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SPECIALIST FORUM

Vol. 24 • No. 2 • February 2024

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Game-changing contraceptives

Osteoporosis: The silent 'crippler'

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References: 1. South African Medicine Price Registry. Database of Medicine Prices, 01 November 2023 [online]. [cited November 2023]; Available from URL: http://www.mpr.gov.za/. **2.** Monthly Index of Medical Specialities. September 2023;63(No. 8):185-191. **3.** Metz DC, Howden CW, Perez MC, *et al.* Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. *Aliment Pharmacol Ther.* 2009;29(7):742-54. doi: 10.1111/j.1365-2036.2009.03954.x. **4.** Gąsiorowska A. The role of pH in symptomatic relief and effective treatment of gastroesophageal reflux disease. *Prz Gastroenterol.* 2017;12(4):244-249. doi: 10.5114/pg.2017.72097. **5.** Frye JW, Peura DA. Managing gastroesophageal reflux disease - comparative efficacy and outcomes of dexlansoprazole MR. *Ther Clin Risk Manag.* 2015;11:1649-56. doi: 10.2147/TCRM.S66680. **6.** Dexilant Professional Information. Takeda (Pty) Ltd, South Africa; August 2021. **7.** Sharma P, Shaheen NJ, Perez MC, *et al.* Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation–results from two randomized controlled studies. *Aliment Pharmacol Ther.* 2009;29(7):731-41. doi: 10.1111/j.1365-2036.2009.03933.x. **8.** Fass R, Chey WD, Zakko SF, *et al.* Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther.* 2009;29(12):1261-72. doi: 10.1111/j.1365-2036.2009.04013.x.

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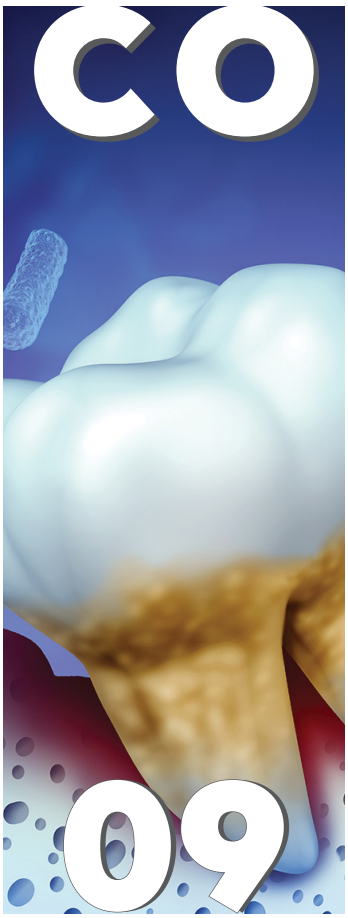

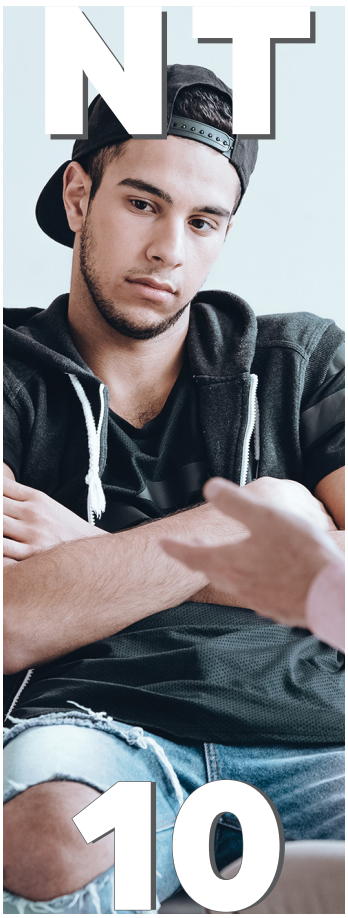

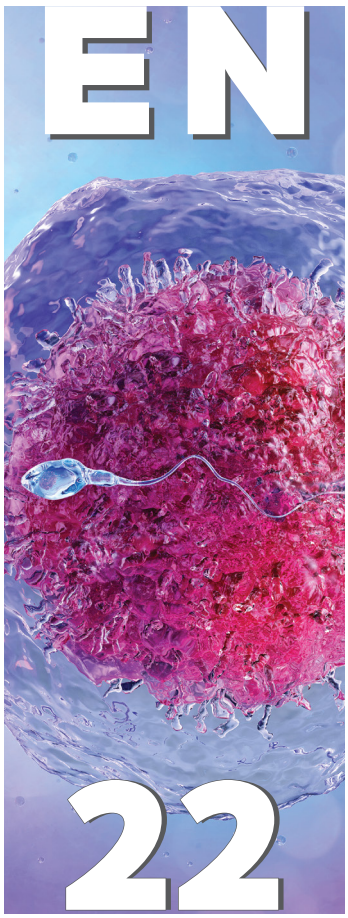

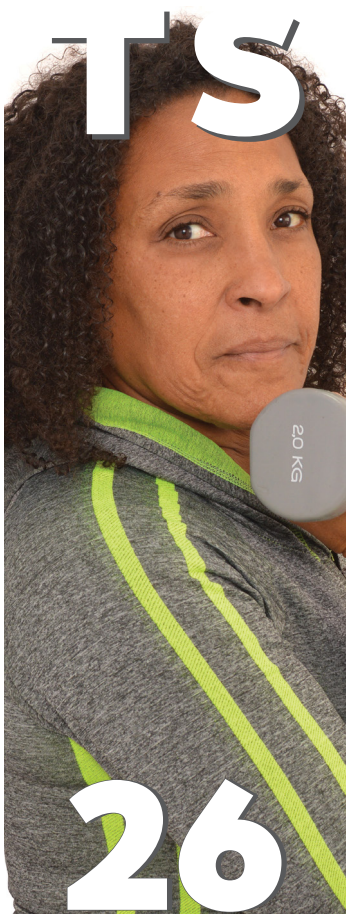

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An editorial extravaganza to celebrate the month of love

As we celebrate the month of love, *Specialist Forum* is pleased to bring you a diverse array of articles covering pivotal aspects of health. Join us on a journey through the pages of this issue and delve into discussions surrounding women's health, rheumatology, psychiatry, rare and infectious diseases, and more.

In recognition of Reproductive Health Month, our spotlight is on hypertensive disorders of pregnancy and the far-reaching consequences of unintended pregnancies. We explore the game-changing role of contraceptives, celebrating their impact on reproductive health and family planning. Empowering individuals with knowledge and choices is paramount for fostering a healthy society.

In celebration of International Women's Health Month, our articles shed light on critical issues affecting women at various stages of life. Osteoporosis, menopause, and cervical cancer take centre stage as we discuss the latest developments in research, prevention, and treatment. By addressing these concerns, we aim to contribute to the holistic well-being of women.

Understanding infectious diseases is crucial in maintaining public health. In this issue, we provide insights into the treatment of intra-abdominal infections and gastroenteritis. By staying informed about these conditions, we can work towards effective prevention strategies and improved patient outcomes.

On February 29th, we commemorate Rare Disease Day by offering a brief overview of some of the most well-known rare diseases. Raising awareness about these conditions is pivotal in promoting early diagnosis, research, and support for individuals and families affected by rare diseases.

Mark your calendar for World Oral Health Day on March 20th, emphasising the symbiotic relationship between oral health and overall well-being. Our oral health article focuses on dental caries and periodontal disease, preventive measures and the significance of maintaining good oral hygiene practices.

Don't miss the upcoming South African Rheumatism and Arthritis Association Congress from February 29th to March 3rd. Our feature article delves into gout, often referred to as the disease of kings and the king of diseases. The congress promises a wealth of knowledge and networking opportunities for professionals in the field.

From March 7th to 9th, the South African Association for Child and Adolescent and Allied Professions invites you to register for an insightful event. Our article sheds light on the challenges and triumphs faced by teens on their rocky road to adulthood. This congress serves as a platform to discuss the latest developments in the field of child and adolescent health.

To stay updated on all the local congresses for 2024, don't forget to bookmark our medical congress calendar. Scan the QR code to access the calendar.

In this month's *Specialist Forum,* we strive to provide a comprehensive exploration of diverse health topics that impact individuals across different stages of life. We encourage our readers to actively engage with the content, stay informed, and participate in the upcoming congresses and events that promise to enrich our understanding of health and well-being.

Remember, health is not merely the absence of illness. It is a holistic journey towards optimal well-being.

Happy reading!

Regards

René Bosman

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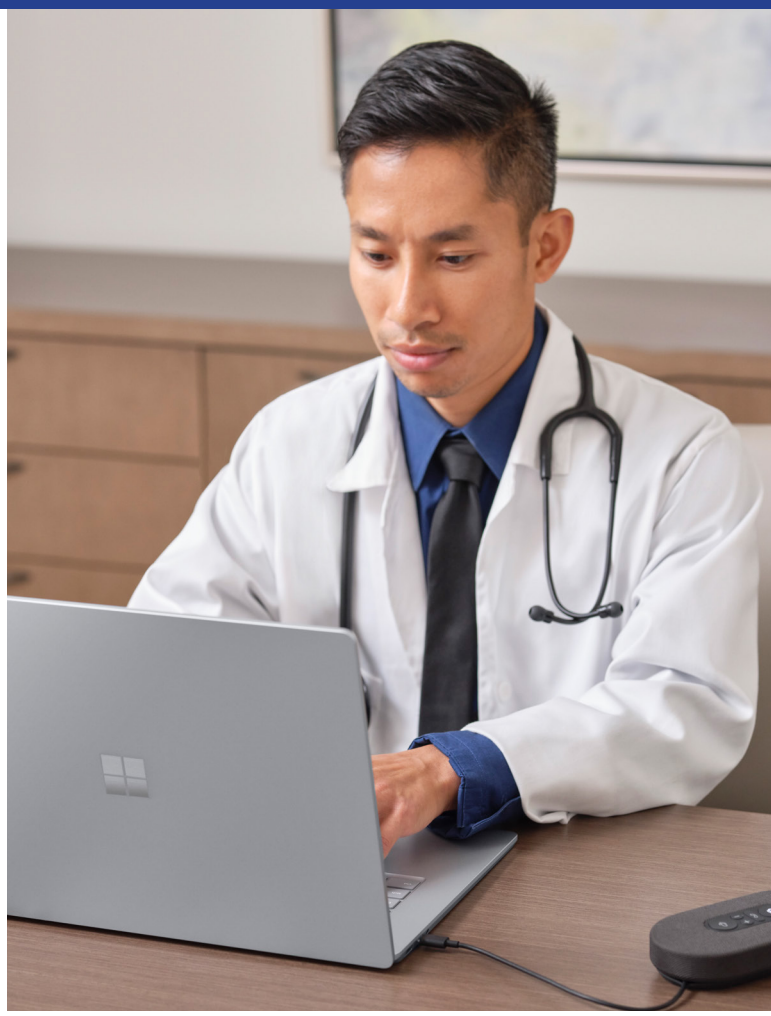

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Do we really need to drink 8 glasses of water a day?

The idea of consuming eight glasses of water daily stems from a 1945 recommendation by the American Food and Nutrition Board, without substantial scientific evidence backing this recommendation. However, there is ample scientific evidence that staying hydrated has several benefits. In this infographic, we look at eight benefits of staying hydrated.

Benefit #1: Improves longevity

A recent study found that optimal hydration may slow down the ageing process, that people who stay well-hydrated develop fewer chronic conditions, such as cardiovascular and pulmonary diseases, and live longer compared to those who may not get sufficient fluids.[4]

Benefit #2: Hydration improves physical performance

Losing just 2% of body water can impact health, especially in athletes who often train in excessive heat. Athletes can lose as much as 6%-10% of fluid as a result of sweating, which may affect their bodies' ability to control temperature, their motivation to train, and can cause excessive fatigue. Maintaining optimal hydration not only prevents these issues but also reduces oxidative stress during intense training, which is crucial considering muscles contain ~80% water.[5-10]

What and how much to drink, based on science

A one-size-fits-all approach is not suitable for every individual or situation. The British Health Service states that water, lower-fat milk and sugar-free drinks, including tea and coffee, all count towards your daily fluid intake.[2,3]

In terms of water intake, various factors, including activity level, humidity, climate, body temperature, and body composition play a role in your body's fluid needs. For optimal hydration, women should drink at least four glasses (1 litres) of water daily, while men should aim for at least six glasses (1.5 litres). Children should be encouraged to drink water when thirsty.[2]

Dietary guidelines recommend that children should be limited to drinking 600ml of milk per day, and starting at age five, all children and adults should opt for low-fat or fat-free milk.[3]

Fruit juice intake should be limited to 240ml per day and sweetened cool drinks (eg carbonated drinks) to 240ml daily – especially for patients living with diabetes, obesity and those who are not physically active. Fruit/vegetable juices and sports drinks should be limited to 240ml a day.[3]

Diet or artificially-sweetened cool drinks can substitute sweetened ones (up to four 240ml servings daily). For unsweetened coffee and tea, adults should have no more than four cups of coffee or eight cups of tea per day with fat-free or low-fat milk and no sugar.[3]

SAVE the DATE!

23 March
World Water Day

Benefit #8: Aid weight loss

Adequate water intake supports weight loss by enhancing satiety and boosting metabolism. Research shows that drinking an extra 500ml of water three times daily before meals over eight weeks led to significant weight and body fat reductions in overweight women. Drinking water 30 minutes before meals, especially 0.5 litres, resulted in a 44% greater weight loss over 12 weeks compared to those who did not.[5,30-33]

Benefit #3: Improves energy levels and brain function

Mild dehydration, even at 1%-3% body weight loss, significantly impacts brain function and energy levels. Studies show that dehydrations can result in impaired mood, concentration, working memory, as well as increased headaches, anxiety, and fatigue. Daily activities, exercise, or high heat can lead to this level of fluid loss, affecting individuals across various age groups.[5,11-17]

Benefit #4: Prevents and treats headaches

Dehydration can trigger headaches and migraines. Studies suggest that staying hydrated may alleviate headaches, with research showing significant improvements in migraine-specific quality of life for those who increased their daily water intake. However, due to limited high-quality studies, further research is needed to confirm the impact of hydration on headache symptoms and frequency.[5,18-21]

Benefit #5: Helps relieve constipation

Boosting fluid intake is commonly advised for treating constipation, supported by evidence indicating low water consumption as a risk factor for constipation across age groups. Hydration increase may alleviate constipation, with mineral water, especially rich in magnesium and sodium, demonstrating improved bowel movement frequency and consistency in individuals with constipation.[5,22-24]

Benefit #6: May help treat kidney stones

Increased fluid intake may aid in preventing the recurrence of kidney stones by diluting mineral concentrations in urine, reducing the likelihood of crystal formation. More research is needed to determine water's role in preventing initial stone formation.[5,25,26]

Benefit #7: Helps prevent hangovers

Alcohol, being a diuretic, causes increased water loss, potentially leading to dehydration. While dehydration isn't the primary cause of hangovers, it can contribute to symptoms. To mitigate hangovers, drinking water between alcoholic beverages and having a substantial amount before bedtime is recommended.[5,28,29]

References available in the online issue

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Sometimes you do need to look for zebras

The medical adage 'think of horses, not zebras' encourages clinicians to consider common conditions before exploring rarer diseases. However, for individuals with rare diseases, this approach can lead to significant challenges, including delayed or incorrect diagnoses and limited treatment options. Less than 5% of rare diseases have available treatments. Rare diseases affect ~300 million individuals globally, constituting 3.5%–5.9% of the world population.

