JOURNAL ARTICLE SUMMARY SERVICE

April 2022

Cannabis use in general and in pregnancy

The use of cannabis during pregnancy is increasing globally. This is occurring because legislation concerning access is becoming more permissive, misconceptions about its benign nature are being spread, and research on its harmful effects in general and in pregnancy, in particular, are only now starting to be published.

Relaxed attitudes

Both legally and socially, attitudes to cannabis use are softening and its recreational use is expanding rapidly. As cannabis commercialisation grows, those with financial interests in its sale underplay its negative effects on health in the same way as the alcohol and tobacco industries have falsified their advertising and hidden evidence. At the same time they remain lax about labelling, supplying product potency information, itemising its use in food-stuffs, and disregard its dangers; for example, the association with driving accidents (Brubacher et al *NEJM* 2022;336:148-56 and Marcotte et al *JAMA Psych* 2022 doi 10.1001/jamapsychiatry.2021.4037) and with psychiatric disorders (VanderWeele *JAMA Psychiatry* 2021 doi 10.1001/jamapsychiatry.2021.1256 and Andreae *Sci Transl Med* 2018;10:eaav0342).

Also contributing to wider uptake is the medical professions laissez-faire approach which does not apply the usual criteria of medication-testing and packaging descriptions to cannabis dispensing. There is little hard data about its efficacy, and the reliance on anecdotal evidence is curious (Nutt *BMJ* 2022;376:n3114). Issuing Cannabis Cards for medical prescribing seems to be two-edged sword with initial reports suggesting more cannabis use disorders resulting from such regulations (Gilman et al *JAMA Netw Open* 2022;5:e222106).

Mechanisms and action

Cannabis contains tetrahydro-cannabinoids (THC) and cannabidiols (CBD) which bind to endocannabinoid receptors in the brain and thus decrease pain perception. The former THC is psychoactive while the latter, CBD is anti-inflammatory so it is unsurprising that self-medication can allow patients to feel “improved” and champion the medical use of cannabis. Without separation of the two main active ingredients and distinguishing and recording their potency it is impossible to judge its medicinal value. It is intellectually dishonest to compare effects without dosages and routes of administration being researched and recorded.

There may well be specific indications for cannabis medication, but there may also be standard treatments available that carry fewer potential harms, such as addiction and the unmasking of psychiatric illnesses. Reviews of cannabis use for gynaecological pain appear to support cannabis use for a variety of conditions, but the spectrum of pathology in which cannabis outperforms traditional drugs may be very narrow (Liang et al *Obstet Gynecol* 2022;139:287-296).

Effects of long-term cannabis use

As cannabis use increases and people expose themselves to its "chronic effects", it is important to know if there are long-term detrimental effects. Only time will tell but initial findings are not reassuring. A study of more than 1 000 New Zealand participants were followed up from childhood to age 45 years. They had both IQ and other cognitive functions tested at least 4 times over the years and their cannabis consumption recorded. Those who reported repeated cannabis use had significant declines in their IQ and other testing compared with their own previous scores. These deleterious results were not present or were less marked "among long-term tobacco users, long-term alcohol users, midlife recreational cannabis users, and cannabis quitters" (Meier et al *Am J Psych* 2022 doi 10.1176/appi.amp.2021.21060664). It has yet to be elucidated whether habitual cannabis use is associated with elevated rates of dementia in later life.

Effects on pregnancy

There is concern that cannabis use may cause epigenetic changes in the fetus (and its subsequent development) similar to tobacco. Research into its short-term teratogenic and long-term behavioural effects is relatively new, but what is being published is not reassuring. Risks associated with cannabis use in pregnancy are:

- THC is slowly metabolised, being detectable in adults for 30 days
- cannabinoid receptors are present in the fetal brain from 13 weeks gestation
- cannabis is **perceived** to be relatively harmless (which it is not) for the management of minor disorders of pregnancy such as nausea, constipation, and anxiety
- more than one third of pre-pregnancy users continue with its use through pregnancy
- cannabis use is associated with the following adverse neonatal outcomes: preterm delivery, birth weight less than 2,500g, small for gestational age (SGA or growth restriction), low Apgar scores, and decreased head circumference (Marchand et al *JAMA Netw Open* 2022;5:e2145653).

