Management of osteoporosis

Osteoporosis is a progressive systemic skeletal disease characterised by low bone mass and deterioration of bone microarchitecture leading to decreased bone strength, and increased susceptibility to fracture, especially of hip, spine, and wrist [1]. For diagnostic purposes, WHO has defined osteoporosis using bone mineral density (BMD) (table 1).

Table 1. WHO diagnostic categories for BMD in post-menopausal caucasian women

1. Normal: BMD not more than 1 SD below the peak bone mass or young adult mean (T-score > -1).
2. Osteopenic: BMD between 1 and 2.5 SD below the young adult mean (T-score -1 to -2.5).
3. Osteoporosis: BMD 2.5 SD or more below the young adult mean (T-score ≤ -2.5).
4. Severe osteoporosis (established osteoporosis): BMD 2.5 SD or more below the young adult mean (T-score ≤ -2.5) and the presence of one more fragility fractures.

BMD: bone mineral density; SD: standard deviation.

As ageing and oestrogen deficiency are major contributors to bone loss, osteoporosis mostly affects post-menopausal women. In the UK, osteoporotic fractures affect one in two women and one in five men over the age of 50 years [1]. In Sri Lanka about 60% of women over the age of 50 years have osteoporosis [2].

Osteoporotic fractures have profound effects on the victim, leading to chronic pain, immobility, loss of independence and increase in mortality. With an ageing population worldwide, osteoporosis has costly implications for public health [3]. Prevention of osteoporosis is important for both the individual and the society.

How do we identify those at risk?

Osteoporosis is greatly under-diagnosed as it is usually asymptomatic till a fracture occurs. Early diagnosis is important in preventing fractures and the ensuing complications.

Many factors predispose to osteoporosis (table 2), and individuals at high risk require further evaluation with measurement of BMD. Age over 65 years, fragility fracture after the age of 40 years, family history of osteoporotic fracture (especially maternal hip fracture), and systemic glucocorticoid therapy for over 3 months are key risk factors identifying people requiring BMD measurement [4].

Table 2. Risk factors for osteoporosis

Major risk factors	Minor risk factors
Age 65 years or over	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40 years	Chronic anticonvulsant therapy
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy >3 months	Smoker
Malabsorption syndromes	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Chronic heparin therapy
Osteopenia apparent on xray film	Weight loss of 10% of weight at age 25
Hypogonadism	
Early menopause <45 years	

What is the use of xrays?

Spine xrays remain the best method for identifying vertebral fractures. The presence of a vertebral fracture increases the risk of a second vertebral fracture by at least 4-fold in 3 years. Post-menopausal women with a past height loss >6 cm, prospective height loss >2 cm, kyphosis or acute incapacitating back pain require spine radiographs to rule out vertebral fractures [4].

What are the management options available?

Preserving bone health needs achievement of optimal bone mass, prevention of bone loss, preserving structural integrity of the skeleton and prevention of fractures [3]. Both non-pharmacological and pharmacological measures are available to improve BMD.

Non-pharmacological measures

A diet rich in calcium and vitamin D, regular weight-bearing exercise (eg. walking), and abstaining from smoking and alcohol contribute to achieving an optimal peak bone mass in the young adult, and retaining bone mass afterwards. It is important to encourage these lifestyle measures in everyone, from childhood onwards, throughout life [1].

Pharmacological interventions

There are many pharmacological agents to prevent osteoclastic bone resorption (eg. bisphosphonates, selective oestrogen receptor stimulators, hormone replacement therapy and calcitonin). Newer agents (eg. parathormone and strontium ranelate) stimulate osteoblasts to increase bone formation (table 3).

Table 3. Pharmacological interventions for osteoporosis

Intervention	Dosing regimen	Route of administration
Alendronate	Treatment: 70 mg once weekly, or 10 mg once daily Prophylaxis: 35 mg once weekly or 5 mg once daily	Oral
Etidronate	400 mg daily for 2 weeks every 3 months	Oral
Ibandronate	150 mg once monthly	Oral
	3 mg once every 3 months	Intravenous injection
Risedronate	35 mg once weekly, or 5 mg once daily	Oral
Raloxifene (SERM)	60 mg once daily	Oral
Strontium ranelate	2 g once daily	Oral (sachet)
Teriparatide	20 µg once daily	Subcutaneous injection
Calcitonin	200 IU once daily	Nasal spray

Routine dietary supplementation with calcium (1000-1500 mg daily) and vitamin D (800 IU daily) is recommended as an adjunct to the main pharmacological therapy [4].

- **Bisphosphonates**

These are the best anti-osteoporotic medication currently available, reducing both vertebral and non-vertebral fracture risk by 50%. Etidronate is only effective in preventing vertebral fracture. Alendronate, etidronate, ibandronate and risedronate are approved for treating post-menopausal osteoporosis; alendronate, etidronate, ibandronate and risedronate for glucocorticoid-induced osteoporosis, and alendronate for treating osteoporosis in men [5]. Zoledronate is safe and effective at once-yearly doses, making this a very attractive treatment option [6].

Bisphosphonates are well tolerated except for upper gastroesophageal side-effects. These could be avoided by taking the tablet fasting with a full glass of water, and maintaining an erect posture without taking food or drink for the next 30-60 minutes [5].