Diagnostic complexities

Diagnosing rare diseases, which number >7000, is complex, with 70% manifesting in childhood and 72% having a genetic origin. The diagnostic journey often imposes a profound physical and psychological burden on patients and their families. The lack of information from healthcare professionals contributes to frustration, anger, and isolation, impacting not only health but also educational and social experiences.

Well-known rare diseases

Several well-known rare diseases include Ehlers Danlos syndrome (EDS), sickle cell disease (SCD), cystic fibrosis (CF), Duchenne muscular dystrophy (DMD), and haemophilia.

EDS, a hereditary connective tissue disorder, requires a multidisciplinary approach for management, as there is currently no cure. SCD, a multisystem disorder, necessitates a comprehensive approach tailored to individual needs.

CF, an autosomal recessive inherited disease, impacts various body systems, with treatment strategies focusing on optimising function and preventing complications.

DMD, the most common hereditary neuromuscular disease, poses physical and cognitive challenges, emphasising the importance of comprehensive management.

Haemophilia, characterised by clotting factor deficiencies, affects males more frequently and requires acute bleeding management and prophylaxis. The treatment of haemophilia involves managing acute bleeding and prophylaxis.

Acute bleeding requires prompt hospitalisation and administration of clotting factor concentrate. Prophylaxis aims to prevent bleeding episodes, with factor VIII dosing based on body weight.

Recombinant factor VIII has improved safety, and ongoing research seeks to enhance its half-life. Other pharmacological options, such as desmopressin, tranexamic acid, and epsilon aminocaproic acid, complement factor concentrates. Physical activity is crucial for maintaining overall health in patients living with haemophilia.

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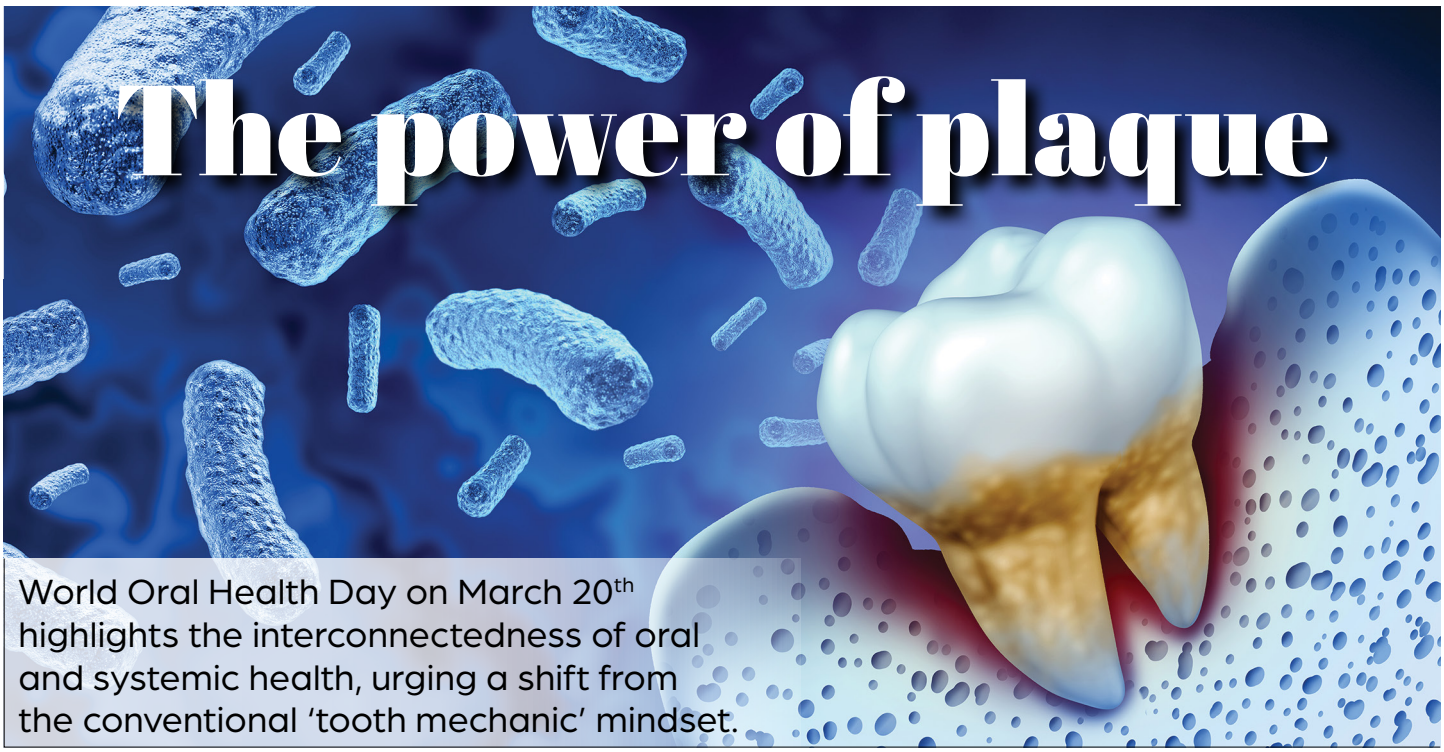
SAVE the DATE!

Rare Disease Day
29 February

Scan for full article and references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The power of plaque

World Oral Health Day on March 20th highlights the interconnectedness of oral and systemic health, urging a shift from the conventional 'tooth mechanic' mindset.

Teicher and Henschel emphasise the need for oral healthcare professionals to consider the broader picture, investigating underlying systemic issues and unhealthy lifestyle habits contributing to oral health problems.

Prevalence of oral diseases

Oral disorders, affecting >3.5 billion people globally, extend beyond dental concerns, impacting essential functions, self-esteem, and overall well-being. Dental caries, influenced by dietary, microbial, behavioural, psychological, and social factors, is the most prevalent oral disease, affecting millions of children. Periodontal disease, a chronic inflammatory condition, affects ~10% of the global population.

Connection between oral and systemic diseases

The oral microbiome, with around 700 different phylotypes and 400 species, plays a crucial role in the onset of systemic diseases. Many oral diseases, including periodontal disease, are associated with non-communicable conditions such as cardiovascular disease, diabetes, cancers, pneumonia, obesity, and premature birth. The reciprocal relationship between oral and systemic health underscores the need for a holistic healthcare approach.

The 'silent epidemic' of oral health

Oral health is described as a 'silent epidemic' by Benjamin, emphasising the potential consequences of untreated diseases, including pain, dysfunction, poor appearance, loss of self-esteem, and difficulty concentrating on daily tasks.

The World Health Organization has taken significant steps, urging member countries to address common risk factors for oral and non-communicable diseases, emphasising preventive approaches and comprehensive care within the primary healthcare system.

Role of general practitioners in oral health

While oral diseases require specialised care, studies reveal that a significant percentage of adults consult general practitioners for dental concerns. Barriers to accessing oral healthcare services, such as limited public-funded care, out-of-pocket expenses, and poor accessibility, lead individuals to seek alternative medical services.

The collaboration between oral healthcare professionals and general practitioners becomes crucial in ensuring a comprehensive and proactive approach to oral health.

Signs and symptoms of dental caries and periodontal disease

Early dental caries may initially have no symptoms, but as decay advances, patients may experience pain, sensitivity, and abscess formation. Periodontal disease warning signs include bad breath, swollen or bleeding gums, painful chewing, and loose teeth. Recognising these signs is crucial for early intervention.

Treatment approaches for dental caries and periodontal disease

The approach to managing dental caries involves detecting initial lesions, assessing caries activity, conducting risk assessments, preventing new lesions, preserving dental tissue, and prolonging tooth longevity.

Non-invasive procedures like remineralisation, biofilm removal, and sealing should be prioritised, with minimally invasive methods used to control cavitated lesions. For periodontal disease, a systematic process begins with professional dental cleaning and oral hygiene instructions.

Managing risk factors, promoting oral care, and encouraging smoking cessation contribute to treatment success. In severe cases, antibiotics and, in rare instances, surgery may be required.

Conclusion

World Oral Health Day serves as a reminder of the intricate connection between oral and systemic health. Emphasising prevention, early detection, and collaboration between oral healthcare professionals and general practitioners are essential for holistic oral healthcare. Recognising signs, managing risk factors, and adopting a proactive approach are crucial steps toward ensuring a happy mouth and a happy body.

Please note, this is just a summary of the article. The full article and references can be accessed on *Medical Academic*. SF

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Turbulent teens

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The South African Association for Child and Adolescent and Allied Professions Congress is taking place from 7–9 March in Cape Town. Adolescence is a pivotal period in human development, spanning from the onset of puberty to the mid-20s.

This phase is marked by significant biological, cognitive, psychosocial, and emotional changes in both boys and girls. While these changes are influenced by earlier life experiences, the brain's adaptive neural plasticity, peaking during adolescence, allows for potential positive transformations.

Biological transformations: Navigating puberty

Puberty, initiated by hormonal changes in the brain, symbolises the transition from childhood to adulthood, encompassing the ability to reproduce. Distinct outcomes in boys and girls are shaped by variations in hormone levels.

Cognitive development during adolescence involves the prolific growth of new brain cells, pruning excess cells, and strengthening connections between cells. A study by Sydnor *et al* reveals that brain plasticity peaks at around 15 years, suggesting a sensitive period for adapting to the environment. The prefrontal cortex, a region exhibiting high plasticity, is particularly susceptible to environmental influences.

Psychosocial and emotional changes: Shaping identity and relationships

Adolescents undergo significant psychosocial changes, transitioning from childhood to adulthood. Personal connections with peers and romantic relationships often take precedence over family ties.

Emotional development, driven by biological and cognitive changes, is influenced by factors like self-esteem, identity formation, and stress. The cognitive shift during adolescence promotes deeper and more abstract thinking, shaping perspectives on the world and influencing the development of morals and values.

Possibilities and probabilities in human development

Human development, as articulated by Belsky *et al* is a complex interplay of various changes and influences, including genetics and environmental factors. Certain psychiatric disorders, such as bipolar mood disorder, schizophrenia, and ADHD, show a genetic component.

Environmental factors like head injury, poor nutrition, and exposure to toxins increase the risk of psychiatric disorders. Social stressors, such as childhood abuse, socioeconomics, and gender-based violence, also impact mental well-being, particularly in regions like South Africa with high levels of racial and gender inequality.

Prevalence of psychiatric disorders in adolescence

Global studies indicate a significant rise in disability-adjusted life years due to psychiatric disorders, making them a top-ten leading cause of disease. Prevalence rates in high-income countries show anxiety, ADHD, oppositional defiant, substance use, conduct, and depressive disorders. In South Africa, limited data suggests a prevalence of psychiatric disorders around 17%, with a substantial burden of substance abuse.

Treating psychiatric disorders in childhood and adolescence

Around 40% of adolescents with one psychiatric disorder grapple with another, emphasizing the need for early intervention. Anxiety disorders, categorized in the DSM-5, include various forms like agoraphobia, panic disorder, and social anxiety disorder. Depressive disorders, such as major depressive disorder and persistent depressive disorder, present with symptoms ranging from low mood to suicidal thoughts. Treatment recommendations encompass non-pharmacological interventions like cognitive-behavioural therapy and pharmacotherapy.

Comprehensive approaches to well-being: Lifestyle and therapeutic interventions

Beyond traditional treatments, a comprehensive strategy involves lifestyle changes and adjunctive interventions. Dietary modifications, exercise, limiting screen time, and nature-based therapies contribute to mental well-being. Omega-3 supplementation, probiotics, vitamin D, and folate are considered adjunctive therapies.

Exercise interventions, particularly yoga and aerobic exercise, prove effective in reducing symptoms. Decreasing screen time and increasing exposure to natural environments are linked to improved mental health. Osteopathic manipulative treatments, although lacking specific studies for anxiety and depression in adolescents, show promise.

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Disease of kings and the king of diseases

Gout is the most common sign of hyperuricaemia, defined as an elevated serum uric acid (sUA) level – usually >6mg/dl in women and >7mg/dl in men. sUA is recognised as a double-edged sword, exhibiting both pro-inflammatory and anti-oxidant effects.[1,2]

Gout, historically referred to as the 'disease of kings and the king of diseases' (because it was thought to be caused by an overindulgence in food and alcohol), is a common cause of chronic inflammatory arthritis.[3]

Gout triggers include a combination of genetic risk factors, concurrent medical conditions, and dietary influences. While most cases is due to a combination of factors, there are rare instances where a genetic defect can be the primary cause, which is often linked to additional medical complications.[3]

The heritability of both hyperuricemia and gout is estimated at ~73%, with 40%–50% of patients reporting a familial risk. Regardless of the specific factors at play, the common outcome is an elevation in sUA levels, which, in some patients, eventually leads to gout symptoms.[3]

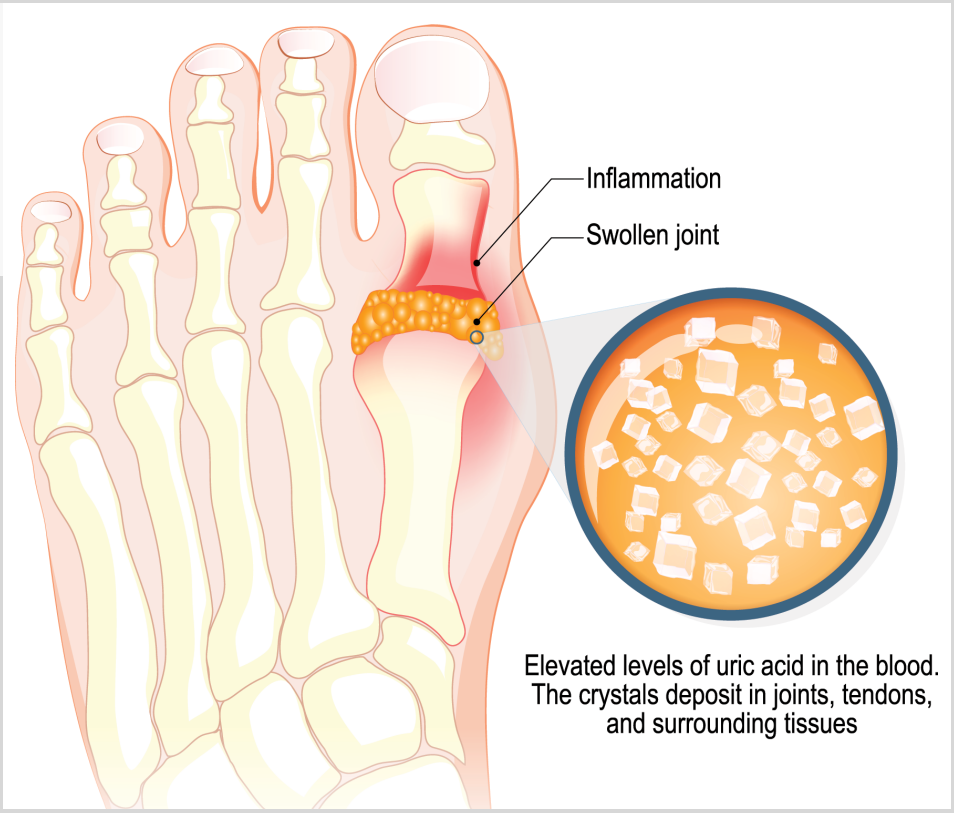
Symptoms of gout include acute flares of inflammatory arthritis, chronic gouty arthropathy, the accumulation of urate crystals in tophaceous deposits, uric acid nephrolithiasis, and chronic nephropathy.[3]

