



The South Africa Menopause Society (SAMS)

Menopause

Focus

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INTRODUCING

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- Is derived from progesterone, not testosterone¹

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REFERENCES: 1. Zoely™ Package Insert, October 2014. 2. Mansour D, Verhoeven C, Sommer W, et al. Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17 β -oestradiol in a 21/7 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. *Eur J Contracept Reprod Health Care.* 2011;16(6):430-443. 3. Duijkers IJM, Klipping C, Grob P, Korver T. Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17 β -oestradiol on ovarian function in comparison to a monophasic combined oral contraceptive containing drospirenone and ethinylestradiol. *Eur J Contracept Reprod Health Care.* 2010;15:314-325. 4. Data on file. 5. Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, et al. (2008) Classification and pharmacology of progestins. *Maturitas* 61:171-180.

SELECTED SAFETY INFORMATION: CONTRA-INDICATIONS: ZOELY™ should not be used in the presence of any of the conditions listed below. Hypersensitivity to any of the ingredients. Presence or history of venous thrombosis. Presence or history of arterial or prodromal conditions. History of migraine with focal neurological symptoms. The presence of severe or multiple risk factor(s) for venous or arterial thrombosis. Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant). Pancreatitis if associated with severe hypertriglyceridaemia. Presence or history of severe hepatic disease as long as liver function values have not returned to normal. Presence or history of liver tumours (benign or malignant). Known or suspected sex steroid-influenced malignancies. Pregnancy. **WARNINGS AND SPECIAL PRECAUTIONS:** If any of the conditions/risk factors mentioned below are present, the benefits of the use of ZOELY™ should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using ZOELY™. **Circulatory Disorders:** The use of any combined oral contraceptive (COC) carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. Thrombosis has also been reported to occur in the other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. The risk of venous thromboembolic events increases with: increasing age, a positive family history of thromboembolism, prolonged immobilisation, major surgery, any surgery to the legs, or major trauma, obesity (body mass index over 30 kg/m²), smoking. The risk of arterial thromboembolic complications or of a cerebrovascular accident increases with: increasing age, smoking, (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age), dyslipoproteinaemia, obesity (body mass index over 30 kg/m²), hypertension, migraine, valvular heart disease, atrial fibrillation, a positive family history of arterial thrombosis. An increase in frequency or severity of migraine during ZOELY™ use may be a reason for immediate discontinuation of ZOELY™ use. **Tumours:** The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Long-term use of ethinylestradiol-containing COCs may contribute to this increased risk of cervical cancer. With the use of the higher-dosed COCs (50 μ g ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to ZOELY™ remains to be confirmed. A meta-analysis of 54 epidemiological studies reported that there is an increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using oestrogen-containing COCs. Benign and even more rarely, malignant liver tumours have been reported in users of COCs such as ZOELY™. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. **Other Conditions:** Women with hypertriglyceridaemia, in women with hereditary angioedema, exogenous oestrogens contained in COCs may induce or exacerbate symptoms of angioedema, worsening of depression, Crohn's disease and ulcerative colitis have been associated with COC use, chloasma may occur, especially in women with a history of chloasma gravidarum. **Reduced efficacy:** The efficacy of ZOELY™ may be reduced in the event of e.g. missed tablets, gastrointestinal disturbances during active tablet taking, or use of concomitant medication. **Cycle control:** Breakthrough bleeding or spotting may occur, especially during the first months of use. Therefore, the evaluation of any breakthrough bleeding or spotting is only meaningful after an adaptation interval of about 3 cycles. The percentage of women using ZOELY™ experiencing intracyclic bleeding after this adaptation period ranged from 15 to 20%. If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. The duration of withdrawal bleeding in women using ZOELY™ is on average 3 to 4 days. Users of ZOELY™ may also miss their withdrawal bleeding although not pregnant. Early bleeding patterns (cycles 2 to 4) are predictive of future bleeding patterns. **SIDE EFFECTS:** Possibly related undesirable effects that have been reported in users are: Very common ($\geq 1/10$): acne and abnormal withdrawal bleeding; Common ($\geq 1/100$ to $< 1/10$): Decreased libido, depression/depressed or altered mood, headache, migraine, nausea, metrorrhagia, menorrhagia, breast pain, pelvic pain and weight increase.

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Editorial

Dr SP Moodley

Editor

Executive Committee Member, SAMS, Ethekweni, Umhlanga and Victoria hospitals, KwaZulu-Natal

I would like to congratulate Dr Carol Thomas on her appointment as President of the South African Menopause Society. Her enthusiasm, knowledge and organisational skills is set to take the society to new levels.

I became editor under the tutorship of the last president, Professor Peter Roos. I am indeed grateful for his ongoing guidance and wisdom. The stand out features of his leadership have been his pragmatic approach to problem solving and ready availability to help when needed.

The papers in the first edition of Menopause Focus for 2017 address a broad range of issues.

It is intuitive to understand the link between menopause and diabetes mellitus. Dr Theo Kopenhager, a stalwart of the society, dissects this link. Estrogen deficiency is responsible for the negative metabolic cascade seen in the climacteric. The lower estrogen levels seen in the obese perimenopausal woman probably explains why they have a more challenging menopause transition. The underlying theme in menopause management is the therapeutic window of opportunity. This certainly applies in the context of diabetes mellitus. It is also important to recognise that estrogen in standard doses has insulin sensitising effects and that high doses of estrogen do not produce improved glycaemic control.

Professor David Marais has provided insight into the treatment of dyslipidaemia. The family practitioner and

gynaecologist have a unique opportunity as part of the menopause consultation to practise preventive medicine. Cardiovascular complications, a major cause of female morbidity and mortality, is under estimated and under recognised. Knowledge of lipoprotein metabolism and the available treatments is one step in the reduction of complications.

Dr Jenny Edge has written a very balanced paper on mammography and breast screening as part of secondary prevention of disease. The challenge is to balance the gain from prevention of advanced disease through screening and the anxiety and risks from over diagnosis of benign lesions and indolent cancers that would not have altered survival of the individual. Genomic assessment may influence this management in the future.

I am indeed grateful to Dr Lisa Kaestner for her ongoing contributions to Menopause Focus. A constant concern for any gynaecological surgeon is the proximity of the urinary tract to our operative field. A thorough appreciation of the underlying pathology and meticulous preparation prior to surgery will decrease the complications. It is most important to recognise the injury, seek appropriate help and most injuries can be repaired without long term sequelae. The latter decreases the potential for litigation. Best wishes for 2017.

Thank you
Percy (SP Moodley)

Menopause, and diabetes mellitus - A unique interaction

Dr Theo Kopenhager

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Abstract

Recent robust studies indicate unique interactions between menopause and diabetes. Menopause results in cessation of sex steroid hormone activity, changes in body composition, changes in body fat distribution and changes in metabolic profile and expression. These changes result in significant interactions with diabetes mellitus.

Negative associations between menopause, be it natural, surgical or premature, and the risk of incident diabetes exist. Some studies dispute this association, but there is enough evidence to support a link between menopause and diabetes risk. Both Type 1 and Type 2 diabetes lead to earlier age at menopause, while menopause hormone therapy attenuates the risk of incident diabetes. With regard to these two scenarios the dose of estrogen is important. Menopause hormone therapy improves glycaemic control in women with existing diabetes, and here too estrogen dose is important. Finally, as the effect of menopause hormone therapy on various co-morbidities has been shown to depend on the 'therapeutic window of opportunity', the same is shown to apply with diabetes.

Introduction

Diabetes mellitus (DM) and menopause frequently coexist, yet the unique interactions between them have only recently become apparent. Recent literature points to a mechanistic link between menopause and diabetes and diabetes and menopause.