- **Hormone replacement therapy (HRT)**

Estrogen inhibits bone resorption and HRT reduces the risk of both vertebral and non-vertebral fractures by 30%. However, HRT increases the risk of breast cancer, cardiovascular disease and thromboembolism[7]. Hence HRT is not recommended solely to treat osteoporosis. For post-menopausal women choosing HRT as a therapeutic option, its anti-fracture effect is an added benefit [5].

- **Selective oestrogen receptor modulators (SERMs)**

SERMs reduce the risk of vertebral fractures but not of non-vertebral fractures. They have a protective effect on breast cancer, with up to 90% risk reduction in oestrogen receptor-positive breast cancer [4]. Adverse effects include flushing, cramps and thromboembolism. SERMs are useful as a second-line option for young post-menopausal women with an increased risk of vertebral fractures.

- **Calcitonin**

Calcitonin reduces the risk of vertebral fractures, but not of non-vertebral fractures. It has a potential analgesic effect which is beneficial in treating post-menopausal osteoporosis, especially in those with painful acute vertebral compression fractures [8].

- **Parathyroid hormone (PTH)**

Intermittent injections of PTH stimulate osteoblasts. Teriparatide (recombinant PTH) given as a daily subcutaneous injection, prevents both vertebral and non-vertebral fractures. PTH injections have caused ostoesarcoma in rats, though no such effect has been reported in humans [8]. Teriparatide should not be used in people with other metabolic bone diseases and malignancies. It is currently recommended to treat severe osteoporosis, in patients who are unable to take bisphosphonates or show a poor response to other anti-osteoporotic medications [4].

- **Strontium ranelate**

Strontium ranelate reduces the risk of both vertebral and non-vertebral fractures in post-menopausal women. Adverse effects are mild and include headache and diarrhoea. It is useful in those who are intolerant of bisphosphonates [5].

Who should be treated?

The 10-year fracture risk can be assessed using BMD and clinical risk factors. Those at moderate risk (10-20%) or high risk (>20%) require pharmacological interventions [4]. An easy way is to offer pharmacological therapy if there is osteoporosis (T score < -2.5) or osteopenia (T score between -1 and -2.5) plus a major clinical risk factor. Therapy with bisphosphonates should be initiated in patients receiving or planning to receive prednisolone 7.5 mg or more per day (or equivalent) for >3 months [3]. Calcium supplementation may be beneficial for all women in Sri Lanka, as our traditional diet is not rich in calcium.

How long should the treatment be continued?

Calcium and vitamin D could be continued indefinitely. Treatment with teriparatide is limited to 18 months. Bisphosphonates are safe and effective up to 10 years. No data are currently available regarding other anti-osteoporotic medication [4].

What is the role of combination therapy?

Combination of antiresorptive therapy increases BMD. Since no data are available regarding fracture risk reduction, combination therapy is not recommended [8].

How can we monitor response to therapy?

Central dual energy xray absorptiometry (DEXA) of lumbar spine and hip may be repeated every 1-3 years to assess response to pharmacological therapy [4].

Conclusions

Osteoporosis and osteoporotic fractures are major health concerns for post-menopausal women and older men [9]. People at high clinical fracture risk require evaluation of BMD with DEXA. Many drugs are effective in fracture risk reduction, in combination with calcium and vitamin D, and most of these medications are available in Sri Lanka at affordable prices. Treatment should be individualised according to patients' needs and response should be assessed with DEXA every 1-3 years.

References

1. Reginster JY. Prevention of post-menopausal osteoporosis with pharmacological therapy: practice and possibilities. *Journal of Internal Medicine* 2004; **255**: 615-28.
2. Siribaddana S, Lekamwasam S. *Clinical Calcium* 2004; **14**: 128-33.
3. AACE Osteoporosis Guidelines. *Endocrine Practice* 2003; **9**: 544-64.
4. Canadian Consensus Conference on Osteoporosis, 2006 Update. *Journal of Obstetrics and Gynaecology Canada* 2006; **28**: S95-S112.
5. Poole KES, Compton JE. Clinical review: osteoporosis and its management. *British Medical Journal* 2006; **333**:1251-6.
6. Rossouw JE, *et al*. Risks and benefits of estrogen plus progestin in healthy post-menopausal women: principal results from the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association* 2002; **288**: 321-33.
7. Black DM, et al, for the HORIZON Pivotal Facture Trial. Once-yearly zoledronic acid for treatment of post-menopausal osteoporosis. *New England Journal of Medicine* 2007; **356**: 1809-22.
8. Rosen CJ. Postmenopausal osteoporosis. *New England Journal of Medicine* 2005; **333**: 595-603.
9. Ebeling PR. Osteoporosis in men. *New England Journal of Medicine* 2008; **268**:1474-82.

Dr. Piyusha Atapattu, MBBS, MD (Col), MRCP (UK). *Senior Lecturer in Physiology, Faculty of Medicine, University of Colombo.*

E-mail: <piyushaatapattu@yahoo.com>.

Benign breast disorders

Benign breast diseases are non-malignant breast disorders which comprise over 90% of referrals to breast clinics. They should be managed appropriately after exclusion of malignancy.

Breast lump

Breast lumps comprise over 60% of referrals to breast clinics. Over 90% of breast lumps are benign and the majority of them do not require surgery [1].