Gout linked to an increased risk of chronic and CV diseases

Studies show that gout is linked to an increased risk of hypertension, obesity, diabetes, chronic kidney disease, myocardial infarction, heart failure, and stroke. Furthermore, metabolic syndrome in gout patients is increasing.[1]

SUA levels have also been implicated in an increased risk of mortality, with hyperuricaemia associated with increased all-cause and cardiovascular (CV) mortality rates.[1]

The impact of hyperuricaemia on cancer risk has also been investigated, revealing conflicting findings. While some studies suggest a lower prevalence of colorectal cancer in gout patients, others report an increased risk of overall cancer incidence and mortality.[1]



The underlying mechanisms connecting gout to cancer risk involve the pro-inflammatory properties of sUA, which overlap with metabolic diseases.[1]

Hyperuricaemia has also been associated with pulmonary diseases such as, decreased lung function in middle-aged men and women. Furthermore, studies report a positive association between sUA and lumbar spine bone mineral density in men.[1]

Should, could and don't

Of the rheumatic diseases, gout is the best-understood and potentially most manageable condition. Complete control is possible with safe and affordable pharmacological treatment, provided it is prescribed correctly and maintained long-term. Despite this, gout often goes untreated or is poorly managed due to inconsistent guideline recommendations, according to Conley *et al*.[4]

A systematic review by the team synthesised recommendations from six high-quality clinical practice guidelines (CPGs). The six identified high-quality CPGs were developed by medical/professional societies from the United States (two), Europe (three), and the United Kingdom (one). The findings were categorised into recommendations with 'Should do,' 'Could do,' and 'Do not do'.[4]

Should do

- Initiate non-steroidal anti-inflammatories (NSAIDs), colchicine, or corticosteroids (CS) as first-line treatment.
- Educate patients about non-pharmacological and pharmacological management options, advice on joint elevation and rest, dietary guidance, and weight loss for patients living with obesity or who are overweight.
- Exercise advice for all patients and smoking cessation guidance are also recommended.
- Screen patients annually for CV risk factors.
- Start prophylaxis before or within the first six months of initiating urate-lowering therapy (ULT), continuing for three to six months, with colchicine as the preferred treatment, followed by NSAIDs, cyclooxygenase-2 inhibitors, and low-dose glucocorticoids if necessary. Reduced prophylaxis doses are suggested for patients with renal impairment.
- Monitor sUA levels and implement ULT based on a treat-to-target strategy in patients with chronic gout. The recommended targets are: sUA <6 mg/dl, lifelong or sUA <5mg/dl for severe or tophaceous gout. Allopurinol is the recommended first-line ULT, starting at 50mg/d–100mg/d (not exceeding 100mg). The dose should be increased by 100mg increments every two to four weeks or four weeks until reaching the sUA target, with a maximum daily dose of 900mg.

Could do

- Use cold therapies, such as ice packs, in combination with other evidence-based treatments. Interleukin-1 (IL-1) inhibitors can be considered for patients living with acute gout or who experience frequent flares, particularly if standard treatments were contraindicated or ineffective.
- Consider febuxostat as a second-line xanthine oxidase inhibitor (XOI) for patients with chronic gout renal impairment or chronic kidney disease, where allopurinol is contraindicated or ineffective.
- Uricosuric agents, either in combination with a XOI or as monotherapy, can be considered for patients with a poor response, intolerance, or adverse reactions to XOIs.
- IL-1 inhibitors can be use if a patient has contraindications or did not respond to standard anti-inflammatory gout treatments.

Do not do

- Avoid IL-1 inhibitors for patients with current infections.
- NSAIDs and colchicine are not recommended for patients living with severe renal impairment or experiencing an acute gouty attack.
- Avoid a SUA level <3mg/dl long-term due to potential adverse effects.
- Allopurinol should be avoided in patients living with chronic gout and human leukocyte antigen-B5801 allele.
- Uricosuric agents, specifically lesinurad or benzbromarone, are not recommended for patients with severe kidney disease. Lesinurad should be avoided after a vascular event in the last 12 months.
- Do not measure urinary uric acid and alkalinizing urine during uricosuric treatment.
- IL-1 inhibitors are not recommended if the patient has a current infection.

Conclusion

Gout is linked to hyperuricaemia, impacting diverse physiological systems. Its association with chronic and CV diseases underscores its systemic nature. While gout is highly manageable, inconsistent guidelines contribute to undertreatment. A recent review synthesised various guidelines developed 'Should do,' 'Could do,' and 'Do not do' recommendations, crucial for effective, tailored management. SF

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Mitigating HDP: *Vaginal micronised progesterone's protective potential*

Hypertensive disorders of pregnancy (HDP) – categorised as chronic hypertension, gestational hypertension, pre-eclampsia (PE)/eclampsia, and pre-eclampsia superimposed on chronic hypertension – affect ~18 million women globally. A recent meta-analysis suggests that initiating vaginal micronised progesterone in the first trimester may reduce the risk of HDP and PE.[1,2]

PE and eclampsia are the primary causes of maternal mortality (18%) in South Africa. An estimated 75% of HDP-related maternal deaths can be prevented.[3]

A history of spontaneous pre-term births, as well as conditions that compromise uteroplacental blood flow and contribute to vascular insufficiency (eg pre-existing hypertension, renal disease, diabetes, obstructive sleep apnoea, thrombophilia, and autoimmune disorders), increase the risk of HDP.[1,4]

Hypertension in pregnancy defined

Chronic hypertension is defined as in-office measurements >140mmHg systolic blood pressure (SBP) or 90mmHg diastolic BP (DBP). Chronic hypertension results in complication in ~5% of all pregnancies, and prevalence rates are increasing due to delayed childbearing.[2,5]

Gestational hypertension is defined as transient hypertension specific to pregnancy or the identification of chronic hypertension in the latter half of the gestational period. Risk factors for gestational hypertension, which can progress to PE, include multiple pregnancies (especially twins), a body mass index >30m^2, age (>35-years), or a family history (especially with a mother or sister affected).[4,5]

According to the American College of Obstetricians and Gynecologists (ACOG), gestational hypertension typically presents after 20 weeks of pregnancy with BP >140/90mmHg on two occasions, or higher severe range pressures, necessitating prompt antihypertensive treatment.[4]

PE superimposed on chronic hypertension occurs in women living with pre-existing chronic arterial hypertension, either primary or secondary, who subsequently develop PE.[5]

Criteria for PE, and eclampsia

The ACOG criteria for PE include >300mg urine protein excretion in a 24-hour period or a protein/creatinine ratio ≥0.3. If these testing methods are unavailable, a urine dipstick can be used, with proteinuria defined as a reading of at least 1+.[4]

It should be noted that PE can be present in the absence of proteinuria if the patient has new-onset hypertension with thrombocytopaenia (platelets <100 000 x10^9/l, renal insufficiency [double of baseline serum creatine or serum creatine >1.1mg/dl], pulmonary oedema, impaired liver function [aspartate aminotransferase and alanine aminotransferase more than twice the upper limit of normal]), or new-onset headache unresponsive to medications with no alternative cause.[4]

Untreated PE causes maternal complications in ~70% of cases and is

associated with maternal morbidity in as many as 14% of women. Between 2%–3% of women diagnosed with PE, progress to eclampsia. Eclampsia is typified by generalised tonic–clonic seizures (typically intra–partum or post–partum up to 72 hours after delivery).[3,4]

Aetiology of PE: A quick overview

Early–onset PE is characterised by incomplete transformation of spiral arteries, resulting in placental hypoperfusion and foetal growth restriction (FGR). In contrast, late–onset PE involves minimal alterations in spiral arteries, often leading to placental hyperperfusion without FGR.[6]

Normal pregnancy involves increased extracellular fluid and plasma volumes mediated by nitric oxide. However, early–onset PE sees a decrease in plasma volume around 14 to 17 gestational weeks, preceding clinical onset.[6]

Placental development in normal pregnancies involves vascularisation and trophoblast invasion. Endovascular trophoblasts invade spiral arteries, inducing transformation for optimal foetal growth.[6]

Syncytiotrophoblasts act as an interface, preventing direct blood mixing. A low–grade inflammatory response reacts to foetal trophoblasts in normal pregnancies.[6]

Reduced blood flow, defective spiral artery remodelling, and acute arteriosus lead to hypoperfusion in early–onset PE. Placental ischaemia–reperfusion injury contributes to hypertension, proteinuria, and thrombotic microangiopathy.[6]

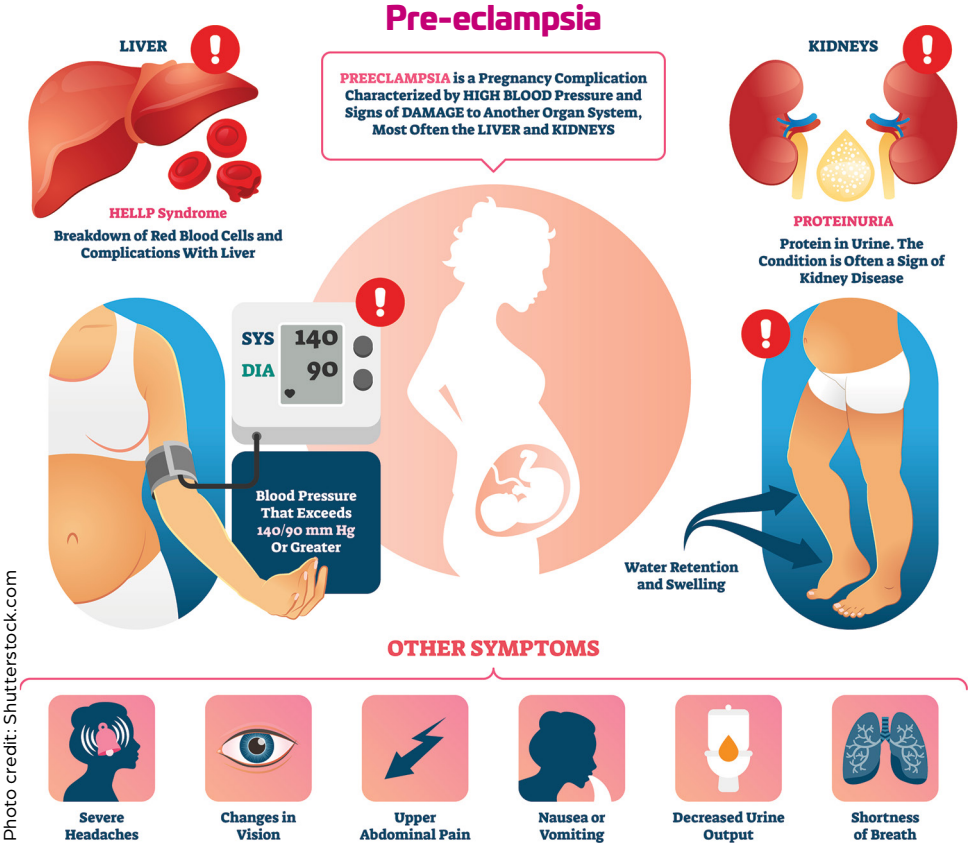
Pro–angiogenic factors (vascular endothelial growth factor [VEGF], placental growth factor, and transforming growth factor–beta [TGF–β]) play roles in placental angiogenesis.[6]

Elevated soluble endoglin levels in PE block TGF–β1 and VEGF actions, contributing to the imbalance in angiogenic factors. Immune factors, type 1 t–helper (Th) 1 immunity, and inflammation are involved in PE, with cytokines indicating an exaggerated inflammatory response.[6]

The renin–angiotensin–aldosterone system (RAAS) and auto–antibodies (angiotensin [AT]–1AA) targeting angiotensinogen (ANG) AT–I receptors also play roles in PE. RAAS downregulation in PE results in increased sensitivity to ANG–II and AT–1AA. Elevated AT–1AA levels may contribute to shallow trophoblast invasion and renal damage.[6]

Hydrogen sulphide (H2S), also implicated in PE, has vaso–relaxant and anti–inflammatory properties. Reduced cystathionine gamma–lyase and cystathionine beta–synthase enzyme expressions in PE affect H2S production, crucial for placental development.[6]

Despite more than six decades of research, the exact aetiology of PE remains elusive. An imbalance between angiogenic and anti–angiogenic factors, immune responses, low oxygen tension, and oxidative stress contribute to generalised maternal endothelial dysfunction in PE, causing hypertension, renal endotheliosis, and blood coagulation.[6]



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Progesterone's role in pregnancy

Progesterone plays a pivotal role in ensuring the success of a pregnancy. Naturally secreted by the corpus luteum (CL) in the latter part of the menstrual cycle, and subsequently by both the CL and placenta in early pregnancy, progesterone prepares the endometrium for embryo implantation. Following successful implantation, the CL persists in progesterone production. However, around eight to 12 weeks into gestation, the placenta assumes responsibility for this function, sustaining the pregnancy.[7]

Progesterone exerts different effects on the immune system through various receptors, including nuclear progesterone receptors (nPR), membrane progestin receptors (mPR), and progesterone receptor membrane components (PGRMC).[8]

During pregnancy, elevated progesterone levels have paracrine and endocrine actions, suppressing myometrial contractility, regulating inflammation in leukocytes, and modulating immune responses.[8]

The balance between nPR isoforms, progesterone receptor A and progesterone receptor B, influences progesterone signalling, with shifting ratios during pregnancy impacting gene expression related to labour.[8]

Non–classical receptors, such as mPRs and PGRMCs, participate in extracellular signalling and cell cycle regulation. In T–cells, membrane–bound progesterone receptors influence signal transduction, calcium mobilisation, and transcription factor phosphorylation, affecting T–cell activation and proliferation.[8]

Progesterone's anti–inflammatory actions involve suppression of nuclear factor–kappa B and mitogen–activated protein kinase pathways, downregulation of pro–inflammatory genes, and modulation of immune cell activity.[8]

In reproductive tissues, progesterone promotes an anti–inflammatory environment, inhibits cervical changes associated with labour, and modulates innate immune responses. Progesterone influences immune cell populations, suppresses inflammatory cytokines, and enhances immune tolerance, contributing to a supportive pregnancy environment.[8]

Progesterone's effects on adaptive immune responses involve interactions with glucocorticoid receptors (GR) and progesterone receptors (PR). During pregnancy, regulatory T–cell (Tregs) proportions exhibit dynamic changes, suggesting alternative immunomodulatory pathways.[8]

Progesterone also modulates peripheral blood T–cell differentiation, favouring Th2

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subsets with increased interleukin (IL)-4 production. Extracellular progesterone concentrations during pregnancy suppress interferon-gamma (IFN-γ) production in CD8 T-cells.[8]

In the menstrual cycle, the progesterone-rich luteal phase associates with a decline in Tregs, leukocyte proliferation, and IFN-γ production, favouring a Th2 cytokine profile.[8]