These data have been collected against a background of cannabis potency that "has tripled in recent decades"; many policy makers are hesitant to allow unconsented toxicology testing, so self-reporting with probably under-reporting is likely; many women using one substance are known to be polysubstance users of alcohol and tobacco, as well as cannabis (Lupattelli et al *JAMA Netw Open* 2022;5:e221964) and where cannabis used disorders are diagnosed in pregnancy, there is often evidence of concomitant substance use disorder or co-morbid psychiatric and medical conditions, to which attention should be given (Meinhofer et al *JAMA Psychiatry* 2022;79:50-58).

Editorial comment: The use of cannabis carries significant health and social risks, and it is my view that all products containing it should have quantities displayed as well as health warnings – especially pertaining to pregnancy.

*There is rightly much talked about mental health in the media, which I applaud and support, but should we as obstetricians not be calling for primary prevention? Children from a single or polysubstance gestational environment are at risk of behavioural difficulties, for example Attention-Deficit/Hyperactivity Disorder (ADHD) which is now reported as affecting more than 10% of monitored cohorts (*Garrison-Desany et al *JAMA Netw Open* 2022;5:e221957). *People diagnosed with ADHD and Autism Spectrum Disorders carry a higher mortality than other adults, enhancing the case for prevention* (Catala-Lopez et al *JAMA Ped* 2022 doi 10.1001/jamapediatrics.2021.6401).

Pregnant women should not use cannabis and we should insist on its regulation to protect the next generation (Skelton et al *JAMA Netw Open* 2022;5:e2145666).

Urinary tract infections in women

- Most women will have at least one urinary tract infection (UTI) in their lifetime
- One in four will experience recurrent UTIs
- Recurrent UTIs are defined as three episodes per year, or two in six months
- Guidelines recommend low-dose, long-term daily antibiotic prophylaxis for UTIs
- In the US the cost of treating UTIs is more than $2 billion annually
- Chronic antibiotic prevention therapy can lead to anti-microbial resistance, so alternatives that "disinfect" urine are being sought.

One such candidate is methenamine hippurate which works by being converted to formaldehyde in the acid environment of the distal tubules of the kidney. Formaldehyde is bactericidal as it denatures bacterial proteins, so methenamine has been tested against conventional antibiotics for chronic UTI prophylaxis (Harding et al *BMJ* 2022;376:e068229).

This was a trial of more than 100 patients in each arm that pitted methenamine head-to-head against antibiotics of the clinicians' choice, to find out if both treatments had similar efficacy and if there were differences in the emergence of resistant strains of bacteria. The methenamine was not inferior to the antibiotics in keeping UTIs at bay and gave rise to fewer resistant micro-organisms over the 12 months of the investigation.

The management of recurrent UTIs is a prime example of where shared decision-making can combine clinical efficacy with antibiotic stewardship, and potentially end up with a win/win option (Hoffman et al *BMJ* 2022;376:o533).

The abortion debate continues

Many countries are repealing laws making abortion a criminal offence and are replacing them with more liberal legislation which allows termination of pregnancy up to prescribed gestational ages. Other countries are legalising remote (on-line) abortion services while the United States seems poised to move in the opposite direction, with the possible rescinding of *Roe v Wade* which at present enshrines American women's rights to reproductive autonomy (Wilkinson et al *NEJM* 2022 doi 10.1056/NEJMp 2119364). Nation-wide changes in the law of the US would have profound effects on the lives of US women who at present consider terminating their pregnancies within legal statutes. The US statistics show that nearly one million abortions are carried out annually and that one in four women will have an abortion in her lifetime (Giglo et al *NEJM* 2022 doi 10.1056/NEJMp2117368).

Abortion statistics in the UK

- More than 200,000 abortions are carried out in the UK each year
- This rate of 20/1000 or 2% of women of reproductive age, and the numbers continue to increase
- Medical (vs surgical) methods have become more popular, with 90% using mifepristone plus misoprostol
- Rates in those over the age of 25 years now exceed rates for those aged less than 18 years.

The journals continue to produce data on abortions which are "self-managed". This is in part due to the Covid pandemic which saw the promotion of "no test" or remote termination of pregnancy mechanisms whereby traditional pelvic examinations and/or ultrasound scans became impractical and postal delivery of the medications was accepted.