Fibroadenoma

Fibroadenomas are aberrations of breast tissue development. They occur due to an exaggerated response of the lobules and stroma of the breast to hormonal stimuli. They are common from adolescence to the mid-twenties and affect 7-13% of women in this age group.

Fibroadenomas are usually firm, rubbery, mobile lumps. Diagnosis is by triple assessment. Lumps less than 4 cm are likely to regress or remain unchanged. These lumps do not require excision. Lumps larger than 4 cm are excised especially if phyllodes tumour is suspected.

Cysts

Cysts are distended involuted lobules, and comprise about 15% of all discrete breast lumps. They have a higher prevalence in pre-menopausal women and persist after menopause if they use hormone replacement therapy. Cysts are smooth discrete lumps which are sometimes

painful, and readily diagnosed by ultrasound scanning. Aspiration is both diagnostic and therapeutic. After aspiration the breast should be re-examined to ensure complete resolution.

Nodularity

Focal nodularity is the commonest cause of a breast lump and may occur in women of all ages. The range of histological features varies from a predominance of ducts, lobules and stroma, to features of fibrous change, sclerosis, and cyst formation.

Other lumps

Lipomas are common in the breast. They are soft, lobulated and radiolucent. Haematomas of the breast commonly follow trauma but can also occur after needle aspiration or core biopsy. Rarely, a carcinoma may manifest as a spontaneous haematoma. Fat necrosis following trauma may form a lump but there is no history of trauma in 60% of cases.

Nipple discharge

Although this symptom is particularly distressing to patients, only about 5% of them are found to have serious underlying disease. Nipple discharge is considered to be pathologic if it is spontaneous, arises from a single duct, is persistent, and contains gross or occult blood. Age is an important risk factor of malignant disease.

A discharge in the absence of galactorrohea is considered to be ductal in origin and classified as either uniductal or multiductal. When the discharge is from one duct, and particularly if it is grossly bloody or the results of testing for occult blood are positive, further investigations are needed.

Ductal exploration allows the removal of pathologic lesions and cessation of the discharge. Multiductal discharge that is clear, serous, green-black, or non-bloody requires only reassurance of the patient. Blood arising predominantly from one or two ducts should be evaluated further [2].

Breast pain

Cyclic breast pain usually occurs during the late luteal phase of the menstrual cycle, in association with the pre-menstrual syndrome or independently, and resolves at the onset of menses [3]. Breast pain interferes with sexual activity and less commonly with activities such as social and school activities [4].

The most important issue in the management of cyclic breast pain is to decide whether to treat. In the absence of a mass or discharge, mild symptoms warrant reassuring the patient regarding the absence of serious disease. Precise fitting of a brassiere to provide support for pendulous breasts may provide pain relief. No standard regimen for moderate to severe breast pain has been widely accepted. Initial recommendations include the use of mild analgesics such as paracetamol, or non-steroidal anti-inflammatory drugs (NSAIDs) [5]. Other drugs are used in the management of mastalgia.

Tamoxifen is effective at a daily dose of 10 mg. It is associated with fewer side-effects than danazol. However, long term use is associated with a risk of deep vein thrombosis and endometrial cancer.

Danazol inhibits pituitary gonadotrophins. It combines androgenic activity with anti-oestrogenic and anti-progestogenic activity. Restricting use to the luteal phase reduces side-effects. **Bromocriptine** is a dopamine agonist which effectively treats breast pain but side-effects are common. Hence, it is rarely used. **Evening primrose oil** has also been used, but recent trials question its efficacy [6]. **Gonadotropin-releasing hormone agonists** eg. goserelin have been used successfully for severe pain [7].

Non-cyclic breast pain is unrelated to the menstrual cycle. Detection of focal tenderness suggests a tender cyst, rupture through the wall of an ectatic duct, or a particularly tender area of breast nodularity. Acute enlargement of cysts and periductal mastitis may cause severe localised pain with a sudden onset.

Non-breast pain

Pain arising from the chest wall may be mistakenly attributed to the breast. Pain that is limited to a particular area and characterised as burning or stabbing in nature may arise from the chest wall. Several types of pain can be distinguished, including localised or diffuse lateral chest wall pain, radicular pain from cervical arthritis, and pain from Tietze's syndrome (costochondritis).

Panel 1. Drugs used in the treatment of mastalgia

Paracetamol
Non-steroidal anti-inflammatory drugs
Tamoxifen
Danazol
Bromocriptine
Evening primrose oil
Goserelin

References

1. Codd R, Gateley CA. Management of benign disease of the breast. *Surgery* 2007; **25**: 266-9.
2. Falkenberry SS. Nipple discharge. *Obstetric and Gynecological Clinics of North America* 2002; **29**: 21-9.
3. Goodwin PJ, Miller A, Del Giudice ME, Ritchie K. Breast health and associated pre-menstrual symptoms in women with severe cyclic mastopathy. *American Journal of Obstetrics and Gynecology* 1997; **176**: 998-1005.
4. Ader DN, Browne MW. Prevalence and impact of cyclic mastalgia in a United States clinic-based sample. *American Journal of Obstetrics and Gynecology* 1997; **177**: 126-32.
5. BeLieu RM. Mastodynia. *Obstetric and Gynecological Clinics of North America* 1994; **21**: 461-77.
6. Blommers J, de Lange-De Klerk ES, Kuik DJ, Bezemer PD, Meijer S. Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double-blind, controlled trial. *American Journal of Obstetrics and Gynecology* 2002; **187**: 1389-94.
7. Mansel RE, Goyal A, Preece P, et al. European randomized, multicenter study of goserelin (Zoladex) in the management of mastalgia. *American Journal of Obstetrics and Gynecology* 2004; **191**: 1942-9.