Progesterone influences B-cell lymphopoiesis, suppressing B-cell development and influencing humoral immune responses. Despite promoting a Th2-dominant profile, progesterone negatively regulates high-affinity antibody production. The mechanism of progesterone action on lymphocytes involves both genomic and non-genomic pathways through different receptors, including mPRs.[8]

Progesterone-induced blocking factor (PIBF), a progesterone-regulated gene, is a potent immune modulator, regulating cytokine synthesis, Th subtype differentiation, and proliferation.[8]

PIBF, abundantly expressed during pregnancy, is crucial for immune tolerance, as reduced concentrations are associated with spontaneous pre-term birth and pro-inflammatory cytokine profiles.[8]

Clinical application of progesterone

Clinical applications of progesterone include its use in treating infertility, preventing miscarriage, and managing pre-term labour.[7]

The efficacy of progesterone in preventing recurrent miscarriage (or spontaneous abortion, which occurs during the first 20 weeks of pregnancy, typically within the first trimester) was investigated in two studies by Coomarasamy *et al*.[8,9]

In the *Progesterone in Recurrent Miscarriages* or PROMISE trial, the researchers tested whether progesterone given to pregnant women with a history of repeated (≥3 consecutive or non-consecutive) unexplained early pregnancy losses would increase the number of pregnancies leading to live births after at least 24 weeks of gestation, compared with placebo.[8]

Participants (n = 836) were randomised to progesterone (400mg twice daily as vaginal capsules) or placebo soon after a positive urinary pregnancy test no later than six weeks of pregnancy, until 12 completed weeks of pregnancy (or earlier if the pregnancy ended before 12 weeks).[8]

The primary outcome was live birth >24 completed weeks of gestation, clinical pregnancy at six-to eight-weeks, ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital abnormalities and resource use.[8]

Secondary outcomes included pre-eclampsia, small size for gestational age (<10th percentile for birth weight), preterm pre-labour rupture of membranes, antepartum haemorrhage, and mode of delivery, as well as neonatal variables such as birth weight, arterial and venous pH, Apgar scores, and need for ventilation support.[8]

The rate of live births after 24 weeks of gestation was 65.8% in the progesterone group, as compared with 63.3% in the placebo group. There was no significant difference in secondary outcomes between the two groups. However, the team did note a 25% reduction in the risk of pre-eclampsia in the progesterone group.[1,8]

In the *Progesterone in Spontaneous Miscarriage* or PRISM study, the live birth rate for women with one or more previous miscarriages, was 75% in the progesterone group compared with 70% in the placebo group. The potential benefit appeared to be most strong for women with three or more previous miscarriages, who had a live birth rate of 72% in the progesterone group compared with 57% in the placebo group. The team noted a 37% lower risk of pre-eclampsia among participants receiving progesterone.[1,9]

Due to the shared aetiology of miscarriage and PE, it has been hypothesised that progesterone treatment may be effective in reducing the risk of PE. Melo *et al* recently conducted a systematic review to summarise evidence that micronised vaginal progesterone can reduce the risk of HDP.[1]

Their review included 11 randomised controlled studies involving 11 640 women. In three studies vaginal progesterone was initiated in the first trimester and in eight studies it was initiated in the second or third trimesters.[1]

The initiation of vaginal progesterone during the first trimester significantly reduced the risk of any HDP (29%) and pre-eclampsia (39%) compared to placebo. However, initiation of vaginal progesterone in the second or third trimesters did not show a significant reduction in HDP or PE.[1]

Conclusion

HDP impact ~18 million women globally. In South Africa, PE and eclampsia contribute to 18% of maternal mortality. The prevention of HDP and PE is crucial, and a recent systematic review report a potential protective effect of vaginal micronised progesterone, especially when initiated in the first trimester. Progesterone, a key hormone in pregnancy, exerts diverse immunomodulatory effects, impacting myometrial contractility, inflammation, and immune responses. SF

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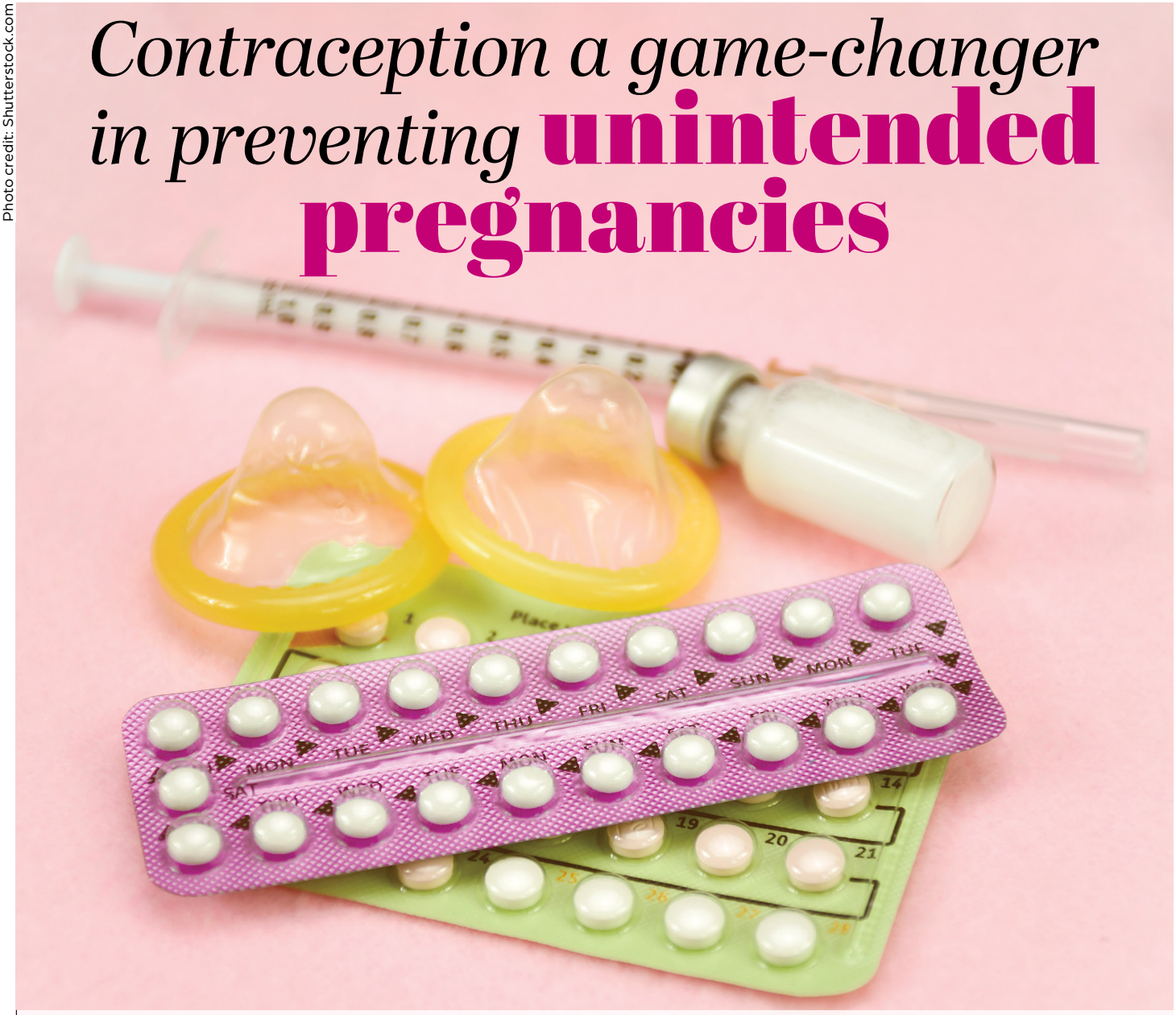
Contraception a game-changer in preventing unintended pregnancies



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February is Reproductive Health Awareness Month in South Africa. Unintended or unplanned pregnancies pose a significant public health challenge in low- and middle-income countries (LMICs), accounting for ~89% of cases globally. This equates to roughly 88 million pregnancies. In South Africa, ~1 960 000 pregnancies occurred annually between 2015 and 2019, with ~1 270 000 being unintended and ~461 000 ending in abortion.[1,2]

Globally 121 million unintended pregnancies occurred between 2015 to 2019. A significant proportion (61%) of these pregnancies ended in abortions each year.[3]

In LMICs, teenage (15- to 19-years) pregnancies, are highly prevalent, accounting for ~21 million unintended pregnancies annually and leading to ~12 million births. As of 2022, ~4% of South African teenage girls reported experiencing various stages of pregnancy in the past 12 months.[4,5]

The prevalence of pregnancy exhibited an upward trend with age, starting at 0.3% among 14-year-olds and exceeding 10% among 19-year-olds. Additionally, there was a 1.1% increase in the incidence of pregnancy among girls aged 14- to 19-years compared to the figures from 2021.[5]

Consequences of unintended pregnancy

Unintended pregnancy refers to a pregnancy that is either unwanted, occurring when no children are desired, or mistimed, happening earlier than desired.[3]

Recent research indicates that globally, about 20% of pregnancies resulting in live births were unintended at conception. The research also shows that 37% of women reported no contraceptive use before pregnancy, a figure that decreased to 24% after pregnancy.[1]

Notably, 54% of women who reported no contraceptive use before pregnancy adopted modern contraceptives afterward, with higher rates among those experiencing unintended pregnancies (73.4%) compared to mistimed (58.8%) and wanted (53.4%) pregnancies.[1]

Mistimed pregnancies were associated with a higher likelihood of maintaining no contraceptive use and switching to less effective methods compared to transitioning to more effective contraceptives.[1]

Unintended pregnancies correlate with adverse maternal and child health outcomes, including increased maternal and child mortality. It also often compels women to grapple with complex decisions, such as undergoing abortion, considering

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adoption, or navigating the responsibilities of raising a child without adequate financial, physical, and emotional support.[3]

The health implications of unintended pregnancies are substantial, and include inherent risks associated with pregnancy, potentially exacerbated by pre-existing medical conditions, as well as the hazards of experiencing multiple pregnancies.[3]

Complications such as haemorrhage, infection, and hypertensive disorders contribute significantly to maternal mortality, particularly in developing regions.[3]

Each unintended pregnancy elevates the risk of substantial morbidity and mortality for women, stemming from factors like poverty, malnutrition, limited access to healthcare, and insufficiently trained healthcare providers.[3]

Negative sentiments about pregnancy are more pronounced among women facing repeat unintended pregnancies, characterised by short birth intervals, a high number of births, undernutrition, and complications from prior unintended pregnancies.[1]

Access to contraceptives crucial to prevent repeat unintended pregnancies

The adverse consequences of unintended pregnancies are substantially higher in women with repeat unintended pregnancies. Although the successful implementation of Millennium Development Goals led to a substantial increase in contraceptive use in LMICs (from 52% to 62% in 2015), ~50% of married women of reproductive age in these countries still lack proper access to modern contraception methods.[1]

Factors influencing contraceptive use include future fertility preferences and socio-demographic characteristics such as women's age, education levels of women and their partners, socio-economic status, and exposure to mass media.[1]

Obstacles to openly discuss and make contraceptive decisions has been identified as an obstacle for teenage girls, especially those with older partners. In specific scenarios, societal expectations may compel girls to marry and bear children after marriage.[4]

These scenarios involve social and peer pressures to engage in sexual activities, conceive, coercion from familial influences, and restricted autonomy in choosing and using contraceptives, all contributing to the incidence of teenage pregnancies.[4]

Overcoming these challenges and ensuring proper access to effective contraceptives post-birth are crucial to prevent repeat unintended pregnancies and their associated adverse consequences.[1,4]

Prevention strategies

Mohamed *et al* identified three potential strategies that may be effective in preventing unintended pregnancies:[4]

1. Primary prevention strategies involve efforts aimed at averting unintended pregnancies from occurring initially. These may involve fostering a supportive family environment, implementing comprehensive sexuality education, promoting contraceptive use, and addressing the prevention and detection of sexual and gender-based violence.
2. Secondary prevention strategies involve early pregnancy diagnosis and counselling on various pregnancy options, including facilitating access to safe abortion care.
3. Tertiary prevention strategies focus on preventing adverse events associated with unintended pregnancies. This includes treating incomplete abortions, providing services for psychosocial trauma, and offering antenatal care and maternity services to prevent maternal morbidity and mortality.

Contraceptives options, patient selection, safety and efficacy

The use of contraception has been hailed as a game-changer in preventing unintended pregnancies. The ideal choice of contraception should consider the values and preferences of patients. Available options include:[6,7]

Intravaginal gel

A new barrier method inserted an hour before intercourse. Maintains acidic pH to inhibit sperm motility and provides a physical barrier. The *AMP002 Phase III Contraceptive Study* or AMPOWER study demonstrated 86.3% contraceptive efficacy with typical use. Adverse events include vaginal burning (18%) and itching (14.5%). Suitable for those desiring non-hormonal birth control on-demand.

Combined vaginal ring

A 13-cycle combined vaginal ring containing segesterone acetate and ethinyl oestradiol. Provides one year of birth control. Effectiveness in pregnancy prevention noted to be 97.3% with typical use. Complete expulsions occur in ~7% of cycles. An option for those seeking longer-acting, reversible contraception without a daily regimen.

Progestin-only pill (drospirenone 4mg)

An option for women with contraindications to oestrogen-containing contraceptives. Studies found that 4mg drospirenone has anti-mineralocorticoid and antiandrogenic properties. Shows effective suppression of ovulation for up to 24 hours after a missed or delayed dose. Provides a 24/4-day regimen with a regular withdrawal bleed. Offers a desirable safety profile with minimal impact on metabolic parameters.

Newer oestrogen options

Oestradiol valerate and oestetrol are alternatives for those intolerant to ethinyl oestradiol. Oestradiol valerate is a quadriphasic combined oral contraceptive (COC) with lower oestrogen doses. Oestetrol is a novel oestrogen with minimal impact on metabolic parameters. Both provide contraceptive efficacy comparable to ethinyl oestradiol-containing COCs.

Transdermal options

A transdermal patch containing 30µg ethinyl oestradiol and 120µg levonorgestrel. Addresses poor adherence associated with oral contraceptives. Concerns about venous thrombo-embolism risks associated with transdermal patches. May be beneficial for those with difficulty remembering daily pills.

Self-administered DMPA-SC

Offers an option for self-administration of depot medroxyprogesterone acetate (DMPA-SC) for improved contraceptive access. Shown to have a higher continuation rate than provider-administered DMPA. Patients find it easy to administer, with high satisfaction rates. Barriers include fear of needles, incorrect administration, and insurance coverage.

What options are available for male contraception?