Estrogen (E) is the principle hormone in reproductive biology but is also a very significant participant in metabolic and insulin regulation.^{1,2} Estrogen effects are mediated through estrogen receptors. Three receptors have now been described, estrogen receptor α (ER α), estrogen receptor β (ER β) and the recently described G protein coupled estrogen receptor¹ (GPER1).³ ER α is the predominant receptor and is ubiquitous throughout body tissue including in insulin sensitive tissue.³ The mechanisms of estrogen action is via the classical and non-classical estrogen signalling pathways and by direct effects on mitochondrial function and regulation.^{4,5} Estrogen deficiency with menopause results in endocrine and metabolic effects.⁶ The endocrine effects produce the classic symptoms and sequelae of the menopause. The metabolic effects involve decreased metabolic rate, increased central adiposity, dislipidaemia, insulin resistance (IR), metabolic syndrome (MS) and DM.

ANIMAL STUDIES

Many animal studies exist revealing an interaction between menopause and DM. Limitations with regards to the length of this article precludes detailed discussion of these studies. Suffice it to mention a few very pertinent findings.

ER α knockout mice become obese and develop IR with consequent abnormal glucose homeostasis. Increased oxidative stress then precipitates β -cell apoptosis and insulin deficiency DM in these mice.^{7,8}

ER α activation reverses IR induced in mice fed with a high fat diet.⁹ Estrogen (E) therapy restores insulin sensitivity and glucose tolerance in ovariectomised mice fed with a high fat diet. This effect is abolished in ER α deficient mice.⁹ Animal studies therefore reveal that E deficiency has a negative effect on DM and E therapy has a positive effect on glucose homeostasis.

HUMAN STUDIES

Studies Supporting an Association Between Menopause and Diabetes Risk

A survey of 10,878 Japanese women, 6,308 premenopausal and 4,570 postmenopausal, found a significantly increased risk of almost exclusively Type 2 diabetes mellitus (T2D) in the post menopausal group as follows: Those with natural menopause, OR =1.40 (95% CI 1.03 – 1.89), those with surgical menopause, OR = 1.59 (95% CI 1.07 – 2.37) and those with early menopause (onset earlier than age 50 years), OR = 1.50 (95% CI 1.18 – 1.91).¹⁰ A cross-sectional study of women attending menopause clinics in Italy, found a significantly increased rate of DM in postmenopausal compared to premenopausal women, OR 1,38 (95% CI 1.03 – 1.84).¹¹

Studies not Supporting an Association Between Menopause and Diabetes Risk

Despite fairly robust evidence in favour of a negative effect of menopause on the risk of DM, a number of studies found scant association.^{12,13,14,15}

Studies Supporting an Association Between Premature Menopause and Diabetes Risk

Premature menopause is defined as menopause with an onset before 40 years of age.

In the Study of Women Across the Nation (Swan Study), women with premature menopause had a greater prevalence of T2D.¹⁶ This finding became non-significant after adjustment for confounders.

The EPIC-InterACT Study, is a subcohort of more than 8000 prematurely menopausal women, nested within the larger EPIC Study. Compared to women with normal age at onset of menopause, women with premature menopause had a greater prevalence of T2D.¹⁷ Two other studies support this association.^{18,19}

Studies Not Supporting an Association Between Premature Menopause and Diabetes Risk

Despite the findings in the EPIC-InterACT Study, analyses of all the women in the EPIC Study (the largest study comparing age at menopause and DM risk), found no association between premature menopause and DM risk.¹⁷ Several other studies found the association tenuous and probably due to confounding factors.^{12,13,20,21}

Surgical Menopause and Diabetes Risk

Women with bilateral oophorectomy in the NHANES¹ Epidemiology Follow-up Study had a higher risk of DM than women with natural menopause, OR 1.57(95% CI 1.03-2.41).¹⁹ Other less robust studies produced the same findings.²² The question therefore is, does abrupt cessation of E secretion have a different biochemical effect than gradual cessation?

Mechanisms Linking Menopause and Diabetes Risk

In the Swan Study, follicle stimulating hormone (FSH) plasma levels correlate with increasing fat mass and expanding waist circumference during menopause transition.²⁶ These changes induce IR and glucose intolerance.^{23,24} Compared to women who are not obese, obese women have lower premenopausal E levels probably because of the inhibitory effect of obesity on E secretion from the ovaries.^{25,30}

In obese post-menopausal women, E levels are higher, because after menopause adipose tissue is the main source of E.^{25,26,27} The potential benefits of relatively higher levels of E in these women are however counteracted by the changes in body fat distribution and the elevation of inflammatory cytokines, which are in turn associated with decreased tissue insulin sensitivity and decreased glucose tolerance.^{28,29,30}

The menopause is characterised by a state of elevated testosterone (T) and greater overall androgenicity. This is as a result of a decline in ovarian E, increased levels of T and decreased levels of sex hormone binding globulin (SHBG). Increased T and decreased SHBG are associated with insulin resistance and diabetes.^{31,32,33}

Type 1 Diabetes and Menopause

Studies report younger ages at menopause in women with Type 1 diabetes (T1D) compared to their non-diabetic sisters, or to non-diabetic unrelated controls. The mean age at menopause in women with T1D was 41.6 years, in their non-diabetic sisters 49.9 years and in non-diabetic unrelated controls it was 48 years.^{34,35} Dorman et al reported that women with T1D were nearly twice as likely to have younger age at menopause compared to non-diabetic women.³⁴ T1D appears to be a significant risk factor for early menopause. The Ovadia Study disagreed with Dorman and Strotmeyer's findings, and argued that improved glycaemic control reduces the effect of T1D on earlier age at menopause.³⁶

Type 2 Diabetes and Menopause

In the largest prospective study of T2D and natural menopause, Brand et al reported earlier age at menopause in women with T2D compared to women without DM.³⁷ A recent report from India links T2D with early menopause onset.³⁸ 300 women with T2D were compared with 300 similar non-diabetic women. The mean menopause age in the group with T2D was 44.6 years and of the non-diabetic group it was 48.2 years. These findings are consistent with the hypothesis that DM has an accelerating effect on age at onset of menopause.

Menopause Hormone Therapy and Diabetes Risk

Large studies report that menopause hormone therapy (MHT) attenuates the risk of metabolic syndrome (MetS) and incident DM. Pentti et al. reported a randomised cohort study showing a 62% reduction in risk of DM in women on current MHT compared to never users of MHT.² Four years of follow-up from the Heart and Estrogen/Progestin Replacement Study (HERS), using conjugated equine estrogen (CEE) 0.625mg and medroxy progesterone acetate (MPA) 2.5mg reported a 35% reduction in DM versus placebo.³⁹ The Women's Health Initiative Study (WHI) after 5.6 years of follow-up, using the same MHT as the HERS, reported a 21% reduction in DM versus placebo.^{1,40} Other randomised and observational studies report a reduction in DM risk with MHT.^{41,42} This reduction in DM is especially achieved with the use of standard doses of E (E₂ 1mg or CEE 0.625mg).⁴³ A meta-analysis of 18 randomised controlled studies found that MHT reduced the risk of DM by 30%.⁴⁴ A meta-analysis of studies from 1997 to 2011 found that combined MHT reduced the incidence of DM by 40%.⁴⁵ In the same meta-analysis, women on estrogen-alone therapy had lower levels of fasting plasma glucose and HbA1C.

