

3.1 Cushing's syndrome in adults – some aspects

The typical striae are wide, purple red, over the abdomen, inner thighs and axillae. The DD consists of obesity, metabolic syndrome, depression and other causes of menstrual irregularities.

The 3 standard case detection tests are

1. 24 hr urinary free cortisol (UFC).
2. Late night salivary cortisol(LNSC).
3. 1mg over night dexamethasone suppression test (ODST).

UFC - The fluid intake should not be excessive and the urine 24 hr volume should not exceed 5 litres (Falsely elevated UFC). The renal function should be normal. Renal failure can decrease UFC. UFC may have to be repeated many times. The UFC should be more than 3 fold above the upper limit of the reference range.

LNSC - This is collected at 11p.m with a salivate collecting device. It assesses cortisol secretion at the physiologic nadir. The upper limit of the reference range is 100ng/dl.

ODST - Normal suppression is defined as a serum cortisol level < 1.8mcg/dl (sensitivity 95%, specificity 80%). The former diagnostic threshold was 5mcg/dl (specificity increases to 95% but sensitivity declines). Anticonvulsants and oestrogen oral preparations accelerate the metabolism of dexta or increase cortisol binding globulin levels.

Ref: Endocrinology Update Mayo clinic 2009; 4 (4): 3-4.

3.2 Metformin and peripheral neuropathy (PN) in diabetes.

Several pathogenic mechanisms contribute to PN severity in diabetics. These include microangiopathy, oxidative stress, polyol flux, mitochondrial dysfunction, insulin deficiency, advanced glycation end products and ligand activation of their receptors.

Vitamin B 12 deficiency may occur in diabetes manifesting typically as an axonal neuropathy. Cobalamin associated metabolites such as methyl malonic acid and homocysteine are more sensitive indicators of early symptomatic B 12 deficiency than serum B 12 itself. Metformin can cause B 12 deficiency. This may be due to competitive inhibition or inactivation of B12 absorption, alterations in intrinsic factor levels, bacterial flora, GIT motility, ileal morphological structure and interaction with the cubulin endocytic receptor. Metformin also impairs calcium dependent membrane activity in the ileum including the complex of B12 with intrinsic factor.

It has been found that metformin for more than 6 months can lower serum B12 levels with higher serum homocysteine and methylmalonic acid levels. The cumulative dose of metformin is important. (N=63).

These findings should not be seen to discourage treatment of diabetic patients with neurological impairment with metformin. Metformin has beneficial effects on advanced glycation end product formation in peripheral nerves and may prevent apoptosis involve in diabetic neuropathy. The recommendation would be to check B12 levels at intervals of 1 year while being on metformin therapy and to initiate treatment with B12 if levels are low. The effects of B12 treatment may be cure of the neuropathy or atleast an improvement if the neuropathy is not entirely due to B12 deficiency.

B12 intra muscularly would be the best way to administer initially. Long term oral or sublingual B12 + folate may be required subsequently if metformin treatment has to continue. Oral Calcium supplementation has also been found to be effective in reversing the bio available B12 deficiency in metformin treated patients.

Comment: Metformin exposure is a potential iatrogenic contributor to the severity of diabetic peripheral neuropathy. Recognition of this readily identifiable and potentially treatable component of disease might improve the quality of life for this large population of diabetic patients.

Ref: Wile D.J. et al Diabetes Care 2010 Jan; 33: 156 – 61.

3.3 Secondary causes of osteoporosis (OP) – some aspects.

Secondary causes of OP is suspected when the Z score is $< - 2.0$. These causes are seen in 2/3rds of men with OP , 50% of perimenopausal women with OP and 20 % of post menopausal women with OP. The following causes have to be looked for.

- 1) Hypogonadism.
- 2) Hyperthyroidism.
- 3) Primary hyperparathyroidism.
- 4) Vit D deficiency.
- 5) Renal insufficiency.
- 6) Chronic hepatocellular disease.
- 7) Malignant disease.
- 8) GIT disorders.
- 9) Drugs.
- 10) Connecting tissue disease.
- 11) Transplantation.
- 12) Genetic disorders.
- 13) Idiopathic hypercalciuria.