There are currently no approved contraceptive options for men except condoms. Behavioural contraceptive methods include penile withdrawal and fertility awareness-based methods, such as natural family planning or the rhythm

method. The effectiveness of withdrawal and fertility awareness relies on patient education, cycle regularity, and commitment to daily evaluation of symptoms.[7]

A meta-analysis reported fertility awareness method failure rates of 22 pregnancies per 100 women-years. Barrier methods like condoms and diaphragms prevent sperm entry and have a first-year typical use effectiveness of 13 pregnancies per 100 women. Current male contraceptive methods currently under evaluation include attempts to suppress sperm count to <1 million/ml and include a testosterone plus progestin topical gel.[7]

Emergency contraception

Emergency contraception (EC) reduces pregnancy risk after unprotected intercourse. The copper intrauterine devices (IUD) are the most effective EC method, reducing risk to 0.1% when placed within five days. Levonorgestrel (LNG) IUDs are now considered for EC. Oral EC, using progestin (LNG) or anti-progestin (ulipristal acetate), blocks or delays ovulation.[7]

LNG EC is available over the counter, while ulipristal acetate requires a prescription. Both should be taken as soon as possible after unprotected intercourse, with ulipristal acetate remaining effective up to 120 hours. Clinicians should discuss EC options with patients starting user-controlled methods and may prescribe oral EC for immediate use if needed.[7]

The pill still the most widely used reversible contraceptive

Oral contraceptives are still the most widely utilised reversible contraceptives. Choosing a contraceptive pill should be based on patient experience due to the absence of comparative effectiveness studies clearly indicating the superiority of one formulation over another.[7]

Monophasic regimens, featuring consistent hormone doses in each pill, offer advantages over biphasic and triphasic regimens. The flexibility of extending cycles by skipping the placebo week is more feasible with monophasic regimens, preventing breakthrough bleeding common in multiphasic regimens.[7]

For ethinyl oestradiol, a dose exceeding 35µg per day is rarely necessary, with starting at 30µg to 35µg providing the best chance of a regular bleeding pattern without added risks. Adjusting ethinyl oestradiol may be considered if oestrogen-associated adverse effects arise.[7]

Various progestins options are available and differ in terms of androgenicity, metabolic effects. Despite structural differences, no evidence supports the superiority of one progestin over another. Patients may prefer a previously used pill, and if suitable, prescribing it is reasonable.[7]

COCs can be dosed cyclically or continuously. Originally, a 21-day active drug cycle with a seven-day placebo trigger for withdrawal bleeding was common. However, extended and continuous dosing, with shorter or no placebo periods, has become popular due to improved efficacy and fewer adverse effects associated with the placebo week. A new vaginal ring (segesterone acetate/ethinyl oestradiol) offers a yearly prescription with monthly removal for seven days.[7]

IUDs and subdermal implants have the highest effectiveness

Long-acting reversible contraceptives (LARCs eg IUDs, copper -IUD, and subdermal implants) provide at least three-year continuous pregnancy protection and do not require any input from users. LARCs have demonstrated greater efficacy in preventing unintended pregnancy among all women in comparison with short-acting methods.[8]

Typical use pregnancy rates for the copper IUD are ~1% per year, with no impact on the user's hypothalamic-pituitary-ovarian axis, allowing uninterrupted ovulation and menstrual cyclicity.[7]

The primary mechanism of action involves spermicidal effects, attributed to copper salts and induced endometrial inflammatory changes. A notable challenge associated with the copper IUD is the potential increase in the amount, duration, and discomfort of menstrual periods, particularly during the initial three to six months of usage.[7]

Importantly, IUD utilisation does not elevate the subsequent risk of tubal infertility. In cases where sexually transmitted infection (STI) testing is deemed necessary, it can be conveniently conducted alongside IUD placement.[7]

This streamlined approach to STI testing during IUD insertion does not amplify the risk of pelvic inflammatory disease. The absolute risk of pelvic inflammatory disease post-IUD insertion remains low, ranging from 0% to 5% in patients living with gonorrhoeal or chlamydial infections and 0% to 2% in those without such infections.[7]

Subdermal implants are progestin-only contraceptives inserted under the skin, delivering hormones steadily and bypassing hepatic metabolism. They lack oestrogen, thus preventing plasma progestin peaks.[8]

The LNG 6-capsule subdermal implants were pioneering reversible contraception methods, demonstrating lower failure rates and one-year pregnancy rates compared to oral contraceptives and IUDs. Bleeding irregularities were the primary cause for discontinuation and the most reported side effect.[8]

Etonogestrel (ENG) implants are a single-rod contraceptive containing 68mg of ENG. Post-removal, normal menses returned in most patients. Despite common side effects like abnormal bleeding, the evidence did not associate higher body mass index (BMI) or weight with hormonal contraceptive effectiveness, making it a first-line option regardless of BMI.[8]

Research suggests extending the approved three-year period for ENG implants, positioning them as discreet alternatives to IUDs for teenage girls. Immediate postpartum implant insertion and post-abortion placement were deemed safe and effective.[8]

The ENG implant shows promise in managing symptomatic endometriosis, offering pain relief comparable to other progestins. The insertion of ENG implants immediately after a surgical abortion do not increase pregnancy risk, further establishing their versatility and efficacy in various reproductive health scenarios.[8]

Conclusion

South Africa faces what some has called a teenage pregnancy epidemic, with rising rates and associated challenges.[9] Unintended pregnancies, prevalent in LMICs, can lead to adverse maternal and child health outcomes, necessitating effective prevention strategies.

Repeat unintended pregnancies pose higher risks, highlighting the need for proper access to contraceptives. Contraceptive options, including innovative methods and male contraception, play a crucial role.

Overcoming societal barriers and ensuring access to contraceptives post-birth are essential for preventing unintended pregnancies. Implementation of primary, secondary, and tertiary prevention strategies can contribute to mitigating the impact of unintended pregnancies, fostering better reproductive health outcomes in South Africa. SF

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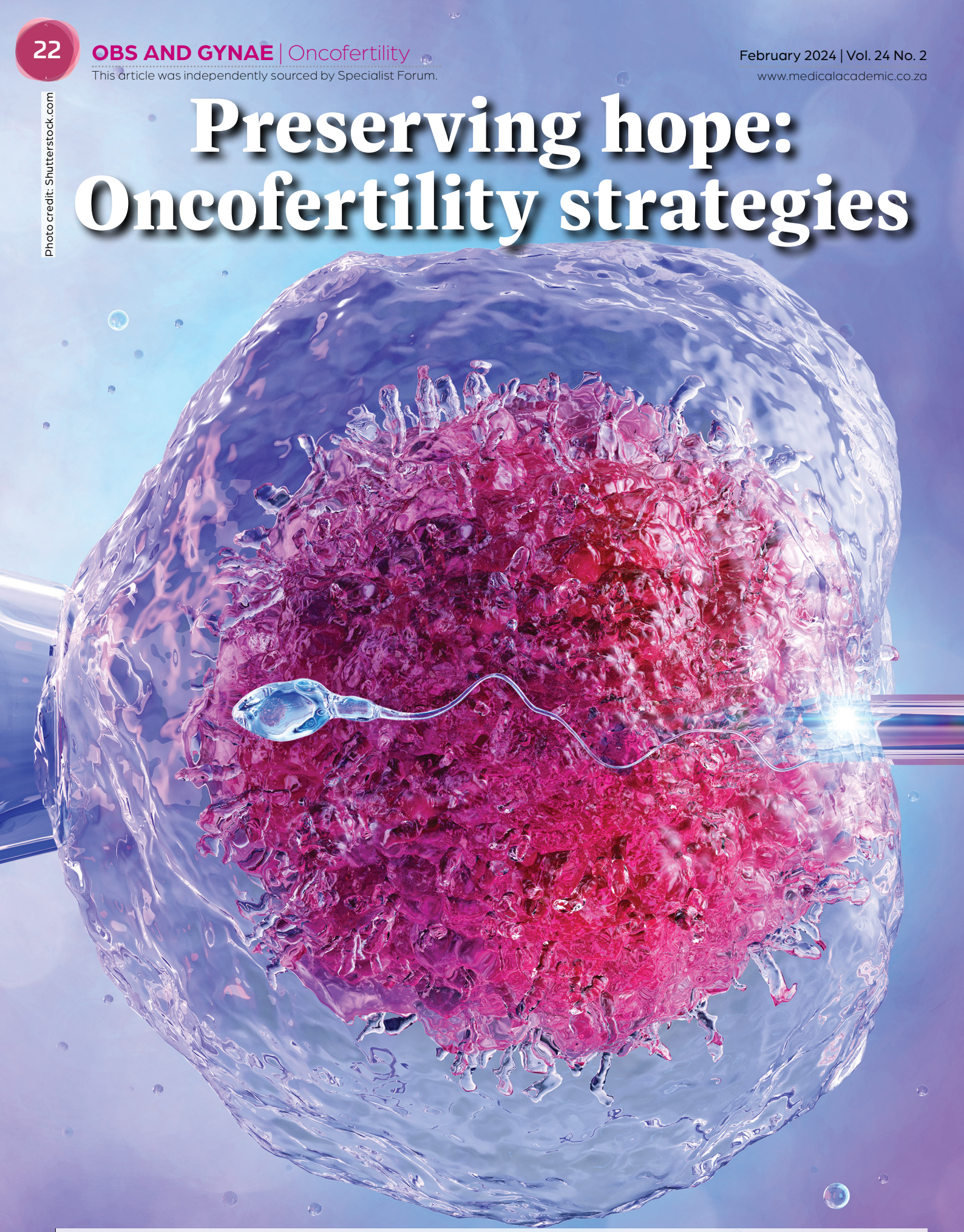
Preserving hope: Oncofertility strategies



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GARDASIL® 9 is a vaccine indicated in **girls and women** from 9 years of age onwards for the prevention of cervical, vulvar, vaginal and anal cancer, pre-cancerous or dysplastic lesions, genital warts and persistent infections caused by the Human Papillomavirus (HPV).

GARDASIL® 9 is indicated in **boys and men** from 9 years of age onward for the prevention of anal cancer, anal pre-cancerous or dysplastic lesions; external genital lesions (including genital warts) and persistent infections caused by HPV.

GARDASIL® 9 offers **wider coverage** with a high efficacy against **9 high-risk HPV-types**[1]

THE 4 TYPES IN GARDASIL®
[Quadrivalent Human Papillomavirus (Types 6,11,16,18) Recombinant Vaccine][2]

can cause genital warts (condylomata acuminata)[1]

6 11 16 18

PLUS 5 ADDITIONAL ONCOGENIC TYPES[1]

31 33 45 52 58

can cause premalignant lesions and cancers affecting the cervix, vulva, vagina and anus[1]

REFERENCES: 1. GARDASIL® 9 approved Package Insert, June 2018. **2**. GARDASIL® approved Package Insert, March 2015.

SELECTED SAFETY INFORMATION: INDICATIONS: GARDASIL 9 is a vaccine indicated in girls and women from 9 years of age onwards for the prevention of cervical, vulvar, vaginal and anal cancer, pre-cancerous or dysplastic lesions, genital warts and persistent infections caused by the Human Papillomavirus (HPV). GARDASIL 9 is indicated in boys and men from 9 years of age onward for the prevention of anal cancer, anal pre-cancerous or dysplastic lesions; external genital lesions (including genital warts) and persistent infections caused by HPV. **CONTRAINDICATIONS:** GARDASIL 9 is contraindicated in patients with hypersensitivity to either GARDASIL 9 or GARDASIL or any of the inactive ingredients in either vaccine. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL 9 or GARDASIL should not receive further doses of GARDASIL 9. **WARNINGS AND SPECIAL PRECAUTIONS:** This vaccine should not be used interchangeably with other Human Papillomavirus (HPV) vaccines (as such use has not been studied). This vaccine should be given with caution to individuals with either thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals. Appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of GARDASIL. **General:** Vaccination with GARDASIL may not result in protection in all vaccine recipients. This vaccine is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal or anal cancers; CIN, VIN, VaIN or AIN. GARDASIL will not protect against diseases that are not caused by HPV. Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with GARDASIL. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL 9. The decision to administer or delay vaccination, because of a current or recent febrile illness depends largely on the severity of the symptoms and their aetiology. Low-grade fever itself and mild upper respiratory infection are not generally contraindications to vaccination. Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection or other causes, may have reduced antibody response to active immunisation. **INTERACTIONS: Use with Other Vaccines:** Results from clinical studies indicate that GARDASIL 9 may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)], and Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] (dTap-IPV). No studies have been performed with OMZYTA (Measles, Mumps and Rubella) and yellow fever vaccines. **Use with Hormonal Contraceptives:** In 7 269 women (16 through 26 years of age, from Protocols 001 and 002), 60,2 % used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9. **Use with Steroids:** Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines. **PREGNANCY AND LACTATION:** Safety in pregnancy and lactation has not been established in well-controlled clinical studies. **SIDE EFFECTS: Medicine-related Adverse Experiences:** Very Common (≥ 1/10) adverse reactions considered by investigators to be causally related to GARDASIL 9 are: headache, erythema, pain and swelling. Common (≥ 1/100 or < 1/10) adverse reactions considered by investigators to be causally related to GARDASIL 9 are: dizziness, nausea, pain in extremities, pyrexia, fatigue, pruritus and haematoma.

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S2 **GARDASIL® 9 Injection**. Reg. No: 51/30.1/0264. Each 0,5 ml dose contains approximately 30 µg of HPV Type 6 L1 protein, 40 µg of HPV Type 11 L1 protein, 60 µg of HPV Type 16 L1 protein, 40 µg of HPV Type 18 L1 protein, 20 µg of HPV Type 31 L1 protein, 20 µg of HPV Type 33 L1 protein, 20 µg of HPV Type 45 L1 protein, 20 µg of HPV Type 52 L1 protein and 20 µg of HPV Type 58 L1 protein.