The Effect of Menopause Hormone Therapy Dose and Diabetes Risk

The Women's Health Study (2007) and the Multi-Ethnic

Study of Atherosclerosis (2009) report a significant association between higher doses of E and increased risk of DM.^{46,33} Standard doses of E have a positive preventive effect while higher doses have a negative preventive effect. The Rancho Bernardo Study (2002) and the Diabetes Prevention Program (2015) did not confirm these findings.^{31,47} Estrogen in standard doses (E₂ 1mg or CEE 0.625mg) increase insulin sensitivity but in higher doses or with progestin co-therapy this effect is attenuated.^{48,49}

Menopause Hormone Therapy in Women with Existing Diabetes

A number of studies recognise that MHT improves glycaemic control in menopausal women with existing diabetes.^{50,51,52} Estrogen in standard doses has insulin-sensitising effects which improve insulin signalling, glucose uptake and transport and thus decreases fasting glucose and insulin levels. Similar findings occur in nature where E exerts a positive effect on insulin action.⁵⁰ High doses of E do not produce improved glycaemic control. This is demonstrated in a study that shows that high doses of E suppress basal and insulin-stimulated glucose oxidation in human myocytes.⁵¹ In natural conditions of high serum E levels such as obesity, pregnancy and polycystic ovary syndrome, the positive regulation of insulin is lost, resulting in increased propensity to insulin resistance and its sequelae.⁵²

A recent small clinical study evaluated the Timing Hypothesis (therapeutic window of opportunity) with regard to estrogen-alone therapy and diabetes.⁵³ This study reports that trans-dermal estrogen application improves insulin-mediated glucose dispersal rate only when therapy is initiated in early menopause (< 6 years), but this dispersal rate deteriorates if therapy is initiated in late menopause (> 10 years).

Conclusions

It is very clear that a fascinating interaction exists between menopause and DM. It is also clear that E has great potential in attenuating the risk of diabetes as menopause encroaches, and in mitigating the sequelae of diabetes and other co-morbidities in this age group. As always, the art of MHT is to administer it at the right time, in the right dose, for the right indications and to the fully informed patient.

May I express my appreciation to Prof Franco Guidozi for his kind perusal of this manuscript and the many corrections he suggested.

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Treatment of Dyslipidaemia: A to Z

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Abstract

Atherosclerosis leads to cardiovascular system complications that result in much morbidity and mortality, both of which can be ameliorated with lifestyle and medication. In most cases the process is multifactorial. Age is the most prominent factor in evaluating the global risk. Lowering blood cholesterol, especially low density lipoprotein (LDL) cholesterol concentration has proven effective and safe. Much higher risk for cardiovascular disease is observed with familial hypercholesterolaemia, a phenotype comprising LDL hypercholesterolaemia of >5mmol/L, tendon xanthomata and premature coronary disease in a dominantly inherited pattern. Here statins and sometimes additional medication, intercept the predominant mechanism that operates in the disease process. Insights into metabolism and technologic advances are making available new and powerful lipoprotein modulation. It is conceivable that gene editing may be successful in the future so that severe dyslipoproteinaemias with a genetic diagnosis should be amenable to correction.

Current Perspective

Cardiovascular disease is of great importance because most people on this planet currently die from cardiovascular disease. Furthermore, the quality of life can be severely affected by debilitating strokes as well as ischaemic heart disease and heart failure. While it was recognised in the previous century that cardiovascular disease was a problem in the Western World, there is a surge in cardiovascular disease in the developing world and it was predicted to be the prime cause of death by 2020.¹ Advances in prevention of atherosclerosis as well as in the treatment of its complications in the Western World resulted in cardiovascular disease being overtaken by cancer as prime cause of death in at least 12 European Countries.²

Limited data are available for populations in Africa, including in South Africa where several subpopulations exist with recognisable genetic and lifestyle differences and tremendous socio-economic changes are likely to promote atherosclerosis. In the Western Cape noncommunicable disease, largely cardiovascular disease, was identified as the dominating cause of mortality after the age of 40 years by a report from the Medical Research Council.³ Genetic disorders of lipoprotein metabolism are recognised as having an higher prevalence in several South African communities, especially familial hypercholesterolaemia

(FH) due to mutations in the low density lipoprotein (LDL) receptor in the white Afrikaans-speaking community, the Gujerati Indian and Jewish communities. It is estimated that in sub-Saharan Africa, there are about 1 million persons who have this disorder which carries a very high risk of premature myocardial infarction (that is now highly preventable).

Statins are now regarded as safe and effective⁴ after 30 years of experience and numerous studies. It is clear that higher risk subjects derive more benefit from drug intervention. As a generalisation for the population at large, a change of 1mmol/L in LDL cholesterol results in a reduction of cardiovascular complications and death by about 25%. This benefit is obtained within a year of treatment and continues year by year. The estimate is that atorvastatin at 40mg/d, lowering LDL cholesterol by about 2mmol/L will at an affordable cost, lower heart disease: in secondary prevention by about 10% and primary prevention by about 5%.

Guidelines attempt to consolidate the experience into recommendations for the patients at large but there is still much incomplete and unequal treatment.⁵ Only 22% of persons who qualify for primary prevention are on treatment, only 53% of diabetic patients, and 47% of hyperlipidaemic patients. Given the cardiovascular risk that prevails in developed nations, about 60% might benefit from statin prescription and only about half of these have had such intervention.

Advances in the understanding of metabolism as well as atherosclerosis are making for better targeted treatment of lipoproteins and modulation of atherosclerosis. Genes affect the background of health and response to injury that may come from lifestyle. Risk factors have long been recognised at nutritional, clinical, biochemical and genetic levels and these may be immutable (age, sex) or modifiable such as hypertension, diabetes and obesity. These risk factors play roles in several aspects of atherosclerotic changes. It is clear that the classical predictive risk factors of LDL cholesterol and high density lipoprotein (HDL) cholesterol in combination are not powerfully predictive unless taken into the context of other risk factors. Relatively minor dyslipidaemias encountered partly on a genetic basis and partly due to environmental stress, can over the long term pose significant risk of atherosclerosis. In particular, remnants of triglyceride-rich lipoproteins⁶ have been identified as increasing the risk. These remnants are identifiable by triglyceride concentration, possibly better by non-fasting sampling. Much study is still required to identify exactly how remnants are associated with

endothelial injury and the inflammation that ensues in the arterial wall. In monogenic disorders such as FH, however, the dyslipidaemia alone poses such a high risk that intervention is warranted at an early age. Genetic disorders that affect the arterial wall with altered collagen (Ehlers-Danlos syndrome) or elastin (Marfan syndrome) as well as vascular malformation pose a high risk of aneurysmal disease. Upon rupture of a plaque that formed below the endothelium clotting and resorption of the clot become important determinants of outcome. Here lipoprotein (a) is re-emerging as a powerful risk factor (**Figure 1**).

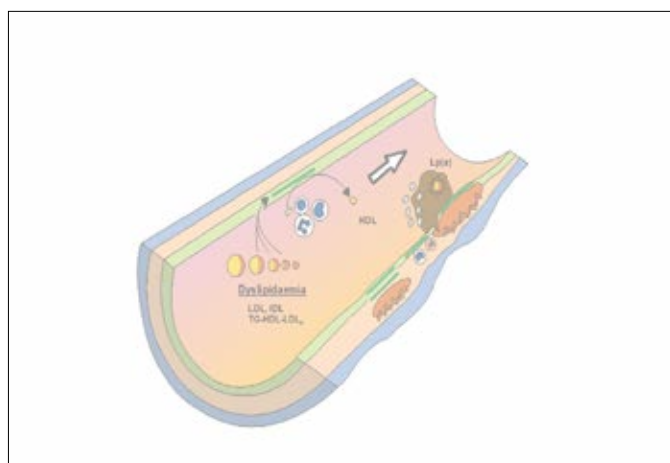


Figure 1. Role of lipoproteins in atherosclerosis. Dyslipidaemias in which LDL, IDL (remnants) and the atherogenic complex of elevated triglyceride and lowered HDL concentration together with small dense LDL, lead to accumulation of lipid in the arterial wall and elicit an inflammatory response of leucocytes. Collagen (green) is deposited in the process forming a fibrous cap (left wall) but lipid accumulation with cholesterol crystals (right wall) with further digestion of collagen results in plaque rupture with consequent coagulation (brown) in which lipoprotein (a) limits fibrinolysis.

