Department of Obstetrics and Gynaecology Refresher Course

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NEW EVIDENCE – OLD ANSWERS: MANAGING DIABETES IN PREGNANCY

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In 2006 there are three important questions concerning the management of diabetes in pregnancy, i.e. (*i*) should we screen for gestational diabetes? (*ii*) can we use oral glucose lowering agents? (*iii*) how tightly should blood glucose levels be controlled in pregnant diabetics?

New evidence has emerged over the past few years but this does not differ from the old answers. Despite the hype around evidence based medicine there is still much to be learnt from careful, accurate observations.

The first case describing the complications of gestational diabetes was written by Bennewitz in 1824, whose patient had all the symptoms of diabetes. He described the large infant delivered as 'of such robust and healthy character whom you would have thought Hercules had begotten'. Alas, this 12 lb baby had obstructed labour which resulted in an intrapartum death. Post-delivery he records: 'With nature to preserve and treat her we dismissed our patient cured.' Professor W P U Jackson accurately described the typical infant of a mother with 'pre-diabetes' in the early 1950s. However, in 1989 Hunter and Kierse stated that except for research purposes all forms of glucose tolerance testing should be stopped.

But the Achois trail by Caroline Crowther emphatically showed that gestational diabetes has increased morbidity and even mortality and this can be reversed by appropriate treatment.

In the 1970s Coetzee and Jackson investigated the role of oral glucose-lowering agents in non-insulin dependent pregnant diabetics. It was felt that this would encourage better adherence to treatment and therefore better outcomes. For the developed world who saw mainly type 1 diabetics this was not acceptable. However, randomised trials by Langer *et al.* on glibenclamide and the widespread use of metformin in polycystic ovarian syndrome has altered this perception. A randomised trial centred in New Zealand on metformin will soon be completed and we look forward to further answers.

Lastly, Eric Skipper in 1943 stated categorically that the road forward to better results in pregnant diabetics was through rigid control of maternal blood glucose levels. All the evidence over the last decades supports this statement, but in July 2006 an article in the *BMJ* stated that perinatal mortality and the prevalence of congenital abnormalities was higher in both type 1 + 2 diabetics when compared with the general maternity population. The old answers are being ignored.

In summary both the old and the new clearly indicate the road forward into 2007:

1) Screen for gestational diabetes
2) Do pre-pregnancy counselling and maintain rigid control of maternal blood glucose levels in all pregnant diabetics
3) Metformin can be used in type 2 pregnant diabetics and glibenclamide certainly in gestational diabetics.

Selected abstracts (received by *SAJOG* by 16 November 2006)

THE MENOPAUSE AFTER WHI: HOW TO ADVISE YOUR PATIENT

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Background

The WHI hormone trials were excellent large, randomised placebo-controlled trials of CEE plus MPA and of CEE only in postmenopausal women. In the CEE plus MPA trial the hazard ratios (HRs) of breast cancer, coronary heart disease (CHD), stroke and venous thromboembolus (VTE) were significantly increased and the HRs of total fractures were decreased. In the CEE only trial the HRs of stroke and VTE were significantly increased, total fracture was significantly decreased but there was a non-significant decrease in the HRs of breast cancer and CHD. The absolute, attributable risks were all 'rare' (less than 1/1 000/year) except for the increase in stroke and VTE and the decrease in total factures. After the report of the CEE plus MPA trial in 2002 about 60% of women stopped hormone replacement therapy (HRT) but 30% of these women have subsequently resumed HRT because of intolerable vasomotor symptoms. The women in the CEE-only trial had more risk factors but lower incidence of CHD and breast cancer. The difference in the results of the trials has not been adequately explained but suggests that the addition of progestins to oestrogens may be deleterious. The trials were mainly of 'older' women (70% 60+y), some had existing CHD or hypertension, 30 - 40% were obese and women with vasomotor symptoms were in general excluded. The benefit of the relief of vasomotor symptoms was not taken into account. The benefits and risks of HRT are critically dependent on age, age at menopause and type of therapy and the WHI trials do not in general represent the healthy younger postmenopausal women with symptoms most commonly prescribed HRT.

Current guidelines

Make a 'Medical Judgment' (Leon Speroff) for each patient.

Indications. Vasomotor symptoms, vulval/vaginal atrophy, premature menopause (HRT is not currently indicated for the prevention of chronic disease except in women with a premature menopause and possibly with osteoporosis if under 60y with vasomotor symptoms).