Dr. Ishan De Zoysa, MBBS (Col), MS (Col), FRCS (Eng), FRCS (Edin), *Senior Lecturer in Surgery, Faculty of Medicine, University of Colombo.*

E-mail: Ishandz@hotmail.com

Management of hump-nosed viper bite in Sri Lanka

Introduction

Hump-nosed viper bite is the commonest venomous snakebite in Sri Lanka [1]. Very often it only causes local pain and swelling at the site [2,3]. However, systemic effects are increasingly recognised some of which have been fatal [2,3,4,5]. Consequently hump-nosed viper is no longer considered to be a moderately venomous snake. It is now classified as a highly venomous snake along with cobra, krait, Russell's viper and saw scaled viper [6]. In hump-nosed viper bite, unlike in the other species of snakes in this group, the occurrence of systemic effects is rare and unpredictable. It is the rarity as well as the unpredictability of the sporadic appearance of these potentially fatal systemic effects of envenoming by the hump nosed viper that have made it one of the most important species of venomous snakes. The problems of management of these systemic effects, other than poor predictability, are compounded by the non-availability of antivenom serum (AVS) specific for hump-nosed viper.

Local effects

The most consistent effects of envenoming are local pain and swelling at the site [2]. In addition some patients develop a haemorrhagic blister at the site, and less commonly regional tender lympadenopathy. These signs when present are extremely useful for the identification of the biting snake when the specimen is not available for inspection.

Panel 1

* Management of local effects requires only paracetamol.
* The routine use of non-steroidal anti-inflammatory drugs and antibiotics for local swelling is not recommended.
* Do not mistake haemorrhagic blisters for gangrene.
* Surgical referral should be avoided.
* Currently available AVS should not be used even for severe local swelling.

Systemic effects of envenomation

Coagulopathy is the commonest and most important systemic effect contributing to morbidity and mortality. Clinical effects of coagulopathy are variable and range from a mere prolongation of the clotting time to excessive fibrinolysis and disseminated intravascular coagulation (DIC), which reflects its complexity and variability in the balance between procoagulant and fibrinolytic activity in envenomed patients [4,8]. An important but rare systemic effect is nephropathy. DIC is implicated in the pathogenesis of acute renal failure (ARF) [8]. Coma and ophthalmoplegia occur very rarely.

Management

The majority of patients require only paracetamol as an analgesic for the local pain and swelling which all envenomed patients develop. Neither swelling nor haemorrhagic blisters at the bite site should be treated with antibiotics. It is a chemical inflammation, which resolves spontaneously. The haemorrhagic blisters are often mistaken for gangrene, particularly when they develop at sites related to toes and fingers, and inappropriate surgical referral can lead to unnecessary surgical debridement of tissue. This diagnostic pitfall can easily be avoided by careful examination of the bite site and attention to detail. It will then be clearly discernible that it is the colour imparted by altered blood underlying the thin layer of skin epithelium that gives the appearance of gangrene.

Currently available AVS in Sri Lanka is imported from India and uses in its preparation the venom from Indian species of cobra *(Naja naja naja*), common krait *(Bungarous caeruleus*), Russell's viper (*Daboia russelli russelli*) and saw scaled viper (*Echis carinatus*). As such AVS should not be used whatever the severity of envenoming as hump-nosed viper bite is not used in its preparation [9].

All envenomed patients should be observed for at least 48 hours for the development of coagulopathy as evidenced by a positive 20WBCT, and if the test is positive they should be selected for intensive monitoring and aggressive therapy aimed at the prevention, early detection and treatment of DIC, thereby diminishing the risk of acute renal failure (ARF). Prolonged or recurrent coagulopathy has been described in North American pit viper bites [7]. All patients who have no systemic effects at the time of admission should be advised at the time of discharge to seek immediate admission to hospital should there be any delayed bleeding manifestations, particularly haematuria (panel 2).

Panel 2

1. Patients who only have local effects should be observed for 48 hours for the development of coagulopathy.
2. Coagulopathy is detected by serial estimations of 20WBCT every 4-6 hours.
3. If there is no coagulopathy, warn them at the time of discharge to get readmitted immediately if haematuria develops.

(WBCT= whole blood clotting time)

Monitoring entails measurements of pulse rate, blood pressure, respiratory rate, urine output, and platelet count. Thrombocytopenia in association with a positive 20WBCT in this clinical setting implies DIC and should be treated as such. Determination of APTT, PT, D dimers, fibrinogen degradation products, and fibrinogen assays will only serve to increase the precision of the diagnosis. In resource poor settings where snake bite is common, none of these tests are necessary to manage the patients. These tests can raise the cost of management, and delay interventions causing disastrous and often fatal consequences (panel 3).