Reports of this shift in practice, to history-only screening and over-the-counter or remote prescribing, have shown that the elimination of in-person requirements have not changed the efficacy or safety of abortions (Upadhyay et al *JAMA Int Med* 2022 doi 10.1001/jamainternmed.2022.0217). The researchers found 95% complete abortions without the need for additional medical intervention with 0.5% major adverse events.

The reduction in work-force requirements using self-managed abortions will have a large impact on clinical services, and appeals to allow this change in practice to be continued and legalised are plentiful (Karlin *JAMA Int Med* 2022 doi 10.1001/jamainternmed.2022.0216).

Editorial opinion – These requests by the medical profession for less legal red-tape have met with political resistance despite backing from organisations such as RCOG and ACOG. Whether it is called "no-test" or self-administered practice, the practicalities are in favour of patient autonomy and efficiency.

I would support a mechanism whereby some form of contraceptive incentive was linked to the provision of remote abortion facilities. Self-service oral contraceptive ordering and deliveries would seem a logical progression – and good preventative medicine.

Is an Amazon-like on-line full contraceptive service an impossible concept?

Vaginal laser therapy – cure or con?

The genitourinary syndrome of menopause (GSM) is a set of symptoms that affects up to half of postmenopausal women and is attributed to the decline of estrogen' s effects on pelvic tissues. In particular, the vaginal epithelium becomes less pliant with fewer ruggae and decreased elasticity, leading to histological changes. If accompanied by dryness, then women experience itching, pain, and dyspareunia, which can be substantive enough for medical treatment to be sought.

Purveyors of fractional carbon dioxide vaginal laser therapy have claimed rejuvenating outcomes following three treatment sessions over one year that have "no side effects" and last "just a few minutes". The theory is that local "thermal necrosis in a fraction of the surface area of the vagina induces reparative changes, setting off a cascade of events that results in the remodelling of vaginal epithelium" – a process which purportedly increases collagen production and circulation leading, in the short-term at least, to a reduction of GSM symptoms.

Published proof of laser's efficacy is limited, with only three randomised trials, the pooled data of which (with fewer than 200 participants) showed no difference in symptoms, sexual function, or objective local health indices. A rigorous study from Australia is the first trial to use controlled sham treatment head to head with full standardised treatment and compared the long-term outcomes (*Li et al JAMA* 2021;362:1381-9). The results showed that symptomatic and objective parameters were not improved by "real" versus "sham" therapy over 12 months.

Editorial comment – The literature over the last few years has been remarkably sparse on the proven effects of what was hailed as a major breakthrough in a field in need of progress. Small, short-term reports are quoted by those with financial interests in "laser success" and advertisements touting "regained femininity" do not ring true physiologically. This latest trial has finally called out those pushing a dodgy form of treatment, and it is time to heed scientists asking for reconsideration of the use of lasers for GSM symptoms (Adelman & Nygaard JAMA 2021;326:1378-80).

The summary above appeared in another JASS publication in which I reviewed the Li et al article in JAMA about transvaginal laser therapy as treatment for Genito-Urinary Syndrome of Menopause. Now a blistering critique has appeared in the Australian ***Friends of Science in Medicine****, Newsletter 31 of 18th March 2022 by MacLennan. He asks, is it "A burning question or a commercial sting?" and states that, in his view "There is no physiological mechanism by which burning atrophic vaginal epithelium will magically rejuvenate it."*

He notes "Burns, infection, increased dyspareunia and scarring have been reported" and warns that complications of its use "outside of ethical trials could become the next medico legal minefield." I presume here he is referring to the mesh/tape debacle. He is one of the most distinguished leaders in O&G and I believe his words of caution should be heard by everyone considering using this therapy.

Genetics in O&G

The sequencing of the human genome two decades ago was one of the greatest advances in biological science. Not only did it define the precise order of all the base pairs of all our genes, it also explained the basis of precision medicine and epigenetics as well as "discovering" the microbiome.

Precision medicine

Precision medicine describes the ideal world where every diagnosis and treatment is based on an individual's genetic code. Certain people will have a genetic predisposition to particular disorders and certain managements will be more effective than others based on their genetic profile.