MSD

Persistent infection with human papillomavirus (HPV) is the primary cause of CxCa, contributing to ~95% of cases. Around 80% of women will be infected with HPV during their lifetime.[2,3]

If left untreated, persistent high-risk HPV infection can progress from precancerous cervical lesions to invasive CxCa. Notably, the progression is often asymptomatic and slow, leading to a high case-fatality rate when women seek treatment at late symptomatic stages.[3]

In South Africa, high-risk HPV types 16 and 18 are responsible for 62.2% of CxCa cases, with HPV 16 being the most prevalent among affected women. The development of CxCa typically takes 15 to 20 years in women with normal immune systems but accelerates to five to 10 years in those with weakened immune systems, such as those with HIV.[3]

Various risk factors influence cancer progression, including the oncogenicity grade of the HPV type, immune status, presence of other sexually transmitted infections, number of births, young age at first pregnancy, hormonal contraceptive use, and smoking.[2]

Vaccination and screening are two of the most effective ways to reduce the risk of CxCa. In South Africa, three licensed HPV vaccines are currently available, all containing synthetic non-infectious virus-like particles produced through recombinant DNA technology.[3]

Both the bivalent and quadrivalent vaccines offer protection against new infections from HPV types 16 and 18. The quadrivalent vaccine provides additional protection against low-risk HPV types 6 and 11, responsible for genital warts. Recently introduced in South Africa, the nonavalent vaccine expands coverage to five more high-risk HPV types (31, 33, 45, 52, and 58).[3]

Brisson *et al* suggest that incorporating twice-lifetime screening can expedite the elimination of CxCa by 11 to 31 years. When coupled with girls-only HPV vaccination at a 90% coverage rate in sub-Saharan regions, this combined approach has the potential to prevent ~3.2 million cases of CxCa.[4]

A recent Swedish study showed that an estimated 47 women per 100 000 who were vaccinated develop the disease. The incidence is double in women who were not vaccinated (94 per 100 000).[5]

An estimated 40% of CxCa cases of occur during women's childbearing years. Cancer, or cancer treatment can cause infertility due to damage to gonadal tissue, gametes or sex hormones.[6,7]

Fertility-sparing options should be part of management plan

The European Society of Gynecological Oncology (ESGO) jointly with the European Society for Radiotherapy and Oncology (ESRO) and the European Society of Pathology (ESP) recently published their updated evidence-based guidelines for the management of patients with CxCa. The guidelines include a section dedicated to fertility-sparing treatment.[8]

Alkylating agents pose a moderate to high risk of causing infertility, with the likelihood correlating with the cumulative prescribed dose (eg >7.5gm of cyclophosphamide in females <20-years, and >5gm in older women).[9]

Platinum agents, anthracyclines, and taxanes carry an intermediate risk of infertility, while mercapturine, methotrexate, 5 fluorouracil, vincristine, bleomycin, and actinomycin are associated with a low or negligible risk.[9]

High-dose chemotherapy (ChT), particularly associated with haematopoietic stem cell transplantation, often leads to severe and potentially permanent infertility in the majority of cases. It is therefore important that options to preserve fertility should be part of the management plan.[9]

Vaccination and screening are two of the most effective ways to reduce the risk of CxCa

Fertility sparing a valuable alternative to radical hysterectomy

According to the authors of the updated guideline, fertility-sparing is a valuable alternative to radical hysterectomy for young patients with CxCa tumours <2cm.[8]

Prior to initiating this therapy, consultation at an oncofertility centre and discussion in a multi-disciplinary team are recommended. Counselling eligible patients includes considerations of oncologic and obstetric risks, along with the risk of therapy abandonment if there are positive resection margins or lymph node (LN) involvement. Such treatment should exclusively occur in gynaecological-oncological centres with expertise in all related surgical procedures.[8]

Uncommon and aggressive histological types should preclude fertility-sparing treatment considering prognostic factors, staging, and preoperative work-up. Imaging tests, such as pelvic magnetic resonance imaging or expert sonography, are mandatory. Negative pelvic LN (PLN) status is crucial, requiring PLN staging (sentinel LN) as the initial step.[8]

Intraoperative assessment and frozen section analysis are recommended to determine LN status. LN staging is not indicated in T1a1 lymphovascular invasion (LVSI) negative cases. In the event of proven PLN involvement, fertility-sparing surgery should be abandoned, directing patients to chemoradiotherapy and brachytherapy.[8]

Para-aortic LN dissection (PALND) for staging may be considered, but ovarian transposition is not recommended in N1 status. The goal of fertility-sparing surgery is the resection of invasive tumour with adequate free margins, preserving the upper cervix.[8]

Intra-operative frozen section aids in assessing the upper resection margin. LN staging follows early-stage management principles. Fertility-sparing procedures include conisation, simple trachelectomy, radical (vaginal) trachelectomy, and abdominal radical trachelectomy.[8]

Conisation and simple trachelectomy serve as appropriate fertility-sparing procedures for T1a1 and T1a2 tumours, regardless of LVSI status. T1b1, LVSI-negative tumours can be treated with conisation or simple trachelectomy, with radical trachelectomy as an alternative.[8]

Simple trachelectomy is a consideration for those without deep stromal involvement and a high probability of adequate endocervical tumour-free margins. Intraoperative placement of a permanent cerclage is advised during simple or radical trachelectomy. For T1b1, LVSI-positive patients, radical trachelectomy (type B) is recommended.[8]

Fertility-sparing therapy for tumours >2cm is associated with a higher recurrence risk. Patients must thoroughly discuss recurrence risks.[8]

Neoadjuvant ChT (NAChT) followed by radical vaginal trachelectomy or abdominal radical trachelectomy or cone has been described for tumours >2cm, with PLN staging before NAChT to confirm tumour-free LN. The optimal ChT cycles, regimen, and extent of cervical resection post-NAChT remain debated.[8]

The authors of the joint ESGO/ESRO/ESP guidelines caution that any pregnancy post-fertility-sparing therapy is considered high-risk. Caesarean section delivery is recommended following simple or radical trachelectomy with permanent cerclage.[8]

Limited evidence exists, but antenatal tools following fertility-sparing therapy may include screening and treatment for asymptomatic bacteriuria, screening for cervical incompetence and progressive cervical shortening, foetal fibronectin testing,

screening and treatment for asymptomatic vaginal infection, vaginal progesterone application, total cervical closure, and cervical cerclage (if not placed during trachelectomy). Routine hysterectomy post-childbearing is not mandatory.[8]

Advanced CxCa fertility preservation options

In advanced cases, fertility preservation options like laparoscopic ovarian transposition, oocyte/embryo/ovarian tissue preservation, and egg donation should be discussed with the patient taking legal ramifications into consideration.[8]

Ovarian transposition

Young women undergoing radiotherapy are at particular high risk of developing premature ovarian failure. The aim of ovarian transposition is to preserve ovarian function in these patients and involves moving the ovaries away from the radiation field.[9]

A recent study showed that midline ovarian transposition worked better in terms of reproductive outcomes. In fact, the percentage of patients with pregnancy (49.2%) and live births (45%) associated with medial ovarian transposition was significantly higher than that associated with lateral ovarian transposition.[9]

Oocyte/embryo/ovarian tissue preservation

According to the International Federation of Gynaecology and Obstetrics (FIGO), oocyte cryopreservation through vitrification (freezing) is the preferred choice for women undergoing fertility preservation. This method involves ovarian stimulation followed by transvaginal oocyte retrieval.[10]

Embryo tissue cryopreservation is more widely available but should only be offered to women in stable relationships and must consider the need for joint legal ownership with the male partner.[10]

Ovarian tissue cryopreservation is the optimal choice for prepubertal patients. It does not require prior ovarian stimulation, enabling immediate cancer treatment, crucial for prepubertal patients.[11]

The advantages of ovarian tissue cryopreservation include greater resistance of the primordial follicles to cryoinjury compared to mature oocytes, preservation of a larger number of primordial follicles, and extended fertility protection, reducing the need for multiple in vitro fertility (IVF) attempts.[11]

The procedure involves laparoscopic removal of ovarian cortex, freezing, and subsequent transplantation, offering not only fertility restoration but also endocrine function resumption and puberty initiation. Studies report high success rates.[11]

A recent study showed that embryo cryopreservation, was associated with a live birth rate of 41%, and oocyte cryopreservation with live birth rate of 32% following IVF.

Finally, the live birth rate after IVF and the spontaneous live birth rate after ovarian tissue transplantation were 21% and 33%, respectively.[12]

Egg donation

IVF with donor eggs was developed for women unable to use their own eggs in fertility treatment. Concerns regarding families formed because of egg donation often highlight the absence of a genetic link between the mother and child. Evolutionary psychology theories, like kin selection theory, suggest that parental investment is disproportionately directed towards genetically related offspring, potentially negatively impacting genetically unrelated children.[13]

However, according to Imrie *et al*, a considerable body of research on unconventional family structures contradicts these theories, emphasising that family processes play a more crucial role in the healthy psychological development of children than the specific composition of the family.[13]

Data from 2018 indicate that IVF cycles with donor eggs resulted in >10 000 live births in the United States and >1200 in the United Kingdom, with increasing numbers annually.[13]

Assisted reproduction – egg donation in particular – are highly regulated in South Africa. A 2020 South African study showed that 95% of egg donors viewed their experience as positive. However, 7% of respondents report not giving proper informed consent.[14]

Conclusion

CxCa remains a significant global health challenge, ranking as the fourth most diagnosed and leading to the fourth highest cancer-related mortality in women worldwide.

In the context of fertility-sparing approaches, especially relevant given that 40% of CxCa cases occur in women of childbearing age, the updated guidelines emphasise the value of alternatives to radical hysterectomy.

Fertility-sparing treatments, including conisation, simple trachelectomy, and radical trachelectomy, are considered for young patients with tumours <2cm. Other fertility-preservation options include laparoscopic ovarian transposition, oocyte/embryo/ovarian tissue preservation, and egg donation. SF

References available in the online issue

Post-menopausal women face soaring CMD risks, increasing the danger of CVD onset

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A recent study has highlighted that post-menopausal women in low- and middle-income countries (LMICs) face an increased risk of cardiometabolic diseases (CMDs), mirroring trends observed in high-income countries.

The study emphasised the urgent need for public health policies focused on early monitoring and interventions to reduce CMD risk and related adverse outcomes in menopausal women in LMICs.

Increased risk of CMD in post-menopausal women

Compared to pre-menopausal women, post-menopausal women demonstrated significant increases in various risk factors for cardiovascular diseases (CVD). These included a 54.13% increased risk of metabolic syndrome, 53.28% increased risk of hypertension, 53.7% increased risk of elevated triglycerides, 54.71% increased risk of elevated plasma glucose, and a 54.95% risk of higher waist-to-hip ratios. Such factors contribute to the higher mortality and morbidity associated with ischaemic heart disease among post-menopausal women, surpassing that of men in the same age group.

Regional variances and lifestyle factors

The study also explored regional variations in CMD risks among post-menopausal women, emphasising the impact of lifestyle and environmental factors.

West African populations, predominantly subsistence farmers, showed lower risks compared to more urbanised South and East African populations. Differences in dietary habits and obesity prevalence were noted, highlighting the role of lifestyle in CMD risk.

Menopausal transition and CV risks

The decline of metabolic health during menopause, has been linked to an increased risk of CVD. Menopausal transition leads to changes in lipid profiles, body composition, and the distribution of body fat. Hormonal changes, particularly the decline in oestrogen, play a significant role in influencing systemic factors related to CVD risk.

Management of metabolic disorders

Managing metabolic disorders in menopausal women involves a multifaceted approach, including pharmacotherapy and lifestyle modifications. Recommendations include maintaining blood pressure and lipid levels within specified ranges, adopting a healthy diet, regular exercise, smoking cessation, limited alcohol consumption, and weight management. The full length article available online also highlights the potential benefits of hormone therapy.

Considerations for hormone therapy

While hormone therapy is not recommended as primary or secondary prevention for CVD, studies suggest a reduction in CV events, coronary heart disease, and all-cause mortality in this specific demographic. However, risks and benefits vary based on factors such as age, timing of initiation, and individual health characteristics.

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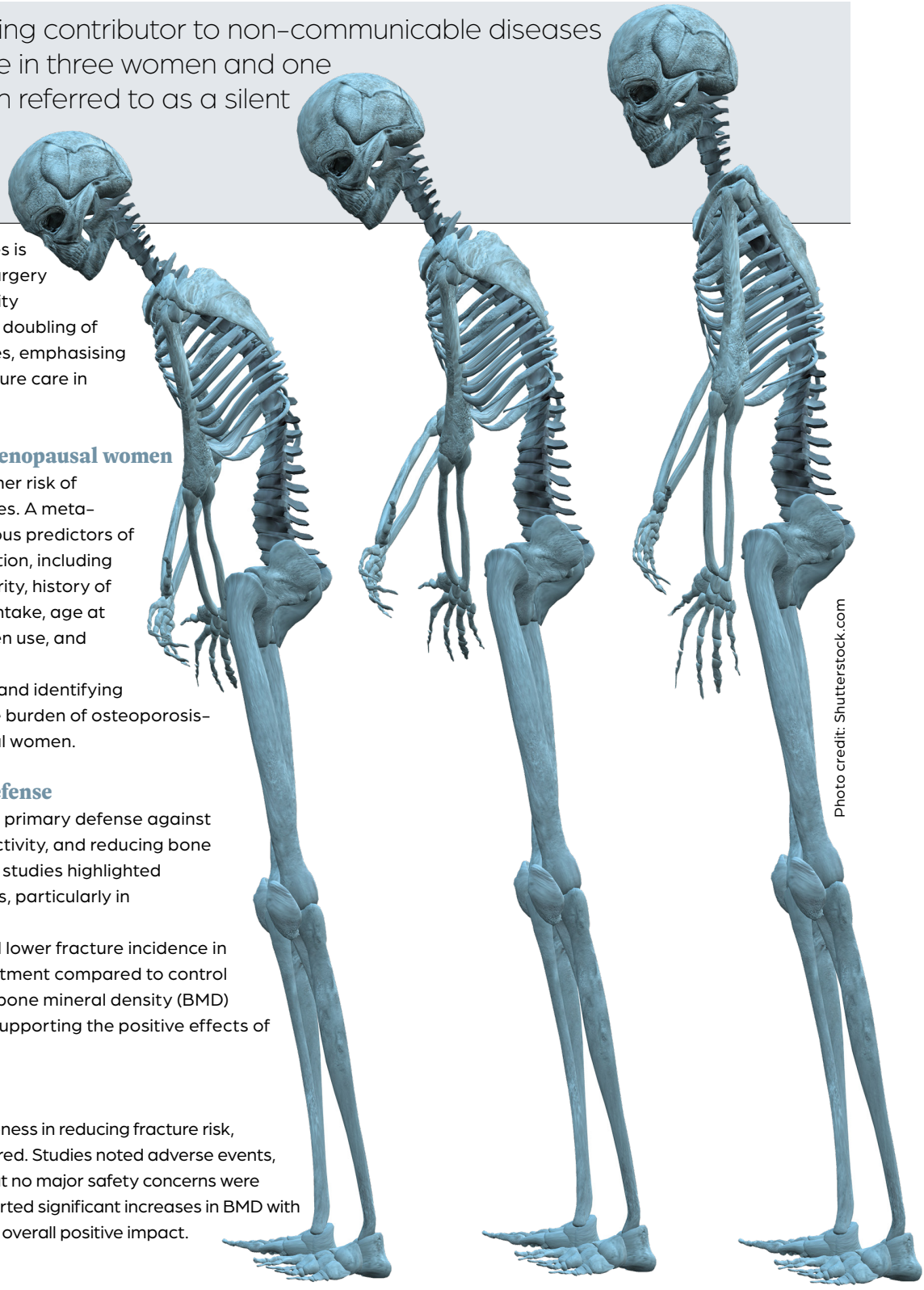
The silent 'crippler'

Osteoporosis is a growing contributor to non-communicable diseases in South Africa, with one in three women and one in five men at risk. Often referred to as a silent 'crippler,' fractures, are the first sign, leading to significant morbidity.



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The incidence of hip fractures is increasing, and delays in surgery contribute to a high mortality rate. Predictions indicate a doubling of fracture rates in the next two decades, emphasising the urgent need to prioritise hip fracture care in the country.

Predictors of fracture in post-menopausal women

Post-menopausal women face a higher risk of osteoporosis and associated fractures. A meta-analysis by Long *et al* identified various predictors of osteoporotic fractures in this population, including age, body mass index, education, parity, history of hypertension and diabetes, alcohol intake, age at menarche and menopause, oestrogen use, and vitamin D supplements.

Focusing on preventive strategies and identifying high-risk individuals can alleviate the burden of osteoporosis-related fractures in post-menopausal women.

Bisphosphonates as first-line defense

Bisphosphonates are considered the primary defense against osteoporosis, inhibiting osteoclast activity, and reducing bone turnover. Imam et *al's* review of eight studies highlighted the effectiveness of bisphosphonates, particularly in post-menopausal women.

Studies consistently demonstrated lower fracture incidence in those receiving bisphosphonate treatment compared to control groups. Significant improvements in bone mineral density (BMD) were observed in the hip and spine, supporting the positive effects of bisphosphonates on bone density.