Patients with Ca malabsorption would not benefit from standard recommendations of Ca intake and would be at risk for severe hypocalcaemia with bisphosphonate therapy. In patients with chronic kidney disease, bisphosphonates can accumulate excessively in the bones when the GFR is $< 30\text{ml/mt}$. 50% of post menopausal women in North America have a 25 hydroxy Vit D level of $< 30\text{ng/ml}$ which is considered inadequate. Idiopathic hypercalciuria is diagnosed by a 24 hr urine Calcium excretion estimation. This condition can cause a decreased BMD in addition to nephrolithiasis (mimics hyperparathyroidism which needs exclusion). Treatment consists of a thiazide diuretic, restriction of dietary sodium and protein. Hypocalciuria can point towards Vit D deficiency or celiac disease and other causes of Ca malabsorption.

Ref: Hamoudeh E. et al Endocr. Pract.2009; 15: 410 – 414.

3.4 Stress hyperglycaemia after cardiac surgery

Post operative hyperglycaemia after cardiac surgery in patients without prior diabetes is occasionally encountered. They may require insulin infusion therapy for a few post operative days. Is this a transient phenomenon or is it indicative of persistent abnormalities in glucose metabolism. 50 consecutive such patients were followed up prospectively. Fasting plasma glucose, 75 gm 2 hr OGT and HbA1C were estimated 6 weeks post surgery. 20% were found to have IFG, 10% IGT, 16% combined IFG and IGT and 18% Type 2 DM (64% abnormal). The FPG alone was a poor indicator of diabetes as 8 of the 9 patients so diagnosed had an FPG of < 126 . Higher the preoperative plasma glucose levels, higher the probability of abnormal glucose tolerance 6 weeks post operatively. A

preoperative FPG of 94mg/dl had a sensitivity of 86% and a specificity of 50% for an abnormal OGTT 6 weeks post operatively.

The probable cause for this stress hyperglycaemia is thought to be LV dysfunction, inflammatory processes, acute hospitalization leading to surgical intervention which causes increased sympathetic stimulation and increased levels of cortisol.

The best test for detection was the 75gm 2 hr OGTT. The FPG was less sensitive and the HbA1C unreliable as all these patients had received blood transfusions intra operatively which distorts the value of the A1C for upto 3 months post operatively. Repeat OGTT at 3 months and 1 year may unmask further cases of impaired glucose tolerance.

Ref: Arora S. et al Endocr. Pract. 2009; 15: 425 – 430.

3.5 Treatment of Gastroparesis (G) - some aspects.

These patients have markedly delayed gastric emptying which may be asymptomatic or there may be severe nausea and vomiting with relatively normal gastric emptying. Synthetic analogues of amylin eg: Pramlintide and GLP analogues can delay gastric emptying. These need to be withdrawn. The next step is to control the glycaemic status well. The diet should be modified to small, frequent meals with less fat which are easier to empty from the stomach than the standard meals. They should be low in fibre to prevent bezoar formation. If adequate calories is difficult to administer, then liquid caloric supplementation with a low fibre version is well tolerated. Nausea and vomiting can be treated with prochlorperazine. Metoclopramide 10mg oral 4 times daily improves gastric emptying by about 26%. Long term side effect is tardive dyskinesia. Erythromycin works on motilin receptors. It is a powerful prokinetic, however, after a few days of use, its effect wears off rapidly because of tachyphylaxis. Lower doses of the drug eg: 125mg t.i.d works better than higher doses. Gastric pacing is a new modality of treatment which delivers a slow wave that increases gastric emptying.

Ref: Endocrinology Update, Mayo clinic 2009; 4(3): 6-7.

3.6 Imaging neuroendocrine tumours (NET).

NETs may secrete hormones that cause distinct syndromes, produce non specific symptoms due to mass effect, or remain asymptomatic until incidentally identified. Clinical variables that determine prognosis are – organ of origin, size, local invasion or remote metastasis. Imaging modalities useful for assessing prognosis are anatomical such as **CT or MRI** scanning or functional as with **pentetreotide, MIBG I131** and recently **fluorodopa F 18**. Fludeoxyglucose (FDG) positron emission tomography (PET) and PET CT detects glucose uptake in tumour cells. The more intense the uptake, the more metabolically active and less differentiated the tumour. The presence of somatostatin receptors are reflected by increased areas of intensity by Indium 111 pentetreotide imaging. These add further information of the extent and location of metastases.

Ref: Zalom M.L. et al Endocrine Pract 2009; 15: 521-527.

3.7 Breast cancer screening

The US Preventive Services Task Force (USPSTF) recommended screening mammography every one to two years for all women age 40 or older in 2002. In 2009, the recommendation was updated. It now recommends against routine screening below the age of **49**. It recommends screening mammography for all middle aged women between the ages of 50 – 74.