Panel 3

1. The first 24-48 hours after the onset of coagulopathy is a critical phase.
2. Patients require close monitoring and aggressive intervention to prevent ARF.
3. Infuse 2-3 l isotonic saline over 24 hrs.
4. Consider FFP if an abnormal 20WBCT is associated with thrombocytopenia (platelet count <100000).
5. Currently available AVS should not be used.

(FFP = fresh frozen plasma)

Patients selected for aggressive interventions on the basis of a positive 20WBCT should receive 2 to 3 litres of isotonic saline over 24 hours to ensure adequate urine output ie. 1 ml / kg body weight/hour. Incremental doses of 3 units of fresh frozen plasma (FFP) are utilised to counter DIC.

Early (within the first 24-48 hours) intervention with intravenous fluid and FFP will serve to improve outcome and prevent ARF and mortality. What is required is an aggressive dynamic approach to management of the

patients who develop coagulopathy. The precise timing of interventions, its dosing and termination should be dictated by clinical judgement, urine output, and serial estimations of the clotting time and platelet counts.

If FFP is not available, patients who develop coagulopathy should be transferred immediately to a centre where this is available. Early intervention is of crucial importance. A delay of 24 to 48 hours can adversely affect the outcome. Similarly those who develop ARF should be transferred early to a centre with facilities for haemodialysis.

Conclusion

I strongly advocate the use of FFP at the earliest sign of coagulopathy. I have used it for hump-nosed viper bite over the past 15 years on the premise that early correction of coagulopathy by replenishment of clotting factors could arrest the cascading vicious cycle leading to DIC, and the consequent depletion of clotting factors and platelets. Additionally fibrin degradation products will perpetuate the bleeding tendency by its antihaemostatic effects. Fibrin deposition in the renal microcirculation will contribute to ARF [8]. In the prevailing circumstances this seems to be the most logical therapeutic option available to clinicians to reduce mortality from hump-nosed viper bite until the availability of species specific AVS.

References

1. De Silva A, Ranasinghe L. Epidemiology of snakebite in Sri Lanka. *Ceylon Medical Journal* 1983; 2**8**: 144-54.
2. Sellahewa K. Lessons from four studies on the management of snakebite in Sri Lanka. *Ceylon Medical Journal* 1997; **42**: 8-15.
3. Sellahewa KH, Kumararatne MP. Envenomation by the hump-nosed viper (*Hypnale hypnale*). *American Journal of Tropical Medicine and Hygiene* 1994; **51**: 823-25.
4. Premawardena AP, Seneviratne SL, Gunatilake SB, de Silva HJ. Excessive fibrinolysis: the coagulopathy following Merrem's hump-nosed viper bite (*Hypnale hypnale*). *American Journal of Tropical Medicine and Hygiene* 1998; **58**: 821-23.
5. Kularatne SAM, Ratnathunga N. Severe systemic effects of Merrem's hump-nosed viper bite. *Ceylon Medical Journal* 1999; **44**: 169-70.
6. Simpson ID, Robert L, Norris MD. Snakes of medical importance in India: is the concept of "Big 4" still relevant and useful? *Wilderness and Environmental Medicine* 2007; **18**: 2-9.
7. Boyer LV, Seifert SA. Fatal recurrent and persistent coagulopathy following pit viper envenomation. *Archives of Internal Medicine* 1999; **57**: 706-10.
8 De Silva A, Wijekoon ASB, Jayasena L, Abeysekera CK, Cheng-Xin, Bao Hutton RA, Warrel DA. Haemostatic dysfunction and acute renal failure following envenoming by Merrem's hump-nosed viper (*Hypnale hypnale*) in Sri Lanka: first authenticated case. *Transactions of the Royal Society of tropical Medicine and Hygiene* 1994; **88**: 209-12.
9. Sellahewa KH, Gunawardena G, Kumararatne MP. Efficacy of antivenom in the treatment of severe local envenomation by the hump-nosed viper (*Hypnale hypnale*). *American Journal of Tropical Medicine and Hygiene* 1995; **53**: 260-2.

Dr. K H Sellahewa, MBBS, MD, FCCP, FRACP (Hony), *Consultant Physician, National Hospital of Sri Lanka, and Chairman Snakebite Committee of the Sri Lanka Medical Association.*

E-mail: kolithah@eureka.lk

Urinary incontinence

Introduction

Urinary incontinence defined as involuntary leakage of urine is common. It reduces the quality of life including that of sexual health, hence proper management of urinary incontinence is restorative. But all leakage of urine is not bothersome. Medicalisation of symptoms which are not bothersome to patients and for which they are well adjusted should be avoided. Giving undue prominence to minimal symptoms and setting unrealistic therapeutic goals is not wise as most pharmacological measures and surgical interventions carry significant risks.

Pathophysiology

Urinary continence is maintained by a coordinated effort between the bladder, urethra, pelvic muscles and the surrounding connective tissue. The function of the lower urinary tract is to store (storage phase) and expel (voiding phase) urine. Continence depends on a bladder that is able to expand while maintaining a relatively constant low pressure in the absence of involuntary contractions. Urinary incontinence occurs when there is dysfunction in the storage function or less commonly in the voiding function of the lower urinary tract. Urethral sphincter dysfunction and bladder dysfunction can co-exist and various components of the continence mechanism may compensate one another [1]. For example, women may experience anatomical or neuromuscular injury during childbirth but remain asymptomatic until there is weakness of the urethral sphincter due to ageing.