On starting HRT exclude contraindications, assess according to age, reassess annually (<50y benefits >> risks treat all women?, 50y - 60y benefits > risks treat if symptomatic 60y 70y benefits = risks 'individualise'?, >70y risks > benefits HRT contraindicated).

Type of HRT. Oestrogen only if uterus absent. Oestrogen plus progestin if uterus present – cyclical if still menstruating; continuous combined in most postmenopausal women.

Share decision-making, put benefits and risks in perspective, management not static. Most women are prepared to accept a small degree of long-term risk in relation to immediate benefit.

Future management

Trends include lower doses of oestrogen and progestins, increasing use of transdermal administration, use of oral micronised or vaginal progestins. increased use of unopposed oestrogens and continued therapy in women established on HRT. *Dependent on outcome of trials of 'Window Hypothesis' in prevention of CHD* (HRT in 'younger' postmenopausal women (50 - 60y) may prevent development of disease later in life but HRT in 'older' women may be of no benefit or may increase the risk of disease).

Elite RCT start 2004 close out 2009. Two groups of postmenopausal women LMP < 6y or > 10 y before start with and without uterus. Oral oestradiol 1 mg/d and progesterone vaginal gel. End points: carotid artery intimal thickness on ultrasound and neurocognitive function.

KEEPS RCT start 2005 close out 2010. Oral CEE O.45 mg/d **or** transdermal oestradiol patch 50 mcg/d **or** placebo with oral micronised progesterone 200 mg/d 12 d month. Three groups postmenopausal women with intact uterus. End points: Carotid artery intimal thickness, coronary artery calcium accrual and comprehensive assessment. **Come back 2010!**

INFORMED CONSENT AND MATERIAL RISK: EPIDURAL ANALGESIA FOR LABOUR

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Informed consent

The Health Professions Council of South Africa guidelines on informed consent appear in Booklet 15 of their Ethical Practice Guidelines series. These guidelines have drafted into and promulgated in the National Health Act (61 of 2003), which became law in May 2005.

Consent for epidural analgesia (EA) for labour is unique; patients are young and healthy and in addition, the intervention may be regarded as non-essential, and the patient may be in severe distress when required to give consent. Most patients want to know more information than is usually divulged, and supplying this information does not dissuade women from consenting to EA. Neither severe pain nor the prior administration of appropriate doses of sedatives and/or opiates invalidate consent. However, particularly in state hospitals in South Africa, the issues of patient autonomy and competence in this matter are controversial in view of the minimal antenatal education of most patients, and the absence of a structured birth plan. Patients are often first encountered by the anaesthetist when in advanced labour, and limited time is available for explanation. Clearly, it would be beneficial if an explanatory brochure could be supplied to the patients, or the obstetrician could explain the basic facts concerning EA, in the antenatal clinic.

Explanation to the patient

The anaesthetist should obtain written consent from the patient. A minor who is pregnant is often competent, is able to understand, and her opinions on the matter of analgesia should be honoured. The following information should be made available to the patient, optimally in the antenatal period, *couched in terms that each individual can understand:*

1. Requirements include an IV line before, and urinary catheter after the procedure.

2. Concerning *pain relief,* the patient can expect that in experienced hands, 90% of epidural catheters will provide excellent pain relief at the first attempt, which is of a better quality than any other method employed in labour. In 10% of cases, either a patchy block or poor analgesia may arise, requiring intervention in the form of withdrawal of the catheter by 1 - 2 cm, or a top-up with the patient lying on the affected side; failing these manoeuvres, the catheter would be re-sited. There may be some discomfort during the second stage of labour. Only rarely is it not possible to obtain effective pain relief.

3. Some degree of *motor block* may occur (usually minimal with 0.1% bupivacaine continuous infusions, unless there is prolonged administration). The patient will be mobile, but it is not the policy of all units to perform 'walking' epidurals. The motor block will not affect the ability to 'push'.

4. Minor side-effects include: *Hypotension, nausea/vomiting, pruritus, and transient respiratory depression,* which are usually easily treated. *Sedation, shivering, and an increase in body temperature* may also occur. Systemic opiate therapy is not devoid of side-effects.

5. Rare major side-effects are: *Inadvertent high spinal block or IV injection of local anaesthetic agents,* resulting in *arrhythmias, convulsions, or cardiorespiratory arrest.* (Emphasise that the anaesthetist is well equipped to deal with these complications.)

6. EA does not increase the likelihood of *caesarean section.* The second stage of labour may be slightly prolonged, and assisted delivery may be more common.