Ref: Ann.Intern Med. 2009 Nov 17; 151: 716.

3.8 A new treatment for obesity – Liraglutide (L)

L is an incretin mimetic which stimulates glucose related insulin secretion and suppresses appetite in Type 2 diabetic patients. It decreases satiety and causes weight loss. Will it work in non diabetic obese subjects?.

564 obese non diabetic patients – BMI 30 – 40 were randomized to either once daily L , placebo or Orlistat. Patients taking L reduced their weight by 4.8 – 7.2Kg at 20 weeks vs 2.8Kg for placebo and 4.1KG for Orlistat. 5% loss of body weight was seen in 61% of L , 44% of Orlistat and 30% of placebo patients. All these differences were significant. Nausea was seen in 1/3rd of L patients and vomiting in 8%. These occurred mainly in the first 4 weeks of treatment with L.

Comment: Incretin mimetics like L represent an important treatment option for diabetes and might also become a useful adjunct to diet and exercise for weight loss in non diabetics. Disadvantage is in the fact that it should be given by daily injection.

Ref: Astrup A. et al Lancet 2009 Nov 7; 374 : 1606.

3.9 Darbepoetin Alpha (D) in patients with Type 2DM, chronic kidney disease (CKD) and anaemia

4,038 patients of this category- median age 68, GFR 20 – 60ml/mt and Hb < 11.0g/dl were randomized to D or placebo. The target Hb was 13.0g/dl. Patients in the placebo arm received “rescue” D when their Hb levels dropped below 9g/dl. Mean follow up was 29 months. Mean Hb with D was 12.5g/dl vs 10.6g/dl for placebo. Significantly fewer D recipients received red cell transfusions. However the primary end point – a composite of death + CV events + end stage renal disease was the same for both groups. Further more, stroke and thrombotic events were more common with D.

Ref: Pfeffer M.A. N.Engl. J.Med 2009 Nov 19; 361:2019.

3.10 A new treatment for Osteoporosis – anti RANKL agent – Denosumab (D)

RANKL promotes bone resorption. D is an antiresorptive agent by antagonizing RANKL. It is useful in osteoporosis when administered sc in a dose of 60mg every 6 months. It is effective when given for 36 months in reducing vertebral fractures by 62%, N= 1468 men, who had been given androgen deprivation treatment for CA prostate. In Post menopausal osteoporotic women, at 36 months D reduced new vertebral fractures by 68% and hip fractures by 40%. All non vertebral fractures were reduced by 20%.

This agent is more expensive than Zoledronic acid which is administered as an iv infusion in saline over 15 mts once yearly. However it can be self administered and is therefore more convenient

requiring no hospital visit. It also can be given in patients with renal dysfunction (GFR < 30ml/mt), whereas Bisphosphonates are contra indicated.

Side effects due to its anti immune action include Eczema and attacks of cellulitis.

Ref: Khosla S. NEJMed 2009 Aug 20; 361 (8): 818 – 819.

3.11 Is prophylactic bilateral oophorectomy (BO) associated with all cause mortality?

BO is often performed at the time of hysterectomy for benign disease to prevent ovarian cancer. In a prospective observational study, investigators assessed the long term consequences of BO which was performed in 56% of 29,000 women who underwent hysterectomy for benign disease. During 24 yrs of follow up, women who underwent BO had elevated risk for

1. All cause mortality (HR 1.12).
2. Fatal + non fatal coronary heart disease (HR 1.17).
3. Stroke (HR 1.14).
4. Lung cancer (HR 1.26).
5. All cancer mortality (HR1.17).

BO had a lower risk for

1. Breast cancer (HR 0.75).
2. Ovarian cancer (HR0.04).
3. All cancers (HR0.90).

Only 34 of 13,305 women with ovarian conservation died from ovarian cancer during follow up. Investigators estimated that one additional long term death would be expected for every 9 BOs performed. Unfortunately outcomes in the subgroup of women who used oestrogen after BO were not reported.

Comment: These data are consistent with reports that late onset menopause is associated with lower risk for premature death from CHD and stroke. Obstetricians should contemplate seriously the necessity for prophylactic BO and limit this surgery to high risk women.

Ref: Parker W.H. et al (Nurses' Health Study) Obstet.Gynaecol 2009 May; 113: 1027.