Consideration of side effects

While bisphosphonates show effectiveness in reducing fracture risk, potential side effects must be considered. Studies noted adverse events, including gastrointestinal disorders, but no major safety concerns were identified. Adami *et al* and others reported significant increases in BMD with bisphosphonate therapy, indicating its overall positive impact.

Conclusion

Osteoporosis poses a significant health threat in South Africa, with rising fracture rates and associated mortality. Identifying predictors, especially in post-menopausal women, and implementing preventive strategies are crucial.

Bisphosphonates is a promising first-line defense, effectively reducing fracture risk and increasing BMD. While potential side effects exist, the overall benefits of bisphosphonate therapy, particularly in post-menopausal women with osteoporosis, warrant consideration in the broader context of fracture prevention and bone health.

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5 clinical challenges of IAI management

Intra-abdominal infections (IAIs) are a major contributor to morbidity and non-trauma mortality. IAIs are the second leading cause of septic shock, affecting 21.8% of patients admitted to intensive care units. According to the Global Alliance for Infections in Surgery patients diagnosed with complicated IAIs have an overall mortality of 2% to 3%.[1,2,3]

Uncomplicated IAIs involve a single organ without any anatomical disruption. Typically, surgical resection is sufficient for managing such infections, and antimicrobial therapy is not required except for peri-operative prophylaxis.[3]

On the other hand, complicated IAIs extend beyond the initial organ, leading to either localised peritonitis (commonly known as abdominal abscess) or diffuse peritonitis. The severity depends on the host's ability to contain the infection within a specific area of the abdominal cavity. Treatment for complicated IAIs usually involves both an invasive surgical procedure for source control and the administration of antimicrobial therapy.[3]

Clinical challenges in the management of IAIs

The management of IAIs are complicated by several clinical challenges:[2]

According to a study by Blot *et al*, the vast majority of IAI cases involve secondary peritonitis (68.4%), followed by biliary tract infection (12.2%), intra-abdominal abscess (6.9%), and pancreatic infection (6.3%). Primary peritonitis, toxic megacolon, peritoneal dialysis-related peritonitis, and typhlitis were less frequent (<4%).[2]

Approaches to IAIs

According to Sartelli *et al*, non-acceptance

The management of IAIs are complicated by several clinical challenges:

1. As mentioned above, severity ranges from uncomplicated to complicated cases (eg fulminant septic shock and multi-organ dysfunction).
2. A broad spectrum of pathogens including Gram-positive and Gram-negative aerobic bacteria, anaerobes, and fungi can be involved.
3. Cultures cannot always readily discriminate true pathogens from harmless micro-organisms.
4. Source control, which includes interventions to eliminate the source of infection, control on-going contamination. Restoring anatomic derangements and physiologic functioning, which is key to successful clinical management, is often difficult to achieve.
5. There is a wide variety of clinical entities within IAI. Besides local abscess formation or solid organ infection (eg liver abscesses and infected pancreatic necrosis), three types of peritonitis (primary peritonitis [peritoneal dialysis-related or spontaneous bacterial peritonitis], secondary peritonitis [following anatomical disruption of the gastrointestinal (GI) tract], or tertiary peritonitis [persistent infection despite adequate source control intervention] are recognised.

TIGECYCLINE

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- **Complicated skin and skin structure infections (cSSTI)** caused by
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- **Complicated intra-abdominal infections (cIAI)** caused by
  Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Stretococcus anginosus group* (includes *S.anginosus, S.intermedius and S.constellatus*), *Bacteriodes fragilis, Bacteriodes thetaiotaomicron, Bacteriodes uniformis, Bacteriodes vulgatus, Clostridium perfringens* and *Peptostreptococcus micros.*

DIRECTIONS FOR USE[2]

No dosage adjustments necessary in patients:

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- the elderly, or based on race or gender.

Use in patients under 18 years of age not recommended.

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of or non-adherence with or lack of access to evidence-based practices and guidelines in hospitals result in the overall poorer outcome of patients suffering from IAIs.[1]

To address these issues the World Society of Emergency Surgery, the Global Alliance for Infections in Surgery, the Surgical Infection Society-Europe (SIS-E), the World Surgical Infection Society, and the American Association for the Surgery of Trauma, have joint forces to develop global clinical pathways for the management of patients diagnosed with IAIs.[1]

Principles of diagnosis

Prompt and accurate detection and treatment are crucial to minimise complications in IAIs. Diagnosis is primarily clinical, with patients typically presenting with rapid-onset abdominal pain and signs of inflammation. Physical evaluation helps narrow down differential diagnoses and guides management decisions, including diagnostic testing, antibiotic therapy initiation, and the need for emergent intervention.[1]

Inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT) offer valuable insights. CRP serves as an indirect marker of infection and inflammation, while PCT rapidly increases in bacterial and fungal infections. Both markers can be used in diagnosing and guiding antibiotic therapy but do have limitations.[1]

Imaging techniques such as ultrasound (US) and computed tomography (CT) complement clinical assessments. Though CT offers higher sensitivity and specificity, concerns about radiation exposure have led to a re-evaluation of the roles of sonography. Staged algorithms using a step-up approach with CT after inconclusive US have been proposed. A multi-centre study recommends US as the initial investigation, with CT reserved for negative or inconclusive cases to minimise radiation exposure.[1]

Magnetic resonance imaging is suggested for pregnant patients when US results are inconclusive. Once diagnosed, initial management involves controlling the infection source, administering appropriate antibiotics, and stabilising the patient with intravenous (IV) fluid therapy.[1]

Principles of source control

Source control includes physical measures to manage invasive infection and restore optimal function in affected areas, particularly complicated IAIs. Proper source control significantly impacts patient outcomes and can shorten antibiotic therapy duration.[1]

Delays in source control can lead to increased mortality. The rules of source control include considerations of time, totalisation, and technique. Swift initiation of treatment is crucial, with each hour of delay negatively affecting outcomes.[1]

Operative and non-operative techniques are used for source control, with surgery being the primary strategy for critically ill patients. Non-operative interventions include percutaneous drainages of abscesses. Surgical source control involves procedures such as resection, drainage, and debridement.[1]

Lavage of the peritoneal cavity is traditionally used but recent studies suggest limited irrigation may be as effective. Planned and on-demand relaparotomies are considered, with advantages for resource optimisation in the on-demand approach.[1]

The concept of an open abdomen (OA) is debated, with potential risks, and closure within seven days is crucial to prevent complications. OA with negative pressure therapy and fluid instillation is a promising approach.[1]

Principles of antibiotic use

Appropriate antibiotic use is crucial in combating infections and preventing antimicrobial resistance. In uncomplicated IAIs, single doses are as effective as multiple doses, and post-operative antimicrobial therapy is unnecessary with adequate source control.[1]

For complicated IAIs, a short course of antibiotics after source control is a reasonable option. Studies have shown that four days of fixed-duration antibiotic therapy can yield similar outcomes to longer courses.[1]

Initiation of empirical antibiotic therapy should be based on immediate treatment needs, considering microbiological data availability delays. Microbiological results from peritoneal fluid cultures are valuable for adjusting antibiotic regimens.[1]

Resistance, particularly extended-spectrum *beta-lactamases* (ESBL), poses a challenge. *Enterococci* and non-fermenting gram-negative bacteria exhibit increased resistance, emphasising the importance of tailored antibiotic selection.[1]

Carbapenems are commonly used for ESBLs, with ertapenem being an option. Ceftolozane/tazobactam and ceftazidime/avibactam are newer options for complicated IAIs.[1]

The global rise in antimicrobial resistance, especially among gram-negative bacteria, necessitates careful consideration of local resistance epidemiology for empiric antibiotic regimens.[1]

De-escalation, adjusting antibiotic therapy based on microbiological results, has been associated with lower mortality rates. Proper dosing and monitoring are crucial, considering altered pharmacokinetics in critically ill patients.[1]

The Global Alliance for Infections in Surgery emphasises the need for daily reassessment, short-course therapy post-source control, and biomarker use like procalcitonin.[1]

In critically ill patients, empirical broad-spectrum therapy should cover likely pathogens and be narrowed based on culture results. Short courses of antibiotics, once source control is established, are effective. Biomarkers like procalcitonin can guide antibiotic duration.[1]

Clinicians with expertise in surgical infections are vital, and infection prevention, control measures, and antimicrobial stewardship programmes should be implemented. Regular monitoring of antibiotic consumption, resistance surveillance, and outcome measures are essential for effective antimicrobial stewardship.[1]

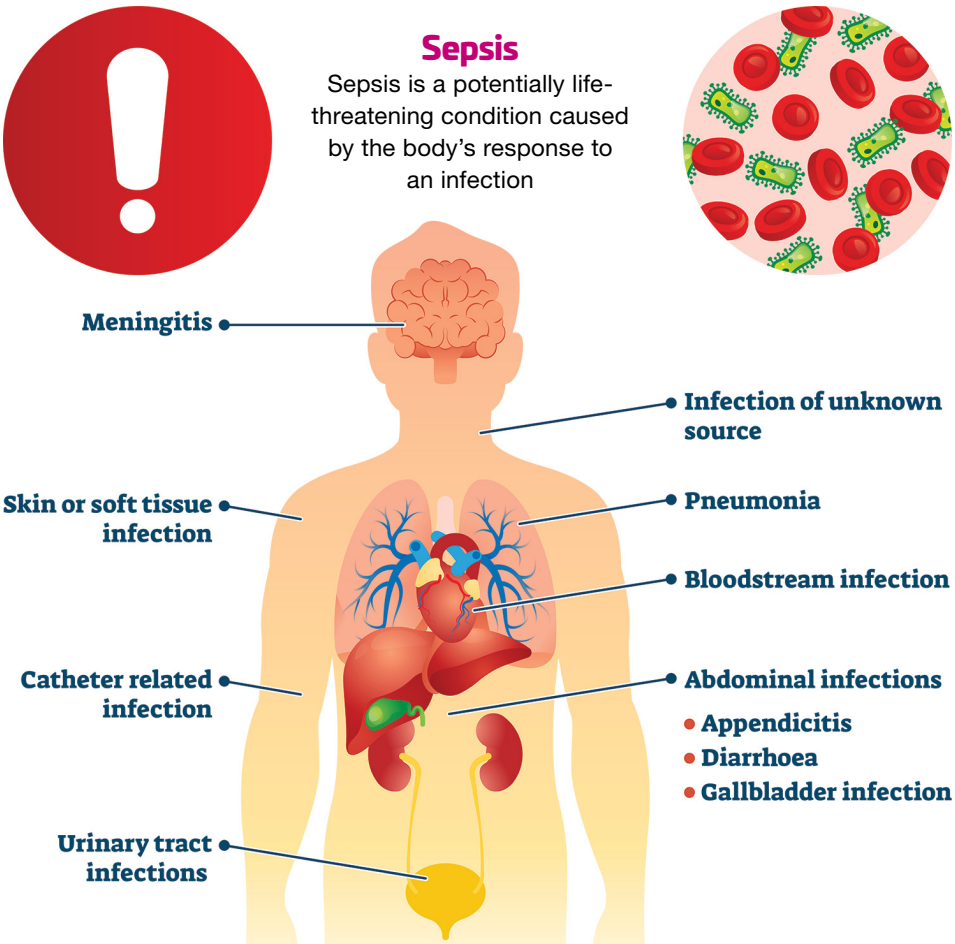
Principles of sepsis management

Sepsis is a complex and multi-factorial syndrome that can lead to varying levels of severity and organ dysfunction if left untreated. A study showed that mortality rates in patients with complicated IAIs were significantly influenced by clinical conditions, with septic shock presenting a high mortality rate of 67.8%.[1]

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) updated previous classifications, defining sepsis as life-threatening organ dysfunction resulting from a dysregulated host response to infection.[1]

Septic shock, a subset of sepsis, is clinically identified by vasopressor requirement to maintain a mean arterial blood pressure of ≥65mmHg and a serum lactate level exceeding 2mmol/l in the absence of hypovolemia.[1]

The pathophysiology of sepsis originates from the outer membrane components of both Gram-negative and Gram-positive organisms, triggering a cascade of inflammatory mediators.[1]



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The development of cardiovascular insufficiency, leading to global tissue hypoxia, is a primary contributor to the high morbidity and mortality associated with sepsis. The Sequential Organ Failure Assessment (SOFA) score can be used to objectively measure organ dysfunction over time in septic patients.[1]

Fluid therapy, crucial for treating sepsis, should be administered based on clinical endpoints rather than predetermined protocols. Aggressive fluid resuscitation, particularly in abdominal sepsis, should be cautious to avoid complications such as increased IA pressure.[1]

Vasopressor agents, such as norepinephrine, play a vital role in restoring organ perfusion when fluid resuscitation alone is insufficient. The timing of vasopressors relative to fluid infusion remains a debated topic.[1]

The Surviving Sepsis Campaign recommends key bundles to improve outcomes in sepsis and septic shock, including lactate level measurement, blood culture acquisition before antibiotic administration, broad-spectrum antibiotic administration, rapid crystalloid infusion for hypotension or elevated lactate levels, and the application of vasopressors to maintain a mean arterial pressure of ≥65mmHg in hypotensive patients after fluid resuscitation.[1]

The role of corticosteroids in septic shock treatment is debated, with guidelines suggesting their use in cases where haemodynamic stability cannot be achieved with fluid resuscitation and vasopressor therapy alone.[1]

Conclusion

IAIs contribute significantly to morbidity and non-trauma mortality, with complicated cases being the second leading cause of septic shock. To address clinical challenges in the management of IAI, the World Society of Emergency Surgery and other global organisations joint forces to develop clinical pathways for IAI management. Diagnosis relies on clinical presentation, inflammatory markers, and imaging techniques. Prompt source control and appropriate antibiotic use, considering resistance patterns, are crucial principles. Sepsis management involves fluid resuscitation, vasopressors, and adherence to Surviving Sepsis Campaign bundles. The role of corticosteroids in septic shock remains debated. SF

References available in the online issue

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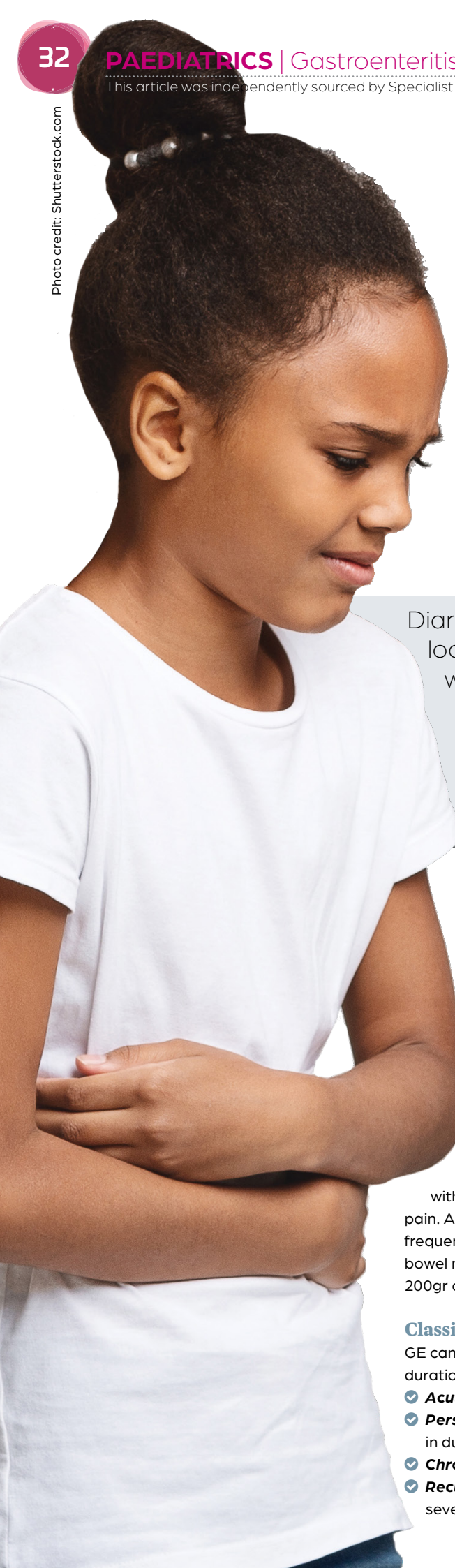
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Gastroenteritis impacts billions of children worldwide