7. EA results, on average, in better *neonatal blood gas* values than systemic opiates.

8. *Headache* may arise due to inadvertent dural puncture, in < 1% of cases in experienced hands. A combination of conservative management and epidural blood patch, should severe headache arise, will usually cure the problem.

9. No new *backache* will arise as a consequence of epidural anaesthesia *per se.* Should the patient develop backache, nerve root pain, bladder dysfunction or weakness, with or without fever and neck stiffness, this should immediately be reported to the maternity centre, so that epidural haematoma/abscess can be excluded.

10. Permanent *neurological damage* is vanishingly rare.

11. *Sepsis and/or abscess formation* is very rare.

12. The patient should be informed that if a caesarean section is required after conventional epidural or a combined spinal-epidural technique, general anaesthesia is usually not necessary, since local anaesthetic may be added via the epidural catheter to allow for surgery.

After the above information has been conveyed, the patient should be given the opportunity to ask further questions.

There is considerable evidence from the literature to support the above explanation.

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ENDOMETRIOSIS UPDATE

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This update focuses on three areas: the pathopysiology of pain, endometriosis in adolescents and aromatase inhibitors.

The majority of chronic pain sufferers are women, yet studies have shown that women's complaints of chronic pain are taken less seriously and their pain is managed less aggressively when compared to men. Endometriosis is a common finding in women with chronic pelvic pain; however, not all patients with endometriosis experience pain. This raises the question *when* endometriosis causes pain. Current evidence indicates that deeply infiltrating lesions and endometriotic foci in richly innervated areas are consistently associated with pain, but there is inconsistent correlation between the stage of disease and the different appearance of endometriotic lesions and pain. The main mechanism of endometriosis-related pain is through sensory innervation of endmetriotic lesions, but many factors play a role in aggravating pain.

Endometriosis in adolescents can present with cyclical or acyclical pain as well as dyspareunia. Adolescents usually suffer from early stage disease; endometriomas, black lesions and adhesions are uncommon findings. A careful history is required. Clinical findings include abdominal and pouch of Douglas tenderness without the typical findings of endometriosis (i.e. retroverted uterus, POD nodularity, endometriomas). Treatment is directed at pain control, the preservation of fertility and the prevention of disease progression. First line treatment includes combined oral contraceptives and/or non-steroidal anti-inflammatories. Young girls (< 16 years) who fail to respond require laparoscopy by an experienced endoscopic surgeon in order to establish the diagnosis and ablate all endometriotic lesions. Follow-up treatment includes continuous combined oral contraceptive treatment, oral progestogens, pain management and complementary therapy. Young women over age 16 may be treated with GnRHa (with or without add-back therapy) instead of laparoscopy. This approach is not recommended in the younger girl due to concerns relating to bone-loss prior to the age of peak bone density. Long-term follow-up is mandatory in all adolescents diagnosed with endometriosis.

Endometriotic tissue expresses aromatase activity. This local production of oestrogen plays a central role in the process of proliferation and inflammation. Aromatase inhibitors (AI) can interrupt oestrogen production in endometriotic tissue. Clinical studies have demonstrated that treatment with AI is associated with significant pain relief in women with endometriosis who failed to respond to standard medical therapy and/or conservative surgery. Although these data show great promise the results of larger studies and randomised controlled trials are still awaited. The concern has been raised that AIs could be teratogenic when administered at the time of organogenesis. Although a recent multi-centre study failed to show an increased risk of congenital abnormalities in infertile women undergoing ovulation induction with AIs, the teratogenic risk associated with the long-term use of AI in women of reproductive age has not been established.

THE TRAGEDY OF THE MONOCHORIONIC TWIN PREGNANCY

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Although the diagnosis of a twin pregnancy is often greeted with awe and excitement by the parents, the reality of carrying a multiple pregnancy is often less idyllic because of the increased risk of poor outcome due to miscarriage, severe prematurity, growth restriction and congenital abnormalities. Although many of these complications cannot necessarily be completely prevented, the targeted ultrasonographic assessment of twin pregnancies is essential for effective management.

The main contribution has come from accurate determination of chorionicity in the first trimester, which allows triaging of multiple pregnancies for further care and is essential in situations of later diagnosed discordance for abnormalities or growth restriction and their management.

Monochorionic twins are at particularly high risk of compromise, either due to twin-to-twin transfusion syndrome, single *in utero* demise or selective growth restriction and the rare complications of conjoined twins and TRAP sequence. The rational management of these conditions is far better in early pregnancy than later and a variety of procedures or interventions are available these days to optimise the outcome. Serial detailed ultrasonographic assessment of fetal growth and wellbeing, including full fetal Dopplers, is of crucial importance in the assessment of these pregnancies to allow timely detection of problems. Monochorionic twins should be monitored frequently in specialised centres, since initial signs of deterioration can be subtle and easily overlooked.

