

# **MENOPAUSE MATTERS**

**OCTOBER 2020**

## **Urinary incontinence in older women**

About a third of post-menopausal women suffer from urinary incontinence in some form or another but most do not seek professional assistance. This failure to engage with medically trained personnel precludes them from the benefits of pelvic floor muscle training which should be the first line of treatment, either on a one-to-one or group basis. Individual therapy is held up as the ideal approach because of it is responsive to personal needs but does group-based training have an equal or non-inferior set of outcomes?

Canadian researchers compared the results of 3 month courses of individual or group therapy for stress or mixed urinary incontinence and found clearly-defined end-points to be similar in both sets of women ([Domoulin et al JAMA Int Med](#) 2020.doi.10.1001/jamainternmed.2020.2993). There was excellent adherence to protocols and a greater than two thirds improvement recorded across the board in episodes of incontinence at the end of the trial and up to one year thereafter.

As observed by [Huang \(JAMA Int Med](#) 2020.doi.10.1001/jamaintmed.2020.2983) there “never will be enough trained pelvic floor therapists” to provide one-to-one care and there may well be advantages in group involvement. De-stigmatisation of the condition by a common acceptance of the problem is possible with an encouraging if not competitive attitude and group support.

It is not inconceivable that this initiative on a targeted therapy could be expanded to include other symptoms or even general physical well-being.

- Do you refer patients to “groups”?
- Do you have a local physio practice that offers “group health exercises”?
- Will the social media assist in making on-line groups that then actually meet?
- Should SAMS take the lead in publicising contacts?

It seems to me that having an on-line resource to which patients could be referred will arrive. How does a close-knit group like SAMS launch such an initiative?

Yoga is a parallel example of single or group-practiced exercises that combines postures, muscle control with mental conditioning. The resultant development of strength, balance and flexibility has clear benefits in reducing the risks of falls ([Tew et al BMJ](#) 2020;370:m3246). These are known as “mind-motor” activities and promote socialising, raise self-esteem and improve cognitive performance ([Mattle et al JAMA Netw Open](#) 2020;3(9):e2017688).

The science of exercise in older people shows beneficial effects in terms of cerebral function that has evidence from animal research and is being extrapolated to elderly humans ([Horowitz et al Science](#) 2020;369:167-73). It was found that certain liver enzymes reached higher levels after exercise and when harvested from plasma and given to non-exercising people, “ameliorated age-related regenerative and cognitive impairments”.

Uncovering of the underpinning metabolic pathways whereby muscular activity expands well-being both physically and mentally, is exciting and encouraging. Will it attract the attention of entrepreneurs who see a gap in the rejuvenation market by reproducing “exercise generated” biochemically similar products? Benefits without the effort? Why do I feel a moral squirm at the notion?

## Gynaecological surgery

Pain relief – It is difficult for non-Americans to perceive the human tragedy of opioid abuse in the United States. The country comprises 4% of the world's population but consumes 80% of its opioids (Bryson "The Body" *Transworld Publications* 2019 p366). Opioid use and abuse costs Americans more than \$500 billion annually and much of that is from prescription medication.

In general the Covid pandemic appears to be exacerbating the opioid epidemic although other illicit substances are increasing faster in popularity such as fentanyl, methamphetamine, cocaine and heroin ([Haley & Saitz JAMA](#) 2020 doi:10.1001/jama.2020.18543). Some of the opioid abuse can be traced back to persistent post-operative analgesia use.

Researchers checking the records of gynaecological procedures, such as dilatation and curettage, myomectomy, hysterectomy, endometrial ablation, tubal ligation and ectopic pregnancy operations found that each had opioids prescribed post-operatively in some but not all cases, and 7% of these patients persisted with their use which has made a substantial contribution to the addiction problem ([Wright et al \*Obstet Gynecol\*](#) 2019;134:250-60, [Huang et al \*Obstet Gynecol\*](#) 2020;136:565-75 and [Wall-Wieler et al \*Obstet Gynecol\*](#) 2020;136:548-55).

Bowel preparation. Is there a place for bowel preparation prior to any gynaecological surgery – and if so what form should it take? To investigate existing practice more than 200 000 hysterectomies were identified and any post-operative infections recorded and correlated with any bowel preparations ([Kalogera et al \*Am Obstet Gynecol\*](#) 2020;223:231.e1-231.e12).