Triglyceride concentration is now viewed as ideally less than 1.7mmol/L. Fasting concentrations of up to 5mmol/L are not uncommon in otherwise well persons. An atherogenic lipoprotein phenotype is typical of these triglyceride concentrations, and includes a lower than average HDL cholesterol, small dense LDL and commonly also insulin resistance and changes in the circulation that declare underlying inflammation. The fact that dysbetalipoproteinaemia, in which remnants of triglyceride-rich lipoproteins accumulate, is highly atherogenic underscores the pathogenic role of remnants. Dysbetalipoproteinaemia is a potential complication of about 2% of the population in whom apolipoprotein E is genetically dysfunctional.⁷ A non-denaturing gradient acrylamide gel electrophoresis is now used routinely in our laboratory for the lipid clinic at Groote Schuur Hospital to discern small dense LDL and higher risk, as well as dysbetalipoproteinaemia.

Clinical Practice Points

Risk assessment involves a full clinical consultation as well as special investigations. The history should include assessment of lifestyle, including macronutrients like lipids and their nature with respect to saturated and unsaturated fatty acids, alcohol which can promote

hypertriglyceridaemia, medication, and smoking. The family history, preferably with testing of the plasma lipid profiles, is of importance to confidently diagnose heritable dyslipidaemias.

The height and mass with the calculation of body mass index is supplemented by the waist and hip dimensions as central obesity is more strongly associated with the atherogenic dyslipoproteinaemia and insulin resistance. A waist/hip ratio of >0.95 identifies most persons with small dense LDL.

For screening purposes a total cholesterol suffices but a triglyceride concentration is of value because occasionally severe asymptomatic hypertriglyceridaemia can be detected and the serious complication of pancreatitis can be avoided by intervention. With the advent of the directly measured LDL cholesterol, the need for fasting has diminished as this was a prerequisite for the indirectly estimated LDL cholesterol in the past. Triglyceride concentration cannot simply predict the LDL size as several other parameters play a role in the production of small LDL. This has not become a routine test but may add value in certain cases of borderline risk. Lipoprotein (a) at concentrations of 50mg/dL (180nmol/L) or higher are associated with very high risk and may in future be amenable to specific treatment.

Secondary causes of dyslipidaemia are considered by testing glucose, thyroid status, renal function, proteinuria, and liver function. Vascular imaging such as carotid intima-media thickness or coronary artery calcium scores can contribute to risk assessment but are not currently incorporated into risk calculations.

Despite the high prevalence of FH and the presence of other severely atherogenic dyslipidaemias there is little support for the complete diagnostic work-up in the private and public sectors of medical practice in South Africa. This may become highly relevant in the future not only for the tracing of monogenic disorders in the family, but also for identifying modulating factors and possibly for specific treatment of defined genetic disorders. Our laboratory investigated genetic causes for FH, and identified 87 mutations in the LDL receptor and several mutations in apolipoprotein B and proprotein convertase subtilisin/kexin 9 (PCSK9).

The importance of a global risk assessment with contextually relevant information can be illustrated by comparing different permutations in the risk calculation programmes. It can also be seen that other factors such as age, smoking, hypertension and diabetes dramatically modify the risk for the ordinary range lipoproteins. This necessitates multifactorial intervention and not simply the prescription of a statin. At the same time, it must be stressed that monogenic disorders and the attendant high risk such as in FH, are more specifically addressed by lipid-lowering treatment.

Prescription of Lifestyle and Medication

It is important to commence an healthy lifestyle from childhood. A family approach helps to ensure that not only the patient is more adherent to changes, but also the patient's family can benefit from intervention. The energy balance should be appropriate for ideal body mass. Exercise promotes health and better glucose homeostasis as well. Carbohydrates, especially simple saccharides, are easily overdone and promote energy storage that can be avoided by dietary changes. Dietary lipids are important qualitatively as well as quantitatively and individual responses can vary as a result of apparently minor genetic traits. Postprandially, the arterial walls are exposed to triglyceride-rich lipoproteins even if the fasted state is acceptable. Prolonged clearance is often reflected in small dense LDL. The unsaturated fatty acids are essential for phospholipid metabolism and especially the n-3 poly-unsaturated fatty acids are of importance in neurons, bringing closure to inflammation (catabasis), retarding platelet aggregation and influence triglyceride-rich lipoprotein metabolism. The response of plasma (LDL) cholesterol to dietary cholesterol is variable. There may well be merit in assessing the contribution of diet by reviewing the lipid profile after a month or more of dietary manipulation

Medication for dyslipidaemia has become affordable with generic statins. Only the statins can be discussed in some detail as they are the most commonly used. Statins, however, are not the answer to all dyslipidaemias. For hypercholesterolaemias due to increased LDL, statins are the most cost-effective but bile acid sequestrants (cholestyramine, colestipol, colesevelam), cholesterol absorption inhibitors (ezetimibe, phytosterols) and nicotinic acid may be of utility. Bile acid sequestrants are no longer available in South Africa and the prescription of ezetimibe is poorly supported. For mixed hyperlipidaemias statins often suffice but fibrates may need to be added for optimal control. Hypertriglyceridaemias of >10mmol/L respond poorly to statins but dramatically to diet, and to fibrates. Newer medications that limit the production of apolipoprotein B-containing lipoproteins (thus LDL) are becoming available overseas: lomitapide has allowed persons with homozygous FH to cease plasmapheresis. Anti-sense oligonucleotides have also shown useful reductions in apolipoprotein B synthesis. Very powerful reductions of LDL are effected with subcutaneous injection of humanised monoclonal immunoglobulins to PCSK9 because the degradation of LDL receptors is impaired and thus the hepatocytes can import more LDL from the circulation.

The statins all have in common a moiety that resembles hydroxymethylglutarate (HMG) so that the HMG coenzymeA reductase is inhibited. Simva- and pravastatin are derived from natural products whereas fluvastatin, atorvastatin and rosuvastatin are synthetic. The doses of individual statins differ for the same effect on LDL

metabolism. For a 30% reduction in LDL the approximate doses in mg/day (or night) will be fluvastatin 80mg, pravastatin 40mg, lovastatin 20mg, simvastatin 10mg, atorvastatin 5mg and rosuvastatin 2.5mg. Atorvastatin and rosuvastatin at maximal doses, 80 and 40mg/day respectively, are the most powerful and lower the LDL concentration by about 54%. Interaction with other drugs that also require cytochrome P450 3A4 for biotransformation happens to a large degree with simva- and lovastatin and to a lesser extent with atorvastatin. This may become important when treatment of cardiovascular disease includes verapamil, amlodipine or other agents such as erythromycin or triazole antifungal agents. Statins had much criticism in the lay press for adverse effects on muscle and some medical practitioners take a similar strong stand against statins. One consensus guideline dealt with this topic comprehensively.⁸ In reality, it is often difficult to gauge muscle complaints and to assign causality. While about 1% of patients note muscle complaints, it is not very dissimilar to placebo in placebo-controlled studies. The muscle effects vary from asymptomatic creatine kinase elevations, to isolated myalgia or myalgia with creatine kinase elevation, and rarely rhabdomyolysis with renal failure. Creatine kinase elevations of >10 times upper limit are viewed as unacceptably high risk of renal failure. Cautious follow-up should be done if the creatine kinase activity is >5 times upper limit of normal. The complaints generally improve within days but auto-immune myositis has been noted with persistence. Such auto-immune myositis is, however, not always in association with statins. In some instances the patient can tolerate a lower dose and still benefit from cardiovascular risk reduction. Lesser elevations in the absence of significant symptoms are acceptable.

