. Epoprostenol is a prostacycline analogue that is used in the treatment of PAH. These prostoglandins mimic the effects of TSH thereby stimulating the synthesis and secretion of thyroid hormone.

In a study of 54 patients with PAH treated with Epoprostenol, followed up over 3 years, 6.7% developed thyrotoxicosis (TRAB –ve) while on treatment with Epoprostenol, which is 9-10 times higher than would be expected in the general population. The drug does not contain Iodine and does not cause thyroiditis. It however increases iodide trapping. The degree of hyperthyroidism is relatively mild but the goiters were large.

**Ref:** Chadha C et al Endocr.Pract 2009 March; 15(2): 116 – 121.

### **1.12 Conditions and situations in which estimation of TSH alone may be misleading in assessment of thyroid disease.**

Highly sensitive TSH estimation gives an accurate assessment of thyroid functional status. Low TSH indicates hyperthyroidism, high TSH – hypothyroidism and normal TSH – Euthyroidism. This is true for the majority of patients and therefore many Endocrinologists use TSH alone as the initial screening test for functional assessment, as free T<sub>4</sub>, Free T<sub>3</sub> increases the expense. However the following may give misleading results if TSH alone is estimated.

1. Non thyroid illness - TSH is usually normal or reduced although the patient is euthyroid.
2. Recent treatment for hyperthyroidism – TSH remains depressed for a longer time than the elevation of T<sub>4</sub> and T<sub>3</sub>. Therefore normal T<sub>4</sub> and T<sub>3</sub> with low TSH is often seen in the early stages even though the patient has been rendered euthyroid by treatment.
3. Central hypothyroidism (hypothalamic or pituitary) - The TSH is normally low or normal although the patient is hypothyroid. Free T<sub>4</sub> estimation is therefore required (low FT<sub>4</sub> and TSH is the norm).
4. TSH secreting pituitary adenoma – Here the patient is hyperthyroid but has an elevated TSH. Free T<sub>4</sub> and Alpha sub unit of TSH estimation is required to clinch the diagnosis.
5. Resistance to thyroid hormone - The TSH is elevated although clinically the patient is hypo, Eu or mixed Hypo hyper thyroid. Free T<sub>4</sub> is elevated.

In the above conditions additional Free T<sub>4</sub> estimation is required.

**Ref:** Gurnell M, Horizons in Medicine 19, 2007; RCP Lond: 277 – 288.

### **1.13 What is the best surgical treatment for multinodular goiter (MNG)- subtotal (ST) or total thyroidectomy (TT)?**

Both these procedures are undertaken for treatment for MNG. However proponents of TT argue that 8 – 14% of MNGs harbour incidental thyroid cancer and if only ST is done then there could be significant residual thyroid cancerous and non cancerous tissue. TT has several advantages in such cases as it removes multifocal disease, aids detection and ablation of metastatic disease with radioactive iodine, reduces risk of anaplastic transformation in residual thyroid disease and

greater sensitivity of serum thyroglobulin levels to predict recurrent and persistent disease. Opponents of TT argue that there is a greater risk of operative complications. It is obvious therefore that TT should be undertaken only by competent Surgeons with a high thyroid surgery turnover.

If ST has been performed and incidental cancer recognized on biopsy, then completion thyroidectomy should be undertaken. In advanced centers, this can be done by using 3 mCi technetium Tc99m during anaesthetic medication and suspicious thyroid tissue with increased activity can be detected using a Gamma probe during the operation. This will detect residual thyroid tissue which can then be removed surgically by a lateral approach safely with acceptable morbidity.

**Ref:** Ulludag M et al Endocr. Pract. 2009 Apr; 15 : 213 – 219.

### **1.14 Idiopathic male infertility (IMI) – Medical therapy – Clomiphene + Vit E.**

Male infertility is present in about 50% of couples who present with infertility. Many of these have no detectable underlying cause for their seminal fluid abnormalities. These are cases of IMI. The anti oestrogen drug Clomiphene citrate and the antioxidant Vit E have been used to raise sperm counts in men with IMI, but data from randomized trials are lacking.

In a 6 months randomized trial, 60 Egyptian men with IMI received daily combined therapy – clomiphene citrate 25mg + Vit E 400mg or placebo. Pregnancy rates were significantly higher in the treatment group than in the placebo group (37% vs 13%). Sperm concentration and forward progressive sperm motility also increased significantly with active treatment but not with placebo.

**Comment:** In this trial, pregnancy rates were higher among couples in which infertile men received clomiphene citrate + Vit E than among couples in which men received placebo. However this is a small, single center study. Therefore the results cannot be considered definitive. Further the investigators did not study each treatment separately. Further trials are required to address the efficacy of these therapies which have been used for many years without adequate proof of its effectiveness.

**Ref:** Ghanem H et al Fertil. Steril 2009 March 5; ahead of print

### **1.15 Do males with infertility have a high risk for testicular cancer?**

Testicular germ cell cancer is the most common malignancy in young men in industrialized countries. Both germ cell cancer and male infertility incidence has been rising in recent decades in these countries. Are these two features linked?

A study of 23,000 men with infertility in California, were assessed. It was found, that among men with male factor infertility, risk for subsequent testicular cancer was higher than that for men in the general population (HR 2.8).

**Comment:** The relative risk for testicular cancer was elevated among infertile men. The absolute risk, however remain low (0.3%). The underlying factors responsible for this association are unknown. Faulty DNA repair could explain both processes.