PERINATAL MENTAL HEALTH IN CONTEXT

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There is an epidemic of perinatal mental health problems in South Africa. This represents a significant unmet public health need with far-reaching consequences for women, infants and communities.

Epidemiology

One in three women in informal settlements such as Khayelitsha suffers from postnatal depression. This is nearly *three times higher* than the usual prevalence in developed countries.

Risk factors

The risk factors associated with perinatal mental health problems are endemic in the setting of socio-economic adversity. These include recent stressful life events; adolescent pregnancy; domestic violence; rape; lack of emotional and logistical support from a partner; and previous mental illness, particularly in the perinatal period and substance abuse. In the local setting, these factors are compounded by the high prevalence of HIV within the community. The vicious cycle is complete as mental disorders exacerbate the circumstances leading to poverty and social adversity.

Consequences

Mental disorders, during and after pregnancy, are associated with serious negative consequences for mothers and their infants. These may be evident in the short term and may persist in the long term.

Antenatal anxiety has a significant impact on the developing fetus, and these effects persist into later childhood. They include organ malformation; premature delivery; low birth weight; neurological impacts e.g. hyperactivity, inattention and behavioral problems and emotional problems.

Depression during pregnancy is associated with an increased risk of low birth weight infants and maternal depression postnatally is associated with infant malnutrition and failure to thrive.

Management

The importance of *screening* for mental illness *in the antenatal period* was highlighted by a recent Confidential Enquiries into Maternal Deaths in the United Kingdom. The report confirmed that suicide is a leading cause of maternal mortality. Notably, in the vast majority of these deaths, there were signs of the mothers' emotional distress in the antenatal period.

When symptoms are untreated, they tend to progress. However, prognosis is improved when management is instituted timeously. For most women, this centres around diagnosis and early detection, counselling using a non-directive, problem-solving approach and antidepressant or anxiolytic medication. Many of the modern antidepressant medications are considered safe during pregnancy and lactation and have shown to be effective in numerous clinical trials.

WHAT IS INSULIN RESISTANCE?

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The polycystic ovary syndrome (PCOS) is the commonest endocrinopathy in women of reproductive years. This condition is categorised by reproductive dysfunction and metabolic disturbances. Insulin resistance is common in PCOS and impacts on the androgen economy and the reproductive dysfunction. It probably influences pregnancy outcome and certainly is associated very strongly with gestational diabetes. Previously the investigation and management of women with PCOS focused on their reproductive needs, but today we recognise that PCOS may result in an increased prevalence of diabetes, dyslipidaemia and coronary artery disease in later life. Because of this, our management of these patients and the way we screen them has, of necessity, changed. Obesity is common in PCOS and worsens the clinical features of this syndrome and impacts significantly on the endocrinopathy. Insulin resistance may be the key metabolic defect in the aetiology and development of PCOS in women with polycystic ovaries. Several mechanisms of action have been proposed including impaired insulin-stimulated glucose uptake, suppression of lipolysis in the muscle and adipose tissue, hepatic glucose over-production and suppression of glycogen synthesis. Obesity, particularly central obesity, impacts on the development of insulin resistance in women both with and without PCOS.

Hyperandrogenism correlates positively with insulin resistance in women with PCOS. This impacts on the disease presentation, the endocrinological abnormalities and the ultimate management of these patients. The diagnosis of insulin resistance may be difficult, but the glucose/insulin ratio is a practical option in routine clinical practice. The long-term consequences of PCOS include metabolic, cardiovascular and neoplastic risk. The metabolic abnormalities are particularly concerning as these may result in increased morbidity in later years. The metabolic syndrome is characterised by abdominal obesity, abnormal lipid profile, hypertension and glucose intolerance and occurs in about 46% of women with PCOS compared with 23% of control subjects. The multiple risk factors for cardiovascular disease include dyslipidaemia, hyperinsulinaemia and hypertension. Insulin resistance may therefore impact on long-term mobility and mortality. Women who present with PCOS need careful assessment. In those with an elevated BMI, ongoing follow-up is mandatory. Appropriate counselling must be offered to siblings and daughters of women with PCOS. Therapy usually concentrates on the presenting clinical problem but the long-term consequences of the condition and management into the menopause and beyond are of considerable importance.