The observation that gain-of-function mutations in PCSK9 cause FH and loss-of-function mutations cause lower than average LDL concentrations and cardiovascular complications, is now applied in a new strategy of monoclonal antibodies to PCSK9. The antibodies need to be fully humanised to avoid the recipient from making antibodies to the injected immunoglobulins. This resulted in the discontinuation of bococizumab while both evolocumab and alirocumab have been marketed in several countries; at high cost. This strategy is more powerful than inhibiting the production of apolipoprotein B by mipomersen which hinders the translation of mRNA. Another antisense oligonucleotide has been developed together with a modification that makes for liver-specific uptake where apolipoprotein (a) production is dramatically lowered.⁹ This approach holds promise for the small proportion of persons whose cardiovascular risk is extremely high by virtue of very high concentrations of lipoprotein (a). This approach could be applied to other proteins as well.

Homozygous FH is an extremely severe condition manifesting with xanthomata in the skin and tendons of children, LDL cholesterol concentration more than

15mmol/L and typically death from myocardial infarction in the teenagers if untreated. That the liver is the chief organ for LDL balance was demonstrated by nearly complete correction of plasma LDL by liver transplantation. A new approach for genetic correction of inherited disorders is looking promising. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) can be used with a DNA editing enzyme to align the desired DNA segment with the original DNA and editing this sequence into the DNA.¹⁰ This procedure has been done to alter PCSK9 in the mouse.¹¹

Conclusion

Atherosclerosis is a multifactorial disease that will affect most people. Lipoproteins play a role in this process. Though the contribution may appear small in most persons, in genetic disorders with marked changes in lipoprotein concentration, the lipoproteins play a powerful role in atherosclerosis. Although LDL has been recognised as the major culprit and is amenable to lowering by statins, other lipoprotein changes still need to be considered for future treatment. Additionally, other processes in atherosclerosis may need intervention for complete arrest of atherosclerosis.

Clinical practice requires not only the traditional assessment at the bedside but also consideration of laboratory investigations to decide on global risk. Lifestyle measures should apply to all. Genetic disorders such as FH need special consideration for earlier commencement and more aggressive correction of dyslipidaemia. For hypercholesterolaemia the mainstay of treatment is a statin but ezetimibe may need to be added to achieve recommended target concentrations.¹² While statins can achieve control in mixed hyperlipidaemias where cholesterol concentrations exceed those of triglycerides, hypertriglyceridaemias require stricter dietary intervention and fibrates.

It is hoped that introducing healthy lifestyles and being proactive with control of dyslipoproteinaemia, atherosclerosis will be greatly lessened in most persons in whom dyslipidaemia is operative and that additional insights into vascular biology and pathology will allow further amelioration of the process. For persons with serious monogenic disorders operating in accessible tissues, genetic correction will hopefully become a reality. Special clinics and laboratories will become essential in providing best care for such individuals.

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Mammography and Breast Screening: The Ongoing Debate

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There are very few topics in the management of breast cancer that arouse as much debate as the question of mammographic screening for breast cancer. It can be argued that every woman should be invited for mammographic and clinical breast screening annually between the ages of 40-75. It can be argued that mammographic screening causes harm and results in very few women being prevented from dying from breast cancer. The papers and statistics that support either viewpoint are legion.

Although I do not benefit directly from a mammographic screening programme, it must be stated from the outset that in my capacity as a breast surgeon, I benefit indirectly from breast screening programmes. That said, I will look at some of the debate on the issue and will confine myself to the screening of women with a normal risk of breast cancer (No woman over 40 should be considered to be at a low risk of developing breast cancer). The controversy surrounding consideration of the financial aspects of screening are beyond the scope of this paper.

Prevention of Disease

There are three modalities of disease prevention:

- **Primary prevention:** for example, asbestosis is prevented by avoiding any contact with asbestos.
- **Secondary prevention:** screening programmes are an example of secondary prevention.
- **Tertiary prevention:** complications of a disease are prevented by better management of the disease. For example, vascular problems may be prevented by improved management of diabetes.

Criteria for a successful screening programme

There are several criteria that should be met before a screening programme is considered.

The disease should be:

- Common in the screened population
- Have an improved survival possibility if diagnosed at an earlier stage
- Have a "pre" stage. There should be an investigation for the disease that:
 - Is reliable and accurate, and
 - Has an acceptable morbidity

Do we have all of those qualifying conditions for breast cancer screening?

There have been three methods of breast screening that have been studied: Self breast examination, clinical breast examination (CBE) and imaging (plus examination). There are many studies looking at clinical screening but only one will be discussed here. A pilot study in Sudan was conducted in two neighbouring countries both which drained to the same breast unit.¹ Volunteers were trained to examine breasts, went out into the community and offered breast examination to any women over the age of eighteen in one county. The other county had no screening programme and was used as a control. Overall 10 309 women were screened and 17 women were diagnosed with either Ductal Carcinoma in Situ (DCIS) or invasive cancer. This contrasted with the control group: 4 women presented with locally advanced cancer. This is a pilot study but encouraging as it was carried out in a low income country where mammographic screening is not an option and showed that clinical breast screening does result in earlier diagnosis of breast cancer.

As mentioned earlier, certain criteria should be met before screening for any disease is contemplated. I will consider each of the points stated earlier and apply them to breast cancer.

1. The incidence of breast cancer increases with age. Using figures from the UK, per 100,000 population, 122 women develop breast cancer in their early 40s, 280 in their early 50s, 350 in their 60s and thereafter the incidence continues to rise slightly.² It is an uncommon disease in women in their early 30s. (29:100 000). Most screening programmes start at either age 40 or age 50. The question as to when a screening programme should be ended is controversial. When the large studies of screening programmes were carried out in the 80s, the average life expectancy for a woman in the UK was 76. It is now 82 years.³ Should the upper age limit be lifted to 75?

Yes: breast cancer is a common disease in women over 50 years of age.

2. Survival from breast cancer has improved markedly overall in the last 20 years. Localised breast cancer is associated with approximately 99% five year survival as opposed to cancer with regional spread which has an 85% survival rate. (Metastatic cancer has a five year survival rate of about 25%.⁴

Yes: life expectancy is improved if breast cancer is diagnosed at an earlier age.

3. DCIS is a recognised "pre" stage before invasive ductal carcinoma. It commonly results in microcalcifications being formed in the breast. These are seen on mammography. DCIS alone is staged as Stage 0 and has a 99% 10 year survival rate.

Yes: breast cancer has a described "pre" invasive stage.

4. There are several imaging modalities that are used for screening for breast cancer. These include mammography, ultrasound, magnetic resonance imaging (MRI), thermography and SureTouch™ imaging. No large mass population studies with long term follow up have been done for either of the last 2 types of imaging. MRI screening is a complex topic and in short is recommended for young women who are BRCA positive and a few other select groups. It is not recommended for population based screening. Ultrasound as a single modality is not generally used. Most of the literature has been about mammography.

The reliability of mammography is a controversial subject. Technology has improved greatly since the 1980 with the introduction of digital 2D mammography which has been surpassed by 3D techniques. The question remains whether new techniques pick up more cancers with an outcome of saved lives. There are no long term studies looking at overall survival data.

The TOMMY trial⁵ conducted in the UK compared specificity and sensitivity of different modalities of mammography: 2D versus "2D and 3D" versus Synthetic (computer generated) 2D and 3D. They found the sensitivities to be 87%, 89% and 88% respectively. Specificity was improved: 58%, 69% and 71% respectively. So better technology results in fewer false positive reports but still misses over 10% of all cancers. All forms of mammography are more reliable in post-menopausal women who tend to have fattier breasts.⁶

A lot of research is being done looking at combination of modalities especially in women who have dense breasts. More cancers are picked up if mammography is combined with US and MRI.⁷ In the future, high risk women with dense breasts may have a mixture of physiological and anatomical screening e.g., combining PET (Positron Emission Tomography) scans with anatomical imaging.⁸

Yes: there is a form of relatively reliable investigation.