3.12 Do oral contraceptives (OCs) contribute to urinary incontinence?

Post menopausal hormone therapy has been associated with elevated risk for urinary incontinence. Is the same true for use of OCs in pre menopausal women. The Nurses Health Study data for nearly 22,000 women (age 37 – 54) were analysed. Use of OCs at any time was found to increase the odds for incidence of incontinence moderately (RR 1.27). Longer duration of use was associated with progressively greater odds of incontinence (P=0.03). Urge incontinence was also associated with ever use of OCs (RR 2.48).

Comment: The mechanism by which urge incontinence is elevated in pre menopausal women and HRT in post menopausal women treated with oestrogens is not known.

Ref: Townsend M.K. et al J. Urol. 2009 May; 181: 2170.
Jakson S.L. and Fihn S.D. IBID : 1989.

3.13 A new adipokine – Chemerin (C)

C is a novel adipocyte secreted factor playing a crucial role in adipocyte differentiation and insulin signalling. It is independently associated with markers of inflammation. Correlations also exist between circulating C and the metabolic syndrome. Levels are also high in patients on chronic haemodialysis. The GFR remains independently associated with elevated C levels. In the associations with the metabolic syndrome- BMI, triglycerides, HDLC, leptin and CRP are the factors associated with elevated C levels.

Ref: Pfau D et al Diabetes Care Jan 2010; 33 (1): 171 – 173.

3.14 Effect of weight loss on diabetics with obstructive sleep apnoea (OSA)

In a study of more than 250 people (mean BMI 37) with OSA (mean apnoea- Hypopnoea index – [AHI], 23 events / hr) and Type 2 DM, researchers assessed whether weight loss affected OSA. Participants were randomized to an intensive weight reduction programme or controls.

At 1 year, the weight reduction group had lost significantly more weight 10.8 vs 0.6 Kg and exhibited a significantly decreased AHI (10 fewer events / hr) compared with the control group . In addition more people in the weight reduction group showed remission of OSA (14 % vs 4%) and the proportion with severe OSA was lower.

Comment: Weight loss in diabetics with obesity and OSA reduced the incidence and severity of OSA.

Ref: Foster G.D. et al Arch.Intern.Med 2009 Sept 28; 169: 1619.

3.15 Hormone therapy in post menopausal women – Does it increase lung cancer mortality?

In the Women's Health Initiative (WHI) in which more than 16,000 post menopausal women with intact uteri were randomized to receive oestrogen + progesterone or placebo – the hormone group had a higher incidence of cardiovascular disease and breast cancer. A post hoc analysis of lung cancer incidence and mortality after 8 years of starting the trial have been now presented.

The incidence of lung cancer in the hormone group began to exceed that in the placebo group after about 5 years and the gap continued to widen, driven entirely by excess non - small cell lung cancers but did not reach statistical significance (HR 1.23). These cancers were more likely to be poorly differentiated and to engender distant metastases.

Comment: Oestrogen receptors are expressed in normal and cancerous lung tissues. The authors suggest that hormone therapy although perhaps not initiating new lung cancers, stimulates more aggressive growth. The absolute risk for lung cancer is small in non smokers but smokers who are considering hormone therapy, even brief courses – should be counselled about this additional risk.

Ref: Chlebowski R.T. et al Lancet 2009 Oct 10; 374: 1243.

3.16 Semen quality and occupational exposure.

Many men with abnormal semen have no identifiable cause. 402 men (age 22 – 55) with infertility without identifiable cause were studied. Only 22% were found to have normal semen analysis (sperm count > 40 million per ejaculate, > 50% progressive motility, > 25% rapid progressive motility and >30% normal morphology).

Exposure to heavy metals (OR 5.4) solvents (OR2.5), various fumes (OR1.9) , polycyclic hydrocarbons (OR 1.9) , pesticides (OR 3.6) or cement (OR2.5) approached significance as important risk factors. Physical risk factors such as mechanical vibration, excessive heat and extended sitting also were associated with sperm abnormalities.

Comment: Exposure and physical risk factors should be looked for in men with poor sperm quality or quantity.

Ref: de Fleurian G. et al J.Androl. 2009 Sept /Oct ; 30: 566.

3.17 Does growth hormone (GH) improve adult height in children born small for gestational age (SGA)?

GH is approved for children above 2 years who were SGA and remain short. A meta analysis of 4 randomized trials in 391 SGA children was undertaken. Half received GH and the other half no treatment, and were followed until adulthood. Therapy started at a mean age of 8.6 yrs and mean duration of 7.3 yrs.