Types of urinary incontinence

Urinary incontinence can be divided into several types. These are stress, urge, mixed, overflow, anatomical, and functional incontinence. Stress urinary incontinence (SUI) is involuntary leakage on exertion, sneezing or coughing. It is the result of weak pelvic floor muscles, poor intrinsic sphincter function or increased urethral mobility. Urge urinary incontinence (UUI) is involuntary urinary leakage accompanied by or immediately preceded by urgency (a sudden strong need to void), and it results from detrusor overactivity. Mixed incontinence is the combination of stress and urge incontinence. Women with mixed incontinence can have both stress and urge symptoms during the same incontinence episode or as discrete episodes of stress or urge incontinence. SUI is the common type of incontinence in younger women [2]. As women age, UUI becomes common.

Overflow incontinence is associated with over-distension of the bladder caused by bladder outflow obstruction or neurological bladder dysfunction. Recent onset nocturnal enuresis is a characteristic symptom of this group of patients which helps to make a quick clinical diagnosis [3]. Anatomical incontinence occurs with anatomical defects eg. vesico-vaginal fistula, uretero-vaginal fistula, ectopic ureter, and ectopia vesicae. These patients leak urine continuously. Functional incontinence results from cerebral and cognitive problems or mobility difficulties.

Patient assessment

General therapeutic measures such as lifestyle modifications and behavioural treatments are common to all types of incontinence. But it is important to identify the type of urinary incontinence because certain treatment options vary according to the type. The aims of assessing the incontinent patient are to identify the type of incontinence, degree of disability, and the potentially modifiable contributing factors.

The history should include the nature of symptoms, obstetric history, coexisting diseases (eg. parkinson disease, stroke, dementia, diabetes, arthritis), previous medical history (eg. pelvic surgery, pelvic irradiation, pelvic malignancies, medications, spinal problems), functional status (eg. wheelchair-bound, bed-ridden), and lifestyle issues (fluid intake, hours of sleep, travelling, job related issues). Proper clinical assessment is crucial to the diagnosis of type of incontinence. A variety of questionnaires are available to help differentiate these conditions, but their relevance and validity in Sri Lankan patients is questionable because of educational, social, and cultural differences. Simple questions tailored to the individual patient are more appropriate, and have high reliability.

Physical examination is important as it may detect modifiable factors or associated conditions and help identify the type of incontinence. It includes a general, abdominal, gynaecological, rectal, and neurological examination. Special manoeuvers such as the stress test can be done if necessary. It involves observation for urine leak with coughing. Evaluation of associated problems such as haematuria, recurrent urinary tract infections, and renal impairment take precedence over incontinence when these are present.

Another component of the assessment of the incontinent patient is measurement of the post-void residual urine volume by ultrasonography, a bladder diary, and urine analysis. A post-void residual volume over 150- 200 ml on two occasions is considered significant and indicative of inadequate bladder emptying [4]. A bladder diary which measures volume and type of fluid consumed, the frequency and volume of urine passed, and the circumstances related to urine leak should be completed by the patient or carer. Normal voided volume ranges from 200-400 ml, and normal daily voiding frequency ranges from 8 to 12, with one void per night [5]. Bladder diary maintained for 3 days is adequate, and helps to assess the incontinence. It may also be used to assess the effectiveness of treatment.

Urodynamics to evaluate bladder stability, bladder capacity, voiding function, pelvic floor and urethral mobility are not routinely indicated [4]. Most therapeutic measures can be initiated based on wise clinical judgment and the basic, non-expensive tests described above. A few patients with complex problems may benefit from urodynamics.

Treatment

At the end of the assessment the patient should be told about the problem and the goals and expectations of treatment. Remember that absolute dryness is not essential as a goal of treatment and that not all leakage is bothersome to the patient. Hence the discussion should aim at setting realistic goals and expectations of treatment. Using the information gathered from the voiding diary the patient can be advised regarding reducing fluid intake at relevant periods of the day, more frequent voids in patients who wait too long between voids, and identifying and avoiding triggers to incontinence episodes.

Reducing weight in obese individuals is helpful in some. Although commonly recommended, cessation of smoking, and reduction of caffeine intake have no proven efficacy in urinary incontinence. Relieving constipation is useful especially in children and disabled patients with urinary incontinence. Many anxious young men complain of a few drops of urine leaking after voiding. This is generally physiological, and no intervention is necessary apart from reassurance. Absorptive devices such as pads play an important role in the treatment of urinary incontinence. Specific incontinence pads and devices are better but more expensive [5].

Pelvic floor exercises (contraction of the pelvic floor musculature) are useful as first-line treatment of SUI. Proper coaching is necessary for effective pelvic floor exercises. Duloxetine, a serotonin and noradrenaline re-uptake inhibitor approved for the treatment of depression, is useful in the treatment of moderate to severe SUI especially when combined with pelvic floor exercises [6]. It reduces frequency of episodes of SUI. Minor adverse effects such as nausea are common but tolerable. Post-menopausal oestrogen treatment is no longer recommended for SUI [7]. Surgical procedures for SUI include Burch colposuspension and the fascial sling. Minimally invasive sling procedures have more recently been introduced. Tension-free vaginal tape (TVT), now widely used, is one example. A modification of the technique involves placement of the polypropylene mesh through the obturator foramen. The tape kits used in minimally invasive sling procedures are expensive but cheaper alternatives made locally are available. All surgical procedures for SUI carry risks, including voiding dysfunction, increased risk of urinary tract infection, and treatment failure.