5. The morbidity of breast cancer screening is mainly twofold: Anxiety formed by recalls and biopsy of masses that prove to be benign and over-diagnosis

of breast cancers that are indolent and would not have caused a problem for the woman during her life. Some radiologists argue that the problem is not over-diagnosis but over-treatment. It is difficult, however, not to treat a woman who has recently been diagnosed with breast cancer. This led to the shocking headline in the New England Journal of Medicine in 2012: "1.3 million women over diagnosed and over treated for breast cancer over the past 30 years". The Cochrane review have stated that for every 2000 women screened, 200 will have anxiety.⁹

Maybe: Many would consider that the morbidity of breast screening is acceptable.

There seems to be a reasonable case for screening for breast cancer using mammography as a means of investigation. Does breast cancer screening conclusively save lives? It is very difficult to accurately and dispassionately assess the data. Breast cancer screening in many countries of the world is as much a political issue as it is a medical one. Having looked at the large screening trials, the Cochrane review concluded that if 2000 women are screened for 10 years, 10 women will be treated unnecessarily and one death will be avoided.

In 2014, a study from Canada published the result from their large study which followed up 89835 women who were randomly assigned to two groups: mammographic screening and CBE or CBE.¹⁰ The outcome 25 years later was that in the mammogram and CBE group, 666 women had been diagnosed with invasive breast cancer and 180 had died from breast cancer. In those who had a clinical examination only, 524 had been diagnosed with invasive breast cancer and 171 had died from the disease. The trial has been heavily criticised but it is important in that it is a large trial with a long follow up.

At postmortems of women who have died of other causes, as many as 10% of women have small invasive breast cancers or areas of DCIS.¹¹ Is breast cancer screening just picking up indolent cancers that would never have caused mortality?

The future of breast screening

The combination of physiological and anatomical screening will probably result in more specific screening and so reduce the call back numbers and lessen anxiety. There are several trials being conducted in the UK and in the USA on who should be treated for breast cancer. The LORIS trial¹² (the Low Risk DCIS trial) randomises women who have been diagnosed with low grade DCIS into two groups. In one arm, they are treated conventionally. In the other arm, they are followed up with imaging. They will be followed up for ten years.

The management of breast cancer has changed significantly over the last decade with more emphasis

being put on the characteristics of the cancer rather than the stage. Several genomic assessments are commercially available and there is increasing evidence that they may be able to determine which cancer or DCIS require management and which do not.

Recommendations

There are few accurate statistics for stage of breast cancer in South Africa but well over 50% of women with breast cancer present with locally advanced disease. Individual breast clinics have their own statistics. From their databases, the percentage of women presenting with locally advanced diseases is 64% in Durban,¹³ 67% in Johannesburg¹⁴ and 54% in the Western Cape.¹⁵ In a study from Baragwanath Hospital, Johannesburg, it was found that women who lived further away from the breast clinic were diagnosed at a later stage.¹⁶ A population based mammographic screening programme in this country is not feasible in many areas and much needs to be done to improve access to health care.

Recommendations for individual surveillance should be based on the recommendations for population screening in HIC. At present, the USA recommends annual mammography for women between 40 and 70. They are reviewing their national policy. The UK recommends 3 yearly screening between 50-70, the Swedes recommend 2 yearly screening between 50-70 and the Swiss are debating whether to stop their screening programme.

The Marmot report¹⁷ was commissioned in the UK to look critically at the issue. Inevitably the review has been criticised as the panel included no one with an interest in breast health. Their conclusions, however, should be considered. They concluded that for every 10 000 women screened, 681 were diagnosed with invasive cancer or DCIS, 129 were "over diagnosed" and 43 deaths were prevented. They recommend that all women between 50 and 79 should be invited for a mammogram and breast examination every 2 to 3 years.

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Staying out of trouble: Urinary tract complications in pelvic surgery

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Urinary tract complications in pelvic surgery are not uncommon. Many of these complications can be avoided by an excellent knowledge of surgical anatomy and insight into possible complex pathologies requiring the involvement of a multidisciplinary team.

This is a review a few basic principles to avoid and manage urological injuries.

General principles

Numerous studies have reported a decrease in complications with experience in laparoscopic pelvic surgery. Awareness of this learning curve should allow prudent case selection for laparoscopic procedures based on complexity of the clinical problem.

Avoiding ureteric injuries

Although the position of the ureter at the pelvi-ureteric junction (approximately the level of the 2nd lumbar vertebra) is quite consistent, the path of the ureter along the psoas muscle is quite variable. The point where the ureter crosses the bifurcation of the iliac vessels to enter the pelvis is also quite consistent. Within the pelvis it runs in the bed of the ovary along the pelvic side wall then medially in the base of the broad ligament below the uterine artery and lateral to the cervix, before entering the bladder. Numerous pathological processes may alter the expected path of the ureter in the pelvis.

In cases of a large pelvic mass, a large uterus or endometriosis, other strategies to identify and avoid the ureter may be necessary. The ureter has a few unique features which distinguish it from other tubular structures in the pelvis. It has characteristic small adventitial blood vessels which are visible through the peritoneum in thin patients. Due to the movement of the kidney with respiration, the ureter also moves up and down with respiration. Ureteral peristalsis can be elicited by touching it gently with an instrument. During dissection in the retro-peritoneum, the ureter tends to move medially with the peritoneum.

The following applied anatomical principles should be considered when the ureter is encountered surgically. The ureteric blood supply enters from medial aspect above the pelvic brim and from lateral sources below the pelvic brim. The capillary network of the ureter lies within the ureteric adventitia. It is imperative that the ureter is not skeletonised as this would render the ureter ischaemic and at risk for stricture or breakdown of repaired injuries. The

inter-capillary anastomoses within the capillary network are reliable above the pelvic brim but unpredictable below the pelvic brim. We therefore tend to do ureteric re-implantation directly into the bladder for injuries below the pelvic brim and end-to-end anastomosis for injuries above the pelvic brim.

There are numerous congenital renal anomalies which should be considered if "odd" anatomy is encountered. Duplications of the ureter are not uncommon. Complete duplication of the ureter is associated with two ureteric orifices. However, the ureter may also bifurcate above the bladder. Duplex ureters have a common blood supply and separating them may damage the common blood supply. They are therefore usually re-implanted in a common sheath. Horseshoe kidneys are the commonest congenital renal anomaly and occur in approximately 1:400. The fusion of the lower poles prevents complete ascent of the kidneys. The kidneys are positioned lower than the expected position and the ureters run anterior to the isthmus connecting the lower poles. Ectopic kidneys may be situated in the pelvis and can be confused with a pelvic mass. The ureters of ectopically positioned kidneys tend to enter the bladder in the normal position.

Ureteric injuries often occur in the emergency "train wreck" procedure with significant haemorrhage and where pathological processes make identification of anatomy challenging. In these cases it should always be remembered that repair of ureteric repair has an excellent outcome. Delayed early repair is preferable over a rushed repair in a shocked, unstable patient.

Although the reported incidence of ureteric injuries during laparoscopy is low, these injuries are usually missed intra-operatively. Thermal injuries to ureters from sealing devices during relatively uncomplicated laparoscopic procedures, classically present at 5-7 days after surgery. As thermal injuries cause ischemia and delayed necrosis, debridement of the ureter is essential to ensure good outcome.