Very few diseases are caused by a single abnormality of a base-pair in a single gene position. However, a set of single-nucleotide variants (SNVs) in various places on different genes may create a pattern that is linked to the increased likelihood of a disorder being present. These sets of SNVs are called polygenic risk scores (PRS) and are being increasingly used to define who is at risk of disorders and therefore should be screened or who will respond to treatments (Shah *JAMA Netw Open* 2021:4:e2119333).

Breast cancer and polygenic risk scores

The best examples of using polygenic risk scores are in breast cancer. PRS give results that yield bell-shaped curves which categorise women into low, medium and high risk in various population groups for combined risks (Yang et al *JAMA Netw Open* 2022;5:e2149030) (Liu et al *JAMA Netw Open* 2021;4:e2119084) for different ancestries.

Another illustration is the "21 gene assay" which can inform those undergoing treatment whether they will benefit (or not) from adding adjuvant chemotherapy to their management schedules (Kalinsky et al *NEJM* 2022;385:2336-47).

Natural selection and epigenetics

The survival of the fittest paradigm relies on random genetic "mis-replications" for the progeny to be better equipped to survive and reproduce. These are chance occurrences in the cell's DNA structure and result in evolution within the species over long periods of time.

Epigenetics is concerned with how the environment affects gene replication, not by changing the DNA sequence, but by influencing gene expression. Gene expression reflects the cell's function, not its structure, and thus the milieu in which the gene produces proteins, for example, will change with the setting.

Teratogens can affect a fetus' cellular division to cause patterns of malfunction within cells, resulting in somatic and physiological aberrations through epigenetic pathways. There are more subtle epigenetic influences whereby maternal socio-economic status, or her mental state, can change fetal growth and development.

The mechanism by which these changes occur is called DNA methylation. DNA methylation is the process of adding methyl groups to the DNA molecule, thereby changing its functional activities. Examples of this process are described in which depression or stress in the mother during pregnancy influence the infant's development and programming in utero with resultant physical and mental detriment.

Example 1: Geneticists monitored women's mental health on six occasions during pregnancy, with particular reference to depression and stress (Tesfaaye et al *Epigenomics* 2021 doi 10.2217/epi-2021-0192). There were 300 participants and that they could define 16 epigenetic changes linked to depression and two to stress, which the researchers cryptically explain "were located close to genes which are known to have important roles in brain development and occurrence of psychiatric disorders."

Example 2: Parental socio-economic status (SES) is associated with adverse obstetric outcomes such as growth restriction, low birth weight, and preterm delivery, but it is unknown how "cause and effect" occurs. One possible mechanism is that lower SES life is more stressful than higher status life and this creates a "hostile" intra-uterine environment for the fetus. Challenged by stress hormones or inappropriate nutrition, the fetus responds by restricting its growth and prepares for extra-uterine existence by maturing its systems which it does by rapid cell replication.

It is possible to measure a cell's replication rate by examining its telomere length. A telomere is the "aglet-like" portion at the end of a gene which becomes shorter by a very small amount every time the cell's DNA reproduces itself. It is a "biological clock" which can estimate not chronological age but the cell's biological age. Telomeres from a fetus which is turning over its cells rapidly will have a shorter length than those from a fetus which is not requiring its cells to have a more mature function.

Investigations from more than 100 neonates showed that telomere length does correlate with maternal SES in that lower status was strongly associated with shorter telomeres (Martens et al *JAMA Netw Open* 2020;3:e204057). The researchers postulate that increased stress from social, environmental or nutritional sources have epigenetic effects on the mother, fetus and neonate that restrict growth, possibly by DNA methylation, causing changes in the fetus adapting to its environment. This would explain small for gestational age infants who are physiologically mature but somatically smaller – the wizen, growth-restricted neonate.

It is feasible to extrapolate SES with other stressors such as maternal mental health, the physical environment (air pollution and natural disasters) pandemics and conflict situations such as war.

Editorial comment – this summary is being written while Russia is invading Ukraine and we should show solidarity for all those innocently caught up in this war. Can the perpetrators have any concept of the future harm they are creating?

These epigenetic influences dictate changes in the fetus, which can result in short-term adaptations (growth restriction) or long-term outcomes (for example: adult cardiovascular pathology) and these traits are passed on to the offspring as intergenerational inheritances. The uterus is not an insensitive incubator, but a responsive organ reflecting a much wider environment.

We have moved from David Barker's fetal origins of disease to an epigenetic explanation that clarifies the developmental origins of health and disorders.