The vast majority of operations, irrespective of whether they were billed as benign (94%) or malignant (87%), had no bowel preparation and when it was used, there was no decrease in rates of surgical site infections, anastomotic leaks or major morbidity. The authors concluded that bowel preparation prior to hysterectomy is redundant and "may be safely omitted."

When planning surgery the approach may influence risk and this applies to hysterectomies for benign indications ([Zhu et al \*Obstet Gynecol\*](#) 2020;136:803-10). Surgeons in the US found an "Increased risk of bowel injury associated with endometriosis and the abdominal surgical approach" including laparoscopically assisted hysterectomy. Vaginal hysterectomy still carries the lowest risk of bowel damage.

## Surgery & Lithotomy positioning

In vaginal surgery and laparoscopic procedures some degree of the lithotomy position is used. Depending on the access required, full or semi-lithotomy positioning is necessary but it can result in post-operative discomfort or more serious neurological sequelae or physical consequences which are fortunately, rare occurrences. However, according to researchers, one third of women complain of lower back pain following lithotomy-positioned surgery.

The commonest types of leg supports are strap or boot stirrups, with boot stirrup use resulting in a significantly better physical function at 6 weeks post-procedure than conventional (or candy cane) stirrup use ([Gupta et al \*Obstet Gynecol\*](#) 2020;136:333-47).

## **Vestibulodynia revisited**

Vestibulodynia is the sensation of pain when pressure is applied to the introital region. It is provoked by intercourse or tampon insertion and it is implicated as the most common cause of superficial dyspareunia. Its origins are obscure with a theory being peripheral receptor sensitisation leading to a “neurogenic inflammatory response” whereby mild or trivial touch is perceived as significant pain or allodynia.

With such a paucity of aetiological knowledge there are a wide range of psychological and pragmatic solutions offered with a recent trial using injections of botulinum toxin A into the bulbocavernosus muscles twice, 3 months apart ([Haraldson et al \*Obstet Gynecol\* 2020;136:524-32](#)). Compared with placebo the active injections showed a non-significant reduction in dyspareunia and tampon use but no change in sexual function or distress although “secondary outcomes suggested positive effects of the treatment.”

## **Low back pain**

Low back pain is one of the commonest and most debilitating symptoms for which patients consult the medical profession and their allies. Its costs in the US alone have reached \$100 billion annually and physical therapies are extensively used as adjuncts to medications but their relative efficacies are difficult to assess and recommend.

Two spinal therapeutic approaches enjoy wide application by those seeking relief from chronic low back pain but it is not known which is more effective and more fundamentally, is either better than placebo treatment. To address this question, a cohort of patients were allocated to the following actions twice weekly for 3 weeks:-

- Manipulation techniques using “high-velocity, low-amplitude force” to the spine as used by chiropractors which is often accompanied by audible joint sounds or “pop” known as cavitation
- Mobilisation techniques using “low-velocity, low force” techniques as used by physiotherapists that do not generally produce audible sounds
- Sham cold laser therapy – as the placebo or inert intervention.

All three groups were assessed for pain and disability at the completion of 6 sessions but no significant differences were apparent leading the authors to conclude that “neither spinal manipulation nor spinal mobilization appeared to be effective treatments for mild to moderate chronic low back pain” ([Thomas et al \*JAMA Netw Open\* 2020;3:e2012589](#)).

Although the trial reported here is not specific to women (who were in a slight majority) it did demonstrate that physical therapies have little to offer in a situation analogous to pelvic pain in women. The exclusion of defined pathology leaves the choice of referral for alternative therapies to shared decision-making with the knowledge that personal preference is as probably as important as evidence-based practices.

## **Athol Kent**

*Menopause Matters is a monthly review of matters menopausal that have recently appeared in the journals. It is produced for the South African Menopause Society and the summaries concentrate on clinical issues although some underlying patho-physiology will be included to ensure a scientific basis for the work. These summaries and opinions do not necessarily reflect the views of the S A Menopause Society.*

*The idea is derived from the Journal Article Summary Service (JASS) which summarises general O&G articles. Information about this service can be obtained from Athol Kent ([atholkent@mweb.co.za](mailto:atholkent@mweb.co.za)) or from the JASS website [www.getjass.com](http://www.getjass.com)*

I am adding an addendum to this month's Menopause Matters.

We are all caught up in the Covid maelstrom and the vaccine is on the horizon.