At the end of treatment, height gain was 9.5 cm in the GH group and 1.6 cm in the untreated group. This was statistically significant.

Comment: The cost per cm of height gained was > US \$ 35,000/=. Studies on long term safety of GH are few. Obviously this treatment will be only available for the very wealthy unless State subsidies are available.

Ref: Maiorana A and Cianfarani S. Paediatrics 2009 Sept;

3.18 Hormone replacement therapy (HRT) in post menopausal women – Is there a safe period?

HRT was shown to have unfavourable balance of benefits and harms in the Women’s Health Initiative (WHI) randomized trials for oestrogen and progestin in 2002 and for oestrogen alone in 2004. At enrollment , women in these trials ranged from 50 – 79 years (mean 63) and only about 1/3rd were between 50 – 59.

In subsequent WHI analysis, data trends suggested that HRT did not lead to excess coronary risk when it was started close to menopause. Although this finding did not reach statistical significance, the idea that HRT was safe or even beneficial (from the coronary perspective) when started shortly after menopause gained acceptance and became known as the “timing hypothesis”. It was suggested that health care providers need not be unduly concerned about coronary risk, when they prescribe short term HRT to recently menopausal women for relief of vasomotor symptoms.

To address this “ timing hypothesis”, the WHI researchers have now published new data from both the WHI randomized trials, which involved about 17,000 women and a parallel WHI observational study

of nearly 100,000 women. They calculated the “gap time” between menopause and first use of HRT. They noted trends towards excess risk for coronary artery disease (CAD), venous thromboembolism (VTE) and breast cancer among early users of oestrogen – progestin and trends towards elevated risk for stroke and VTE among early users of oestrogen alone. The authors did not indicate whether the excess CAD events actually occurred during the first several years of HRT use, when the women were still in their 50s or later on. The authors concluded that the unfavourable balance of benefits and risks observed in the oestrogen – progestin trial as a whole also applies to recently menopausal women. There is therefore little support for the oestrogen timing hypothesis concerning CAD risk.

Comment: Clinical research has not identified a window of time after menopause during which HRT can be confidently considered to be free of risk.

Ref: WHI investigators JAMA 2002 July 17; 288:321.

JAMA 2004 Apr 14; 291:1701.

JAMA 2007 Apr 4; 297: 1465.

Prentice R.L. et al Am.J.Epidemiol. 2009 July 1st; 170:12.

IBID : 24.

3.19 Exenatide (E) vs Liraglutide (L) in Type 2 DM.

E and L are incretin mimetics. E requires b.d injections while L is injected once daily. 464 Type 2 DM patients on maximally tolerated doses of metformin, sulphonylurea or both were randomized to either E or L for 26 weeks. At the end of this period, L had a significantly greater mean decline of HbA1c (-0.79% vs 1.12%). L was also significantly more likely to achieve HbA1c levels <7% (43% vs 54%). Mean weight loss and number of adverse events were similar in both groups. This study was funded by the manufacturer of L.

Comment: Both L and a weekly form of E appear to have clinical and convenience advantages over twice daily exenatide. A direct comparison between the weekly injected exenatide LA vs L has not been carried out.

Ref: Buse J.B. et al Lancet 2009 Jul 4; 374:39.

3.20 Does Hormone Replacement Therapy (HRT) elevate risk for ovarian cancer?

In several observational studies, HRT has been associated with elevated risk for ovarian cancer. Danish investigators prospectively followed 900,000 women (age 50 – 79) who had at least one ovary. During mean follow up of 8 years, 2,681 new cases of ovarian cancer were diagnosed. Ovarian cancer was elevated by a highly significant 44% for current users of HRT and by 15% which was barely significant for former users. The risk declined after cessation of HRT and approached baseline values after 2 years. There was no difference in risk between use of oestrogen alone and use of combined oestrogen progesterone and no relation between duration of use and risk. Risk for continuous and cyclical therapy were roughly equal, as were risks for different progesterone preparations. Risk was elevated by 13% for transdermal oestrogen therapy and by 23% for vaginally administered oestrogen. Neither risk differed statistically from that of oral administration. The absolute risk was roughly one extra case of ovarian cancer per 8,300 HRT users.

Comment: HRT is a potential risk factor for ovarian cancer but the absolute risk is low.

Ref: Merch.L.S. et al JAMA 2009 Jul 15; 302:298.

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