The interplay of the maternal-fetal interface with the wider context of the human condition is elegantly discussed in Sarah Richardson's book "*The Maternal Imprint: The Contested Science of Maternal-Fetal Effects"* The University of Chicago Press. For an summary see Lyerly *Lancet* 2022 doi 10.1016/S0140-6736(22)00117-9.

The human microbiome

Probably the most unexpected discovery associated with the sequencing of the human genome, was not the actual structure of our genes and the code they carry, but something altogether different, the microbiome.

Our human microbiome consists of trillions upon trillions of microbes that live on us and in us.

Different sets of micro-organisms exist in every system and every orifice we possess where they perform vital functions that keep us healthy. These fellow travellers used to loosely be called commensals, but are now named microbiota, and are collectively known as a microbiome. There are microbiomes peculiar to various regions of our skin, hair, ears, nose, throat, genitourinary tract – even our eyes and brain, but by far, the largest is the gut microbiome which weighs about 2kg and contains bacteria, viruses, fungi and other micro-organisms. Our combined microbiomes have at least 150 times more genes than our human genome.

An example of how knowledge of the microbiome may assist clinical gynaecology can be found in the connection between the gut and the brain – and how this can be influenced by gonadal hormones.

The gut & the brain

The microbiome of the gut is integral to the enteric nervous system. The enteric nervous system is a complex integration of nerves (for example the vagus nerve) and hormones (neurotransmitters) that feedback in both directions creating the "gut-brain axis". The gut microbiota thus have a direct effect on our cognitive function, which may be important in dictating susceptibility to dementia in later life (Meyer et al *JAMA Netw Open* 2022;5:e2143941).

Basically, we need a diverse mix of microbes in our gut to maintain health and homeostasis throughout our bodies. This diversity is described as a "richness" or variation, whereas a paucity of variation or dominance of any set of flora is harmful, and it is called dysbiosis. There are specific short-chain fatty acids produced by normal gut microbes that are essential to normal brain function and the lack of these microbiome products is implicated in accelerated cognitive decline.

Microbiome changes through the menopause

The decline in estrogen status through the menopause transition leads to changes in the vaginal, urinary tract, oral, gastro-intestinal plus many other microbiomes. The question now being asked is whether menopausal hormone therapy affects the microbiota in these systems and, if so, do the changes reflect any benefit or harm (Pru *Menopause* 2022;29:253-4)?

Research sampling duodenal micro-organisms from a variety of pre- and postmenopausal women has shown that taking estrogens and progesterone change the microbiome to approximate that of premenopausal women (Leite et al *Menopause* 2022;29:264-75).

Postmenopausal participants (not on MHT) had less diversity in their duodenal microbiota, higher fasting glucose levels and lower testosterone levels. This is an example of dysbiosis as the result of lowered estrogen levels that is linked to metabolic dysfunction. Those taking hormones had microbiomes associated with superior cardiovascular prognostic indicators which may in turn be related to future improved cognitive function. Is it possible that MHT could be used to maintain cognitive function through its effects on gut microbiota?

Editorial thoughts – These explanations may allow changes of attitudes to management. Perhaps using hormones perimenopausally will be viewed through a different lens. Rather than being seen as "imposing non-natural laboratory products" they could be perceived as "restoring natural gut flora" and re-establishing a desirable symbiosis.

Maybe hormone therapy will have a series of physical and neurological benefits that will be rationally added to their relief of vasomotor symptoms? The benefit/harms ratio could be judged in a less negative way because more understanding leads to less suspicion, and less fear.

I look forward to the day when MHT is accepted in the same way that oral contraceptives are.
Very good at their primary function but with advantages associated with their use which improve the quality of the woman's life.

Medication	**Oral contraceptives**	**Menopausal Hormone Therapy**
Primary indication	Prevention of pregnancy	Prevention of vasomotor symptoms
Beneficial effects	Decreased menstrual loss Decreased dysmenorrhoea Improved iron stores Treatment of PCOS and Endometriosis Less acne Lower ovarian cancer risk	Improved mood & sleep Fewer night sweats Decreased bone loss Healthier CVS function Healthier metabolic function Fewer wrinkles Reduced GUSM symptoms Less libido loss
Harmful effects	Raised thrombotic risk	Raised thrombotic risk Raised breast cancer risk

In summary – MHT is not a capitulation – it is a smart option.