Antimuscarinic drugs (propantheline, oxybutynin, tolterodine, derifenacin and solifenacin), bladder training, neuromodulation and botulinum toxin A detrusor injection are useful in the management of UUI. Bladder training is non-invasive, inexpensive, and easy. This includes pelvic floor muscle exercises and a scheduled voiding programme with gradual increase in the duration between voids. Antimuscarinic (anti-cholinergic) drugs reduce the involuntary contractions of the bladder and are useful in UUI. Propantheline and tricyclic antidepressants are cheap but side-effects are common. Flavoxate has less side-effects but is also less effective. Toltoredine and derifanacin are more uroselective, and have a better side-effect pattern [8]. A modified-release preparation and transdermal patches of oxybutynin have been introduced, and are claimed to have less side-effects. Antimuscarinic drugs should be used with caution in the elderly because of unacceptable side-effects. Patients with associated poor bladder emptying may develop worsening of symptoms and urinary retention. Patients who do not respond, or have disabling symptoms of UUI can be offered major surgical procedures such as bladder augmentation or substitution, or urinary diversion.

The cause of inadequate bladder emptying should be identified and corrected in patients with overflow incontinence. Patients with neurological bladder dysfunction, or who are unfit for major surgery, can be trained to perform clean intermittent catheterisation. Patients with anatomical causes for urinary incontinence require corrective surgery eg. repair of fistula, ureteric reimplantation, urinary diversion.

A minority of patients with urinary incontinence who fail to respond to any of these may require external appliances or indwelling catheters as a last resort.

References

1. Santiagu SK, Arianayagam M, Wang A. Urinary incontinence – pathophysiology and management outline. *Australian Family Physician* 2008; **37**: 106-10
2. Holroyd-Leduc JM, Tannenbaum C, Thorpe KE, Straus SE. What type of urinary incontinence does this woman have? *JAMA* 2008; **299**: 1446-56.
3. Abeygunasekera AM, Jayasinghe RJ, Duminda MT, Chamintha TH, Guruge RW. Significance of recent onset nocturnal enuresis in adult men: a prospective study. *Ceylon Medical Journal* 2004; **49**: 79-81.
4. Rogers RG. Urinary stress incontinence in women. *New England Journal of Medicine* 2008; **358**: 1029-36.
5. Fitzgerald MP, Stablein U, Brubaker L. Urinary habits among asymptomatic women. *American Journal of Obstetrics and Gynecology* 2002; **187**: 1384-8.
6. Thuroff J, Abrams P. Guidelines on urinary incontinence. In: *Pocket Guidelines of European Association of Urology* 2006; 131-41.
7. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T. Postmenopausal hormones and incontinence: the heart and estrogen/progestin replacement study. *Obstetrics and Gynaecology* 2001; **97**: 116-20.
8. Drugs for urinary frequency, enuresis and incontinence. British National Formulary, Number 52. BMJ Publishing Group: London 2006; 426-9.

Dr. Anuruddha M Abeygunasekera, MS, FRCS, *Urological Surgeon, Karapitiya Teaching Hospital, Galle, Sri Lanka.*

E-mail: amabey@sltnet.lk

Metformin in pregnancy and lactation

Summary

Metformin improves insulin sensitivity and reduces hepatic glucose output in patients with diabetes. It offers potential benefits for pregnant women with gestational or type 2 diabetes because both conditions are associated with increased insulin resistance. Some cohort data are available and randomised trials are currently in progress to compare metformin with insulin, but strong evidence is not yet available to guide management. There are no long term follow-up data to provide reassurance about the safety of metformin, given its passage across the placenta, although recent evidence suggests that there is no significant risk of teratogenesis. Limited amounts of metformin are transferred into breast milk, but the risk of neonatal hypoglycaemia is negligible.

Key words: birth defects, gestational diabetes, hypoglycaemic drugs, insulin.

(Aust Prescr 2007; 30: 68-9)

Introduction

Oral hypoglycaemic drugs have been viewed with suspicion for many years in the management of women with diabetes during pregnancy or breastfeeding. Pregnant women with type 2 diabetes are often switched to insulin. However, there is long experience with use of the biguanide metformin in pregnant women in South Africa. Metformin increases insulin sensitivity, reduces hepatic glucose release and is associated with a tendency to lose weight.[1]

Increasingly metformin is being used in the management of women with polycystic ovary syndrome, as the syndrome is associated with insulin resistance. Metformin reduces hyperandrogenaemia and, as it allows more effective ovulation to occur, it is now widely used in the management of infertility.[2] If a woman with polycystic ovary syndrome becomes pregnant while taking metformin, a decision has to be made whether to continue treatment.

Teratogenicity

Caution is needed when using metformin in pregnancy. In the Australian categorisation of risk metformin is in category C.The product information recommends switching to insulin during pregnancy. It is important for any changeover to insulin to be done under specialist supervision to maintain optimum glucose control and reduce the risk of congenital anomaly from maternal hyperglycaemia.