We may well be asked by our patients whether they should avail themselves of inoculation when it arrives and I did not feel I was in a position to discuss vaccines with anyone since I am not up-to-date in the field.

I therefore read up about vaccines in general and some that concern us in particular.

What follows is a meander through what was an unfamiliar world for me – enjoy!

### **Addendum for SAMS readership**

## **Vaccinology for non-vaccinologists**

Vaccines have saved more lives than any other medical discovery.

Vaccines have reduced or eliminated diseases responsible for major morbidity and mortality with the Global Alliance for Vaccine and Immunisation (GAVI) becoming one of the most important institutions world-wide for its role in promoting and distributing vaccines ([Berkley JAMA 2019](#) doi: 10.1001/jama.2019.13190). Under GAVI's auspices an estimated 13 million deaths have been prevented over the last two decades and its success is about to expand exponentially because of advances in vaccine technology ([Pardi et al Curr Op Imm 2020;65:14-20](#)).

### **Vaccine technology**

Modern antiviral vaccine technology can be described as falling into 2 camps

- Protein-based or
- Gene-based

Protein-based vaccines use whole but inactivated (killed or attenuated) virus material to elicit the immune reaction – the technique used in polio or flu vaccines. Other similar approaches use subunit vaccines and virus-like particles – for example in human papillomavirus and hepatitis B vaccines. The principle is to convey the protein antigen to the cell which will then produce the antibody.

Gene based vaccines work differently using a more indirect approach. These vaccines carry the genetic instructions from the virus to the host's cell which then makes the protein antigen itself. In effect the vaccine brings the virus's "genetic recipe" to the cell that recognises a foreign substance/protein it has made and this triggers an immune response. These genetic instructions are DNA or messenger RNA (mRNA). Since it is now possible to sequence these genetic strands and reproduce them, scientists can find the code of pathogens (such as Covid 19) and create a gene-based vaccine.

In the gene-based technique this viral genetic code can be carried into the cell by various mechanisms. These are naked nucleic acid transfer or using vectors such as carrier nanoparticles or piggy-backed onto less harmful viruses such as a common cold adenovirus. This is the viral vector technique.

Advantages of these new vaccine production platforms are:

- Neither protein- nor gene-based technology relies on cell cultures to grow the antigen. They are made in laboratory tanks by catalysing chemicals so they are cheaper and quicker to make and “up-scalable” for mass- production.
- It may be possible for a single inoculation to “simultaneously target multiple antigens and pathogens” reducing the number of vaccinations required ([Maruggi et al \*Mol Therapy\* 2019;27:757-72](#)).
- One vector could carry 50 antigens (or the code for them) and usher in a new era of “single-shot” immunology. This would have major effects on costs and inoculation programmes.
- The vaccines can be made thermostable meaning they do not require a cold-chain network for distribution
- These techniques are being used to develop vaccines against influenza, rabies, Ebola and Zika with the promise of a broad-spectrum vaccine for all (known) corona viruses.

### HPV vaccine

Human Papillomavirus vaccination is unusual in that it is given to children aged 11 or 12 years old initially or as catch-up vaccination to those up to the age of 26 years ([Marks et al \*JAMA Dermatol\* 2020 doi.10.1001/jamadermatol.2020.2927](#)). Although there is no evidence of links to the incidence of autonomic dysfunction in women some parents hesitate to have their children vaccinated ([Hviid et al \*BMJ\* 2020;370:m2930](#)). Governments, schools and paediatricians have taken stances against children whose parents do not abide by regulations concerning HPV vaccination ([Ko et al \*JAMA Pediatr\* 2020;147:861-7](#) and [O’Leary et al \*JAMA\* 2020;324:1105-7](#)).

The latest Swedish data show the incidence of invasive cervical cancer up to the age of 31 years is substantially reduced following **early** vaccination. The rate ratio was 0.12 (CI 0.00 - 0.34) meaning an 88% reduction in the disease ([Lei et al \*NEJM\* 2020.383:1340-8](#)).

### Influenza vaccines

In February of each year, WHO and the US Centers for Disease Control (CDC) decide on the composition of the “Flu vaccine” for the year. It is based on the strains circulating in Eastern Asia that are likely to reach Europe and the Americas at the start of the northern hemisphere’s autumn and winter seasons. There are 2 types of protein on the flu virus’s surface – haemagglutinin and neuraminidase – and each has 5 strains – hence the H and N plus a digit used to define the strain. The H5N1 strain is particularly virulent one also known as “bird flu”.