Athol Kent

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April 2022

Dear Colleague

The April issue of JASS is controversial in that new frontiers are being presented with limited clinical proof. Nevertheless, JASS's remit is to bring the latest developments to your attention for your consideration, so it is up to you to put the information into your clinical context for your patients.

The social and emotional impact of the pregnant woman's mental health on the fetus opens a whole world of intrigue and I wonder when we are going to combine with our psychologist colleagues to alter the thrust of our ante-natal care/instruction?

There is both a lot of editorial comment which is my own and not that of JASS board or any organisation – national or otherwise so do not attribute any of it to anyone else!

There are also a number of explanations about the underlying science and physiology behind the topics and I hope it does not read too much like a tutorial. I had to work quite hard to get my head around some of the concepts, so I am sharing them with you, so please bear with me.

I am happy to engage with you if you disagree or have comments so let me know at atholkent@mweb.co.za if you feel so moved.

We in South Africa are looking towards the lifting of Covid regulations and I trust the same is happening in your country. JASS goes to subscribers in 44 nations, so this is a world-wide wish.

Kind regards

Athol Kent

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Monthly Questions – April 2022 **True/False**

1. Cannabis is harmless if used in pregnancy _____
2. Methenamine hippurate is as effective as long-term antibiotics in treating recurrent urinary tract infections in women _____
3. The number of abortions in the United Kingdom is declining _____
4. Self-managed abortions appear to be as safe and effective as those where "in-person" requirements are demanded _____
5. There is adequate evidence that laser vaginal therapy is safe and effective in the management of the genitourinary syndrome of menopause _____
6. Epigenetic mechanisms operate by changing a cell's DNA structure _____
7. A woman's mental health in pregnancy has been scientifically proven to affect fetal outcomes _____
8. The length of a telomere can be used to measure a gene's biological longevity _____
9. The composition of the gut microbiome cam be altered by menopausal hormone therapy _____
10. The abnormal distribution of micro-organisms in the gut microbiome is called dysbiosis _____

Please ask for the Annual Answer Sheet from JASS administration if you intend trying for CPD points using JASS. Requests to atholkent@mweb.co.za
The Annual Answer Sheet will be emailed to you so you can fill in your answers each month.
Do not send copies of this Monthly Questions page or subsequent question documents.
The completed Annual Answer Sheet should then be scanned and emailed to JASS at the beginning of next year and your CPD certificate will be sent to you.
For South African subscribers, the HPCSA will also be notified electronically of your CPD points achievement.

Index 2022

Gynaecology

Abortion	Access to abortion II	10
	Abortion	23
	The abortion debate continues	27
Contraception	Comparative Family Planning	18
	Contraceptive safety & new methods	11
	Ethics & contraceptive incentives	12
	Opportunistic salpingectomy	17
Gender issues	LGBTQ+ further coverage	13
	LGBTQI– what gynaecologists need to know	1
	The trans debate	3
Infertility	Assisted Reproductive Technology	18
Menopause	Vaginal laser therapy – cure or con?	28
Ovary	Ovarian cancer – fact file	17
Polycystic Ovary Syndrome	PCOS – the most common endocrine condition in women	5
UTI	Urinary tract infections in women	27

Obstetrics

Antenatal care	Anti-seizure medication	22
Caesarean deliveries	Caesarean section skin incisions in obese women	22
Epidurals	Neuraxial analgesia in labour	21
Labour	Preparing the cervix for induction	10
Preterm	Preterm deliveries	20

General

Antibiotics	An inconvenient truth – antibiotic resistance	24
Beverages	Tea, coffee or both?	16
Cannabis	Cannabis use in general and in pregnancy	25
Covid	Quick Covid reports	9
DEI	Diversity, Equity & Inclusion (DEI)	14
	Diversity, Equity and Inclusion	23
Genetics	Genetics in O&G	29
LGBTQ+	LGBTQ+	23
Medicolegal	A medico-legal conundrum – wrongful conception	16
Physical activity	Exercise and health	6
Policy developments	Progress in the UK in 2021	8
Sex	Sex – cancer, coronaries and Covid	13
	The G-Spot & the C-Spot	24
Supplements	Vitamin D	16
	Vitamin D supplementation	23