**Ref:** Walsh T .J. et al Arch. Intern Med. 2009 Feb 23; 169:

### 1.16 Which is better for Type 2 DM – Liraglutide (L) or Glimepiride (G)?

Exonatide, the only incretin mimetic drug available currently in the US requires twice daily injection, although a weekly formulation has undergone a few trials but is not available for use. L is an investigational incretin mimetic drug that can be **injected once daily**.

746 patients with early Type 2 DM were randomized to daily L ( 1.2mg or 1.8mg) or the sulphonylurea G (8mg/d). Mean baseline HbA1C and FPG were 8.2% and 171 mg/dl resp. After 1 year, patients who received high or low dose L had significantly greater declines in mean HbA1C values than did patients who received G (declines of 1.14%, 0.84% and 0.51% resp). Mean FPG levels also declined more with L (26mg, 15mg, and 5mg/dl resp). On average patients who received L lost 2Kg of body weight whereas G recipients gained 1 Kg – a significant difference. L recipients experienced fewer episodes of hypoglycaemia but more episodes of nausea.

**Comment:** This one year study, suggest that L is superior to G for patients with early Type 2 DM. Its efficacy compared to Metformin (the currently recommended first line drug) its long term effects on clinical end points and its role in treatment of more advanced disease remain to be established.

**Ref:** Garber A et al Lancet 2009 Feb 7; 373: 473.

### 1.17 Does steroid treatment prevent pre term births?.

**A single dose** of corticosteroids, given for threatened pre term delivery, lowers risk for neonatal mortality, respiratory distress syndrome and intraventricular haemorrhage. If pre term delivery remains a threat at 1 week or more after initial treatment, some clinicians administer repeat steroid doses. But trials of **weekly** steroid doses in this setting have yielded mixed results, and some evidence suggest that multiple doses of steroids diminish foetal growth or have long term adverse neurologic effects.

Investigators enrolled 1,858 women between 25 and 32 weeks gestation who received one dose of steroids but had not delivered 14 – 21 days later. These women were randomized to receive doses of Betamethazone or placebo **every 2 weeks** until 35 weeks of gestation or delivery.

Infants from the treatment group on average weighed 114g less, were 0.9cm shorter and had head circumferences 0.6cm smaller than those from the placebo group – all significant differences.

**Comment:** Women who remain at risk for pre term birth after initial dosing of corticosteroids should not receive follow up doses.

**Ref:** Murphy K.E. et al Lancet 2008 Dec 20 /27; 372: 2143.

### 1.18 Does intensive glucose control (IGC) benefit ICU patients? – NICE – SUGAR trial.

Prior studies of IGC in critically ill patients have yielded conflicting results. Now, in a multicentre trial (NICE – SUGAR), investigators randomized more than 6,000 critically ill patients (63% medical, 37% surgical) to either IGC with target glucose 81 -108mg/dl or conventional glucose control with target glucose 144 – 180mg/dl. All patients had insulin infusions.

The primary end point of death by 90 days occurred significantly more often in the IGC group than in the conventional group (27.5% vs 24.9%). When data were analysed separately for

medical and surgical patients, results were similar to those for the whole cohort. Severe hypoglycaemia (< 40mg/dl) was significantly more in the IGC group. No differences between the groups were observed in median number of ICU or hospital days, days on mechanical ventilation or renal replacement therapy.

**Comment:** The results of this trial suggest that IGC harms critically ill patients in terms of death (number needed to harm 38) and episodes of severe hypoglycaemia. This does not mean that one can revert to neglectful means of glucose control such as insulin sliding scales. Instead, clinicians should strive for reasonable control with glucose levels near 150mg/dl in such patients.

**Ref:** NICE – SUGAR study N.E.J.Med 2009 arch 26; 360: 1283.  
Inzucchi S.E. and Siegel IBID 1346.

### 1.19 Oestrogen deficiency.

Dutch investigators evaluated 5,600 women with hot flushes for bone mineral density. They found the average BMD was inversely proportional to the frequency of flushing. Women with the most frequent symptoms had mean BMD of the lumbar spine which was 0.022g/cm<sup>2</sup> lower than that of asymptomatic women.

In another study of 217 post menopausal women, it was found that insomnia scores related to a greater frequency of moderate to severe hot flashes. Hot flashes was associated with greater night time wakefulness and a higher number of long – wake episodes but not related to total sleep time or sleep latency.

**Comment:** Hot flushes are associated with lower BMDs and night time wakefulness. Whether women with severe flushes should be subjected to early BMD screening is not known.

**Ref:** Gast G. et al Menopause 2009 March/April; 16: 231.  
Ensrud K.E. et al IBID : 286.

### 1.20 A new treatment for obesity – drink more water!

Does water consumption prevent children becoming over weight?. A clinical trial in 32 schools of two neighbouring German cities was conducted. Outcomes of 1,641 2<sup>nd</sup> and 3<sup>rd</sup> grade students at 17 intervention schools were compared with 1,309 students at 15 control schools. The children in the intervention schools were actively encouraged and provided the means to drink more water. At the end of the school year, 23.5% of children in the intervention group and 27.8% of children in the control group were over weight – a significant difference.

**Comment:** Drinking more water should be encouraged in both children and adults to prevent obesity. Sweetened beverages should be actively discouraged.

**Ref:** Muckelbauer R et al Paediatrics 2009 Apr; 123: 661.