Diarrheal disease (DD), characterised by frequent and loose or watery bowel movements, is associated with 1.5 to 2.5 million deaths per annum. Worldwide, DD affects more than three to five billion children annually. It is the second most common cause of morbidity among children <5-years. In South Africa, DD is the third leading cause of childhood mortality.[1,2]

World Health Organization (WHO) data show that deaths related to DD among children occur in Africa and South-East Asia. Deaths are and often linked to suboptimal nutrition and inadequate hygienic conditions.[2]

DD is most commonly caused by gastroenteritis (GE), which refers to inflammation of the stomach and intestines and is characterised by an increase in bowel movement frequency with or without vomiting, fever, and abdominal pain. An increase in bowel movement frequency is defined by ≥3 watery or loose bowel movements in 24 hours or at least 200gr of stool per day.[1,2]

Classification

GE can be classified according to the duration of symptoms:[1]

- ***Acute:*** 14 days or <14 days in duration
- ***Persistent:*** >14 days but <30 days in duration
- ***Chronic:*** >30 days in duration
- ***Recurrent:*** Diarrhoea that recurs after seven days without diarrhoea.

Acute GE accounts for 10% of hospitalisation and 19% of deaths in children around the globe. Furthermore cases of persistent diarrhoea account for 3%–20% of all diarrhoeal episodes in children <5-years and up to 50% of all diarrhoeal death.[2,3]

What causes GE?

Causes of GE include bacterial, viral, fungal, and parasitic infections. The most common cause of acute infectious diarrhoea are viruses (eg norovirus, rotavirus, and adenovirus).[1]

Bacterial causes are responsible for more severe cases than other infectious aetiologies. In South Africa, the most common parasites, which cause diarrhoea include *Cryptosporidium* and *Giardia lamblia*.[1,3]

Differential diagnosis of acute bacterial GE includes other causes of GE such as viral and parasitic GE. Common foodborne illnesses also should also be considered in differentials.[1]

Ingestion of food containing toxins (eg *Staphylococcus aureus*) may cause rapid onset of vomiting and diarrhoea. Due to increased rates of overseas travel, traveller's diarrhoea caused by a range

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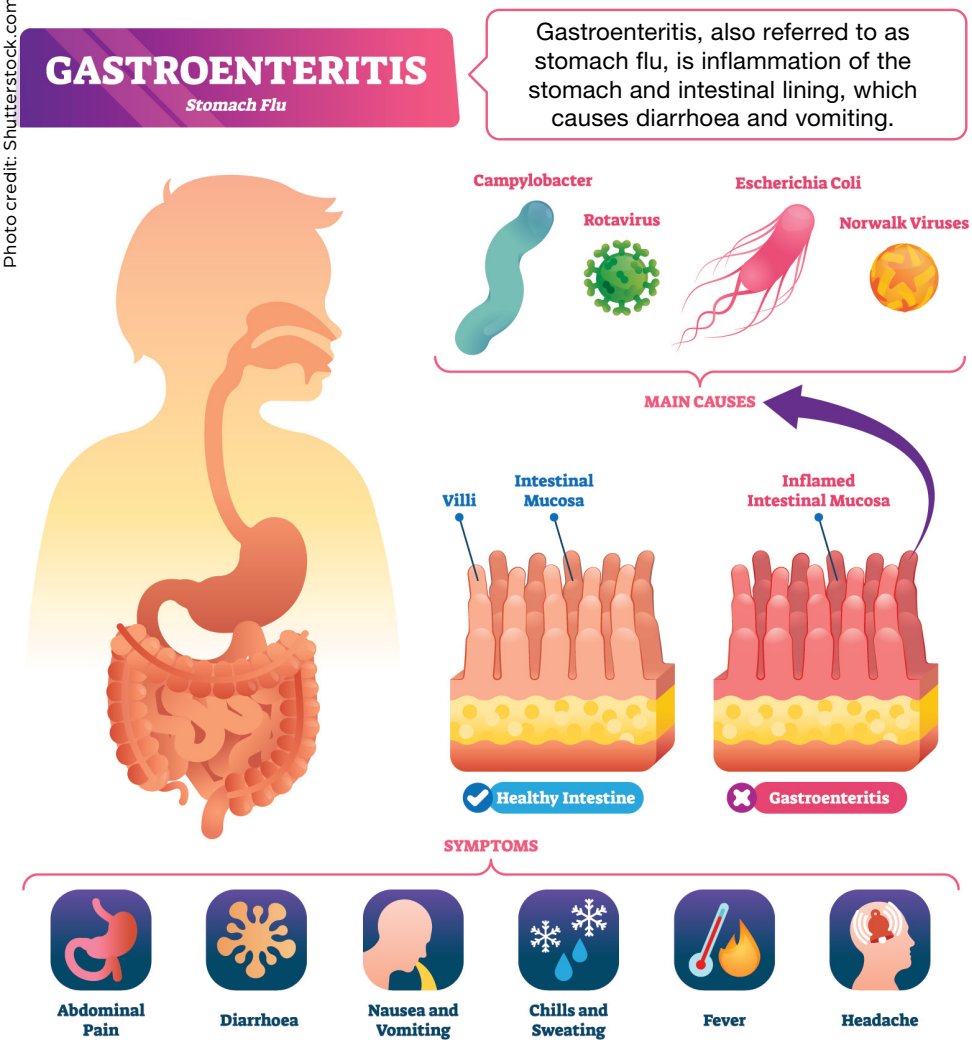

of organisms not normally seen in that environment, is occurring more frequently.[3]

Other diseases that can cause watery diarrhoea are Crohn disease, *pseudomembranous* colitis, microscopic colitis, acute HIV infection, irritable bowel disease, and lactose intolerance. Bloody diarrheal disease other than dysentery includes ulcerative colitis. Celiac disease and malabsorption syndromes also cause diarrhoea.[1]

Risk factors

Risks for GE include immune deficiency, onset of diarrhoea at <3-months, measles, malnutrition, lack of breastfeeding and environmental contamination with increased exposure to enteropathogens.[3]

Malnutrition increases the risk for diarrhoea and associated mortality several-fold, especially so with micronutrient deficiencies. In children with vitamin A deficiency the risk of dying of diarrhoea, measles or malaria is 20%–24%, and with zinc deficiency 13%–21%.[3]

Symptoms and signs to watch out for

Apart from diarrhoea (watery or bloody in dysentery), the most common symptoms of GE include:[1]

- Nausea
- Vomiting
- Abdominal pain
- Fever (suggests an invasive organism as the cause).

Dehydration and depletion of electrolytes are the most common complications of GE, and some patients may require hospitalisation. The following are considered red flags:[1]

- Dry mucous membranes (dry mouth)
- Decreased skin turgor
- Altered mental status
- Tachycardia
- Hypotension, orthostasis
- Bloody stools
- Recent hospitalisation or antibiotics
- Age >65-years
- Comorbidities such as HIV and diabetes.

Other complications that are common after acute gastroenteritis are the transformation of acute into chronic diarrhoea which can lead to lactose intolerance or small-bowel bacterial overgrowth.[1]

Some other post-diarrhoea complications include exacerbation of inflammatory bowel disease, septicaemia, enteric fever, and Guillain–Barre syndrome, a complication likely after *Campylobacter* infection. Reactive arthritis may occur, particularly after *Shigella*, *Salmonella*, *Campylobacter*, or *Yersinia* infections.[1]

Treatment strategies

As mentioned, the most significant complication in acute GE is dehydration, especially in children <5-years. Recent research suggests that lactose-free formulas can be considered for managing acute gastroenteritis in hospitalised children.[2]

The recommended first-line treatment for all children with acute dehydrating gastroenteritis involves administering oral or intravenous rehydration solution. It's generally advised to avoid anti-diarrheal medications in children with acute GE as they may hinder the elimination of infectious agents from the gut.[2]

Probiotics are considered safe and do not have interactions with medications. Their mechanism involves degrading and modifying dietary antigens while balancing the anti-inflammatory response of cytokines. Probiotics may be particularly beneficial in children with GE, aiding in balancing the immune response against foreign antigens.[2]

When is antimicrobial treatment needed?

The WHO does not recommend the routine use of antimicrobials for acute GE in children, except in clinically severe cases. Antibiotic treatment is specifically indicated in instances such as cholera, shigellosis, dysenteric presentation of campylobacteriosis, and non-typhoidal salmonellosis when they lead to persistent diarrhoea.[4]

Additionally, antimicrobial therapy is warranted when the host's immune status is compromised due to factors like severe malnutrition, chronic disease, or lymphoproliferative disorders.[4]

Consideration for antimicrobial treatment is also given in cases of moderate to severe traveller's diarrhoea, diarrhoea accompanied by fever and/or bloody stools, and instances where diarrhoea is associated with another acute infection (eg pneumonia), which require specific antimicrobial therapy. SF

References available in the online issue

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Bringing you medical news that matters

SPECIALIST FORUM

Dear Specialist Forum Readers,

Welcome to the first issue of 2024.

In this issue of *Specialist Forum*, we include some of our most popular CPDs from 2023.

Start your New Year with nine (9) CPD points in the bag!

The CPD articles included are:

Preventing stroke: A global public healthcare priority and **Apixaban: An effective treatment option for VTE**

Please note, to complete the quiz, you need to read this article as well: **DACC-coated wound dressings: A breakthrough in preventing SSIs**. To access this quiz, click **here**.

New FDC levofloxacin- dexamethasone for post-cataract surgery: A potential turning point. To read the article and complete the quiz, click **here**.

Moving towards personalised medicine in psychiatry. To complete the quiz, click **here**.

Earlier this month, we published an oncology guide to bring you up to speed on the latest developments and innovations in the oncology field. To access your copy, click **here**. To read our CPD articles online and access the quiz, click **here**.

Symposium news

Don't forget to register for the Cardiac Arrhythmia Society of Southern Africa Symposium, which will be held in Johannesburg from 24 - 25 February. To register for the symposium, click **here**.

We have developed a South African medical congress calendar for your convenience. To access your copy, click **here**. If you would like to see your congress featured in our calendar or if you would like to advertise, send an email to charissa.piek@newmedia.co.za.

Don't miss our article ***Understanding the role of ventricular arrhythmias in sudden cardiac death***.

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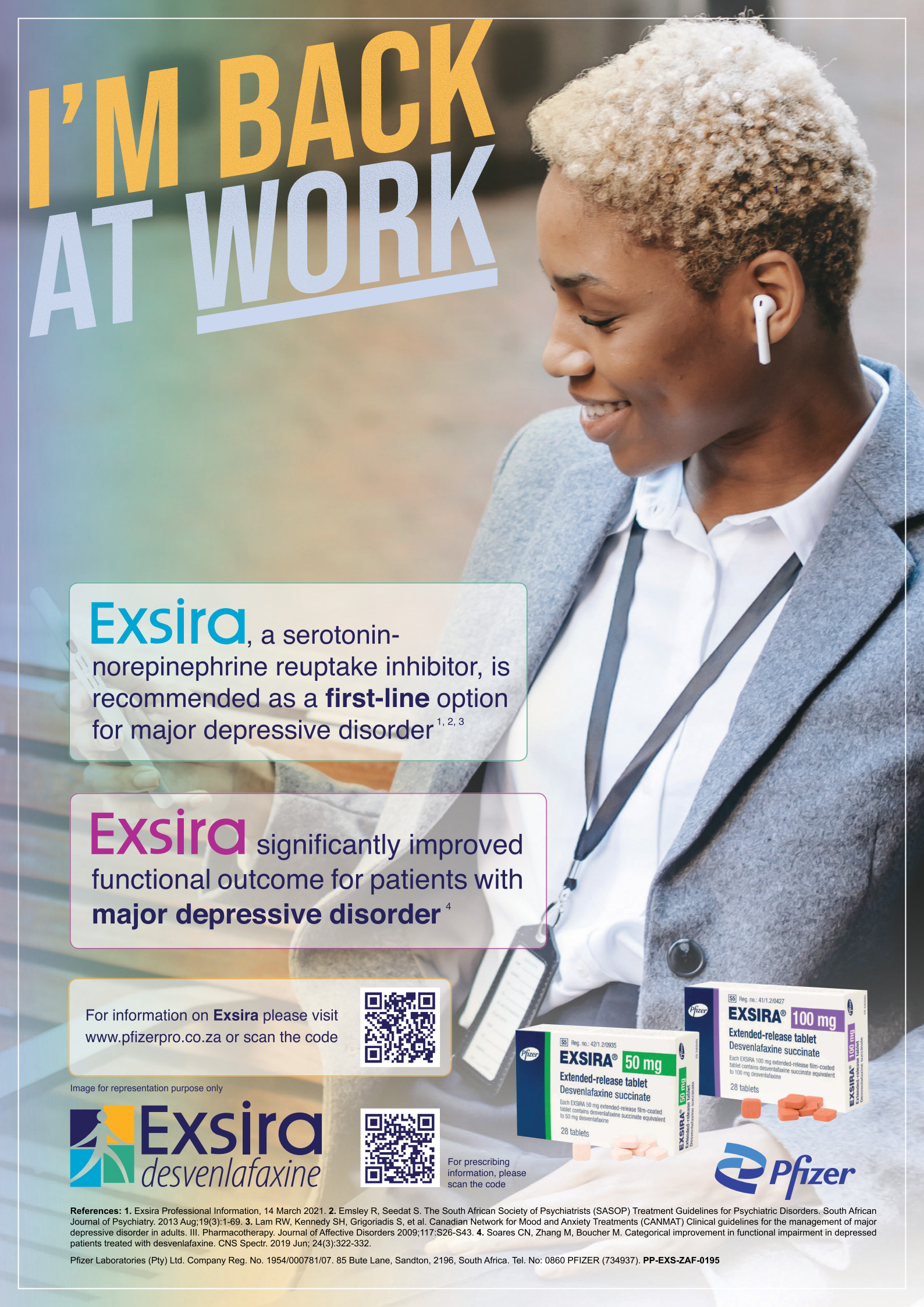

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Exsira significantly improved functional outcome for patients with **major depressive disorder** [4]

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