Intra-operative cystoscopy may be useful to exclude ureteric injury. Although retrograde pyelography is the gold standard to exclude an injury, clear jets of urine from ureteric orifices will usually exclude significant injury.

In challenging cases, pre-operative ureteric stenting may assist in identification of the ureters and will assist in intra-operative diagnosis of injuries. Stenting has not been shown to decrease the risk of ureteric injuries. Although it is tempting to open the bladder or perform ureterotomy to intubate a ureter during a difficult procedure, both should

be avoided. Poor wound healing related to complicated surgery will increase the risk of stricture or leak. Intra-operative cystoscopy will allow insertion of ureteric catheters. This can be done in a supine patient using a flexible cystoscope which could avoid changing position to lithotomy intra-operatively.

How to find the ureter intra-op

Look for the characteristic appearance and movement, as described earlier, just above the pelvic brim. You may see it through the peritoneum. It may be easier to find where it crosses the iliac bifurcation to enter the pelvis. If you have already dissected the retroperitoneum ensure that it is not being retracted medially with the peritoneum. If all else fails, cystoscopy and ureteric stents will allow identification.

How do “missed” ureteric injuries present?

Although most patients will present with a urine leak, they may also present with less obvious symptoms like pyrexia, sepsis, flank pain and renal dysfunction. If copious clear fluid drains from a drain, send the fluid for creatinine measurement. If it is higher than serum creatinine, it is urine.

How to confirm a ureteric injury

The hallmark of a ureteric injury on contrast-enhanced computed tomography scan (CT) is contrast leak from a ureter. Request delayed images or “CT-IVP” as without delayed contrast-enhanced images, the injury may be missed. Hydronephrosis, urinomas and ascites may also suggest ureteric injury.

Intravenous pyelogram may not identify a significant injury, especially if the ureter involved is obstructed.

Retrograde pyelography is the gold standard for diagnosis of ureteric injuries.

How to manage/repair a ureteric injury diagnosed intra-operatively

If the patient is unstable, definitive repair can be delayed for a few days. In such cases the ureter should not be mobilised to preserve vascularity. A small feeding tube can be inserted into the kidney through the ureteric injury and brought out through the skin to temporarily drain the kidney. This tube can be secured to the ureter with a purse-string suture with a non-absorbable suture. Alternatively the ureter can be tied off and percutaneous nephrostomy can be done post-operatively. It may take a few days for the kidney to dilate enough for this to be done.

In the stable patient, management is dictated by the location of the injury, the extent of the injury and the extent of ureteral loss or devascularisation. Usually injuries below the pelvic brim are repaired by direct re-implantation into the bladder due to concern about the vascularity of the ureter.

A simple injury with minimal devascularisation <2cm and less than 50% of the diameter transected can be repaired by end-to-end anastomosis over a double-J stent.

More extensive injuries and thermal/energy source instrument-induced injuries should be debrided and repaired by “end-to-end” anastomosis. Omentum can be mobilised and be used to wrap the repaired ureter. The omentum is useful as it is easily mobilised off the transverse colon and assists healing by improving vascularity around the ureteric repair site.

The basic principles of end-to-end ureteric repair are as follows:

- Debride the ends of the ureter
- Spatulate the ureteric ends
- Restrict crushing the ureter due to manipulating it with instruments by using a strict “no touch” technique
- Complete a tension-free end-to-end anastomosis with absorbable sutures over a double-J ureteric stent for internal drainage
- Place a pencil drain or other non-suction type drain over the area of the repair
- Isolate the repair with peritoneum or omentum
- If a repair cannot be done without tension then a Psoas hitch, Boari flap, transuretero-ureterostomy or Monti-Yang ileal interposition may be necessary

How to manage a ureteric injury diagnosed post-operatively

If diagnosis is made post-operatively, cystoscopy and retrograde will confirm the injury and allow assessment of the nature and extent of the injury. If a DJ stent can be placed past the injury, it may be reasonable to allow a period of conservative management. Although these injuries may heal with internal drainage, many will heal with stricture. If a stent cannot be passed, definitive repair should be done. If there is a contra-indication to formal repair at that time, percutaneous nephrostomy should be done to relieve obstruction, if present, until definitive repair can be done.

Avoiding bladder injuries

The bladder is boat-shaped with a base, dome and lateral walls. Note the relation of the trigone/ base of the bladder to the cervix during a trans-abdominal approach to the bladder. Injuries which are presumed to involve the dome often involve the base of the bladder where the injury or attempted repair may involve the ureter. During the vaginal approach it should be noted that injuries more than 2,5cm from the external urethral meatus may involve the trigone. Intra-operatively the bladder neck can be identified by palpating the bulb of the urethral catheter. Prolapse may significantly alter the expected location of the bladder neck.

How to diagnosis bladder injuries intra-operatively

Few bladder injuries will declare themselves by clear fluid in the operative field and a visible catheter bulb. Small bladder injuries are easily missed on simple inspection, especially during laparoscopic procedures. Distension of

the catheter drainage bag with gas during laparoscopy is an obvious sign of bladder injury however instillation of dilute methylene blue through the urethral catheter may be required to confirm a suspected bladder injury. Although clear urine in a urine drainage bag is comforting to surgeons, the lack of haematuria does not exclude an injury. Frank haematuria should prompt intra-operative assessment to exclude bladder or ureteric injury.

Cystoscopically an injury may be suggested by an obvious breach of the mucosa with dark spaces visible between detrusor muscle fibres, or visible fat or a frank defect into the peritoneum with bowel and other peritoneal contents visible. An inability to distend the bladder and progressive abdominal detention strongly suggests an intra-peritoneal bladder injury. In doubtful cases, an intra-operative cystogram can be done by filling the bladder with dilute contrast and using a C-arm for fluoroscopy in the AP and oblique plane.

How do “missed” bladder injuries present?

Haematuria and copious amounts of clear fluid draining from a drain, wound or from the vagina are obvious signs of bladder/ureteric injury. Decreased urine output, ascites and progressive abdominal distension are also common signs of a urinary leak. Urinary ascites may present with a relatively benign feeling distended abdomen without peritonitis. Urinary ascites or retroperitoneal urinomas often cause ileus. Renal dysfunction may be caused by obstructive uropathy or by urinary ascites where the urine filled peritoneum acts as a dialysis membrane causing increases in serum potassium, urea and creatinine. Sepsis from an infected collection may also be a presenting sign. Patients may present at 5-7 days post operatively with signs of a leak due to ischaemic necrosis of the bladder or ureter.

How to diagnose bladder injuries post-operatively

Bladder injuries are missed more often during laparoscopic surgery than during open surgery. The use of energy sources close to the bladder or thinning the bladder during dissection may increase the risk of late leaks due to ischaemic necrosis. Elderly women may have extremely thin bladders which are more prone to injury.

Fluid draining from wounds or drains may be sent for creatinine measurement to determine whether the fluid is urine. Investigation should include assessment of the bladder and the ureter as injuries to both are not uncommon.

Contrast-enhanced CT and intravenous pyelogram are insufficient to exclude a bladder injury if passive bladder filling is used. Ultrasound of the abdomen may identify suggestive features of a bladder injury, such as a collection or ascites, but will not diagnose the bladder injury.

CT cystogram or standard cystography will identify the injury and confirm whether an intra-peritoneal or extra-peritoneal injury is present. On standard cystography

an extra-peritoneal injury is confirmed by flame-shaped leak of contrast from the bladder. Intra-peritoneal leak of contrast from the bladder is characterised by contrast visible around loops of bowel.

How to manage a bladder injury

Intra-peritoneal injuries should be repaired. Extra-peritoneal injuries, except complicated/large injuries should be managed conservatively with prolonged catheter drainage.