Limited data are available about the pharmacokinetics of metformin during pregnancy. In one small study of seven women, the clearance of metformin increased with gestation and the associated increased renal elimination.[3] More data are required to clarify the possible need for dose adjustment as pregnancy proceeds. Studies of the passage of metformin across the placenta suggest that there is a rapid transfer of metformin into the fetal circulation.[4]

Recent data provide some reassurance about the safety of metformin in respect of lack of teratogenicity when taken in early pregnancy, although no long-term follow-up data are available.[5] Properly conducted randomised trials are required, as well as a large enough database to exclude rare unanticipated adverse outcomes, such as birth defects.

Outcomes

It is not known if continuation of metformin in early pregnancy provides any better outcome than either ceasing the drug (in women with polycystic ovary syndrome) or changing to insulin (in women with type 2 diabetes). In some circumstances, use of metformin may be preferred, but patients should be individually advised of the harms and benefits.[6] Ideally they should be recruited into appropriately designed studies.

Non-randomised data from New Zealand, where a number of pregnant women with type 2 diabetes have been treated with metformin, suggest that there may be no difference in outcomes when compared with similar women treated with insulin.[7] A small randomised trial in Australia showed no difference in fetal beta cell activity, as measured by cord C-peptide concentrations at delivery, between the babies of women with gestational diabetes treated with metformin and the babies of women treated with insulin.[8]

The randomised Metformin in Gestational Diabetes trial is currently underway to establish the efficacy of metformin compared with insulin, using neonatal outcome as a primary end point. The results may be available soon. After reviewing the results from 600 women, the independent data monitoring committee recommended that the trial continue as there was no indication for early closure.

Metformin improves plasma concentrations of some markers of endothelial activation in people with impaired glucose tolerance, unrelated to changes in glycaemia, lipids, weight or insulin sensitivity.[9] This is a potential benefit for pregnant women with diabetes, as they are at increased risk of problems associated with endothelial activation, such as pre-eclampsia. Few data are currently available to assess the outcome of such therapy. A secondary outcome in a small randomised placebo-controlled trial in 38 pregnant women with polycystic ovary syndrome was significantly fewer severe pregnancy complications in the women taking metformin.[10]

Any potential benefit of metformin on future childhood obesity and later development of diabetes is hypothetical. Long-term follow-up data from the current studies are required.

Lactation

There are three published studies of metformin in breast milk. The milk:serum or milk:plasma ratio varied between 0.18 and 1.00, while the estimated mean infant dose as a percentage of the mother's weight-adjusted dose varied between 0.18% and 1.08%.This dose is much less than the usual 10% level of concern.[11] Women can be reassured that it is unlikely that there will be any significant effect on their babies. In particular, there is no risk of neonatal hypoglycaemia, in contrast to the use of drugs stimulating insulin release, such as the sulfonylureas. Maintenance of maternal euglycaemia during lactation remains an important principle to reduce the risk of subsequent obesity in the child.[12]

Conclusion

Evidence is emerging that metformin may improve insulin sensitivity during pregnancy. This may be of benefit in gestational diabetes, but further evidence is required. Metformin can be used by women who are breastfeeding.

References

1. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med* 2002; **137**: 25-33.
2. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003; **327**: 951-3.

3. Hughes RC, Gardiner SJ, Begg EJ, Zhang M. Effect of pregnancy on the pharmacokinetics of metformin. *Diabet Med* 2006; **23**: 323-6.

4. Charles B, Norris R, Xiao X, Hague W. Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit* 2006; **28**: 67-72.

5. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril* 2006; **86**: 658-63.

6. Simmons D, Walters BN, Rowan JA, McIntyre HD. Metformin therapy and diabetes in pregnancy. *Med J Aust* 2004; **180**: 462-4.

7. Hughes RC, Rowan JA. Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? *Diabet Med* 2006; **23**: 318-22.

8. Hague WM, Davoren PM, Oliver J, Rowan J. Contraindications to use of metformin. Metformin may be useful in gestational diabetes. *BMJ* 2003; 326: 762. [R]

9. Caballero AE, Delgado A, Aguilar-Salinas CA, Herrera AN, Castillo JL, Cabrera T, et al. The differential effects of metformin on markers of endothelial activation and inflammation in subjects with impaired glucose tolerance: a placebo-controlled, randomized clinical trial. *J Clin Endocrinol Metab* 2004; **89**: 3943-8. [R]

10. Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. *Hum Reprod* 2004; **19**: 1734-40. [R]

11. Briggs GG, Ambrose PJ, Nageotte MP, Padilla G, Wan S. Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol* 2005; **105**: 1437-41.

12. Plagemann A, Harder T, Franke K, Kohloff R. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. *Diabetes Care* 2002; **25**: 16-22.

[R] randomised controlled trial.

Conflict of interest: none declared.

William M Hague, *Senior Consultant Physician in Obstetric Medicine, Women's and Children's Hospital, and Clinical Senior Lecturer in Obstetrics, University of Adelaide.*

Self-test questions

The following statements are either true or false

3. Women with polycystic ovary syndrome who are planning pregnancy should not take metformin.

4. Metformin is contraindicated in breastfeeding because of the risk of neonatal hypoglycaemia.

This article is published by courtesy of the *Australian Prescriber*. The *SLP* thanks the *Australian Prescriber* for permission to publish it.