Not everyone who catches the flu virus is infected by the same strain so each year’s current flu vaccine offers limited coverage – in the order of 30-40% but this is sufficient to reduce morbidity and hospital admissions. The present circumstances demand that hospital resources be conserved to deal with the Covid pandemic making valuable any reduction in the use of facilities.

There are concerted efforts to reach as many people as possible this year with special appeals to health-care workers, the elderly, children, those with asthma, diabetes and pulmonary diseases ([Kuehn \*JAMA\* 2020;324:1025](#) and [Jaklevic \*JAMA\* 2020;324:926-7](#)). There is an opportunity prevent the complications of cardiovascular disease as any viral illness exacerbates the possibility acute cardiac syndromes, stroke, thromboembolic events and heart failure ([Sperling et al \*JAMA Cardiol\* 2020 doi.10.1001/jama.2020.16968](#)).

Pregnant women should be especially encouraged to receive flu vaccinations as both they and their fetus are afforded protection. Any fears that vaccination could be associated with autism disorders in offspring have been reassuringly dealt with – at least concerning the H1N1 “swine flu” vaccine that affected large numbers of people 10 years ago. Research by Swedish workers found no link between vaccination at any stage of pregnancy and autism spectrum disorders ([Ludvigsson et al \*Ann Int Med\* 2020 doi. 10.7326/M20-0167](#)).

The data on respiratory syncytial virus vaccination in pregnancy is less convincing. Although it is the commonest cause of respiratory infections in infants, maternal vaccination in late pregnancy reduced infections from 2.5% to 1.5% which did not reach significance ([Madhi et al \*NEJM\* 2020; 383:426-39](#)).

### **Anti-vaxxers**

Those who refuse to be vaccinated or hesitate to have their children vaccinated are known as anti-vaxxers. Their views are contrary to medical science and they steadfastly deny the balance of benefit and harms of vaccination for them or the communities in which they live. Although emotionally it is tempting to confront and ridicule their stand-point, this approach is likely to be counter-productive and entrench their ideas ([Ritchie \*The Post\* 2020](#) and [Rosenthal et al \*JAMA Pediatr\* 2020;174:916](#)).

### **Covid vaccines**

On 10<sup>th</sup> January 2020 Chinese researchers released the genetic sequence of the newly identified Covid 19. Being a corona virus it had a specific spike protein on its surface so immediately vaccinologists set about creating vaccines, some using protein-based and others gene-based platforms. Experience with the acute respiratory syndrome and the Middle East outbreaks gave developers a head start and phase 1 and 2 trials on efficacy and safety followed rapidly. It took 66 days for the first mRNA phase 3 (clinical trials in humans) to begin.

As of September 2020 there are 140 vaccines in pre-clinical development and 30 vaccines in clinical trials. For robust data to be collected the placebo controlled trials have to attract 40 000 to 60 000 participants and achieve an efficacy of (ideally) more than 70% although 50% would probably be acceptable according to [Fauci](#) and the [FDA](#). One factor that limits effectiveness is host immunity to the viral vector which means the person's immune system may eliminate the – say – adenovirus carrying its Covid mRNA load thus rendering the process unsuccessful. To circumvent this, scientists are using non-replicating adenoviruses that infect chimpanzees, and not humans, as the carrier ([Folegatti et al \*Lancet\* 2020;396:467-78](#)). This is the route being followed by the AstraZeneca and Oxford University group but a battery of other candidate vaccines use protein- or gene-based techniques and various vectors and delivery mechanisms so there is no single “right” road to a successful anti-Covid vaccine.

It is hoped that several vaccines will be efficacious as well as safe and that some may prove better for specific groups such as children, the elderly and those with co-morbidities. Quantities of the strongest candidate vaccines are being stock-piled in anticipation of clinical success, regulatory ratification and then distribution. Distribution will be an ethical minefield beyond the remit of this meander ([Persad et al \*JAMA\* 2020 doi. 10.1001/jama.2020.18513](#)).

The most optimistic estimate for the launch of the first legitimate Covid vaccine – accepted by the medical community – is towards the end of November or early December 2020 although this is purely speculative as no other vaccine manufactured by these methods has ever been clinically tested in large trials so there is no precedent on which to base guesswork. Let us hope that new technology will supply a defence against a new pathogen and provide faster answers in the future.