Two layer vesicorrhaphy with absorbable sutures is recommended. Ensure a mucosa-mucosa anastomosis and closure of the detrusor. Ensure good drainage with a catheter of at least 18Fr or larger. If severe haematuria is present, consider inserting a larger catheter which is less likely to become blocked by clots. A blocked catheter will cause over-distension of the bladder and breakdown of the repair. Place a pencil or other non-suction type drain close to the repair. Consider placing omentum or a Martius flap over the repair. The catheter can be removed at 7-10 days in uncomplicated cases. Consider control cystography prior to catheter removal in complex cases.

Martius flap-“the omentum of the perineum”

The Martius flap is a vascularised labial fat pad which can be used as a second layer over closure of bladder and urethral injuries. It is commonly utilized during vesico-vaginal fistula and urethral diverticulum repair. It improves vascularity and creates a second watertight layer over the repair. It also facilitates dissection if delayed secondary procedures are necessary. It is easily mobilised and, surprisingly, causes little asymmetry of the labia.

Summary

Many urological injuries are inevitable due to the underlying pathological process. Most injuries can be repaired with few long-term sequelae. Repairs will heal if well vascularised, tension free, done with absorbable sutures and drained well internally and externally for an appropriate amount of time. Managing complications can be challenging and are best managed in the setting of a multi-disciplinary team.

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Comments by the President

In the first edition of 2016, Pete Roos, our immediate past president, quoted Mahatma Gandhi: "If now violence is the law of our being, then the future is with women".

Despite the timeline since the original words were spoken, and even since Pete quoted them, this sentiment has not been realised. Indeed, safety and autonomy of the vast majority women appears to be under even further threat nationally, on our continent and, particularly, globally. Not allowing women the right to reproductive and sexual health directly affects their well being and status in life. Ageing, however, adds another layer of vulnerability which contributes to a pervasive perception by society (and some women) that women past their reproductive capacity become virtually invisible until, for example, their 'wisdom' translates into the childcare of grandchildren.

The past president, however, has spent his entire career counteracting this notion, to the point of earning the title of 'honorary woman' in some circles. His support, guidance and mentorship to fellow colleagues, coupled with an apparently effortless participatory style of leadership, is worth emulating in the future.

Pete Roos ended his term of office with the co-ordination and oversight of our exciting SAMS conference in November 2016. Pete was supported by his experienced and illustrious scientific team, Tobie de Villiers, Johannes van Waart, Alan Alperstein and Paul Dalmeyer, who meticulously sourced international scientific content which highlighted the practical clinical approaches needed for our daily practice, while not neglecting the importance of the basic sciences in supporting our individualisation of menopausal management and therapy.

Theo Kopenhagen's dedication and contribution to medicine in the most 'mensch'-like way possible earned

him our accolade of life-long honorary membership. Despite his relative youth, Tobie de Villiers, immediate past president of the International Menopause Society, received a similar award in recognition of his contribution in firmly placing South Africa and, by extension, Africa within the global menopause arena.

At the first council meeting in March we will redefine and align our goals with the intent and spirit of serving the needs of older women and supporting all levels of health service providers who have their interest at heart.

The logistics of increasing our continuing medical and patient education reach to beyond the major urban centres remains challenging, but remains a moral imperative. Cross-border collaborative exchange is also envisaged to explore possible best practice models for the relatively low resource settings we may have in common.

Thanks to an unrestricted educational grant, all available council members will be attending the international RCOG conference in Cape Town, keen to update and up-skill so that we may all be well equipped to be part of your continuing medication network.

With the publication of the South African arm of the CLOSER study in Climacteric, driven by Prof. Franco Guidozzi, the paucity of credible research and work on women in Southern Africa is starting to be addressed.

In the meantime, for women now and in the future - we aim to add value to their lives in a comprehensive, integrated way with passion, purpose and integrity.

Help SAMS do this and join us as we roll into 2017.

Carol Thomas

SAMS Mission Statement

The South African Menopause Society (SAMS) is one of South Africa's leading nonprofit organisations that is dedicated to promoting women's health during midlife and beyond, through the understanding of menopause. It boasts a membership of over 190 leaders in the field (including clinical and basic science experts from medicine, nursing, sociology, psychology, nutrition, anthropology, epidemiology and education). This allows SAMS to be the dominant resource on all aspects of menopause to both healthcare providers and the public.







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For full prescribing information refer to the package insert approved by the medicines regulatory authority.

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The progestin in ZOELY™, nomegestrol acetate, has an elimination half-life of 46 hours.¹



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SELECTED SAFETY INFORMATION: CONTRA-INDICATIONS: ZOELY™ should not be used in the presence of any of the conditions listed below. Hypersensitivity to any of the ingredients. Presence or history of venous thrombosis. Presence or history of arterial or prodromal conditions. History of migraine with focal neurological symptoms. The presence of severe or multiple risk factor(s) for venous or arterial thrombosis. Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant). Pancreatitis if associated with severe hypertriglyceridaemia. Presence or history of severe hepatic disease as long as liver function values have not returned to normal. Presence or history of liver tumours (benign or malignant). Known or suspected sex steroid-influenced malignancies. Pregnancy. **WARNINGS AND SPECIAL PRECAUTIONS:** If any of the conditions/risk factors mentioned below are present, the benefits of the use of ZOELY™ should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using ZOELY™. **Circulatory Disorders:** The use of any combined oral contraceptive (COC) carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. Thrombosis has also been reported to occur in the other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. The risk of venous thromboembolic events increases with: increasing age, a positive family history of thromboembolism, prolonged immobilisation, major surgery, any surgery to the legs, or major trauma, obesity (body mass index over 30 kg/m²), smoking. The risk of arterial thromboembolic complications or of a cerebrovascular accident increases with: increasing age, smoking, (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age), dyslipoproteinaemia, obesity (body mass index over 30 kg/m²), hypertension, migraine, valvular heart disease, atrial fibrillation, a positive family history of arterial thrombosis. An increase in frequency or severity of migraine during ZOELY™ use may be a reason for immediate discontinuation of ZOELY™ use. **Tumours:** The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Long-term use of ethinylestradiol-containing COCs may contribute to this increased risk of cervical cancer. With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to ZOELY™ remains to be confirmed. A meta-analysis of 54 epidemiological studies reported that there is an increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using oestrogen-containing COCs. Benign and even more rarely, malignant liver tumours have been reported in users of COCs such as ZOELY™. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. **Other Conditions:** Women with hypertriglyceridaemia, in women with hereditary angioedema, exogenous oestrogens contained in COCs may induce or exacerbate symptoms of angioedema, worsening of depression, Crohn's disease and ulcerative colitis have been associated with COC use, chloasma may occur, especially in women with a history of chloasma gravidarum. **Reduced efficacy:** The efficacy of ZOELY™ may be reduced in the event of e.g. missed tablets, gastrointestinal disturbances during active tablet taking, or use of concomitant medication. **Cycle control:** Breakthrough bleeding or spotting may occur, especially during the first months of use. Therefore, the evaluation of any breakthrough bleeding or spotting is only meaningful after an adaptation interval of about 3 cycles. The percentage of women using ZOELY™ experiencing intracyclic bleeding after this adaptation period ranged from 15 to 20%. If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. The duration of withdrawal bleeding in women using ZOELY™ is on average 3 to 4 days. Users of ZOELY™ may also miss their withdrawal bleeding although not pregnant. Early bleeding patterns (cycles 2 to 4) are predictive of future bleeding patterns. **SIDE EFFECTS:** Possibly related undesirable effects that have been reported in users are: Very common ($\geq 1/10$): acne and abnormal withdrawal bleeding; Common ($\geq 1/100$ to $< 1/10$): Decreased libido, depression/depressed or altered mood, headache, migraine, nausea, metrorrhagia, menorrhagia, breast pain, pelvic pain and weight increase.

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