

September 2020
Metabolomics – What it is – and why you should know about it

- Metabolomics is the study of metabolites. Metabolites are the products of metabolism.
- In the process of living, organisms and cells metabolise substances and this involves the break-down of complex molecules into smaller molecules.
- Metabolites can be viewed as the waste-products of cells.
- These are “chemical fingerprints” which reflect the processes that have taken place.
- A collection of these small metabolites in a person’s blood gives a profile of the cellular activities which may be physiological or pathological.
- A cell’s or tissues’ complete set of metabolites is called its metabolome.

Where this becomes of interest is when pathological processes occur in a cell and abnormal metabolites are shed into the blood-stream. The detection of these pathological metabolites – whether singly or as a set making up a fingerprint – can indicate that a malignancy exists somewhere. With the advent of ever-more precise finger-printing and machine-learning algorithms, metabolites from specific organs can be identified.

The combination of malignant metabolites with their particular signature, plus learning algorithms, can pin-point the tissue from which these waste products arise. For example, it is possible to screen post-menopausal women for endometrial cancer by looking for specific metabolites in their serum.

In a pragmatic study, more than 1 500 women with a mean age of 68 years had blood samples taken and analysed through a machine-taught algorithm mechanism. Some were known to have a diagnosis of endometrial cancer but the vast majority were asymptomatic so the “ensemble” was tested to check-out clinically relevant information ([Troisi et al JAMA Netw Open 2020;3:e2018327](#)). The system performed well identifying all 16 actual cases of endometrial cancer plus 2 false positives and no false negatives giving a high degree of accuracy.

Editorial comment: This proof of concept research showed robust outcomes with sensitivity, specificity and accuracy all greater than 99%. It is inexpensive and non-invasive so it could be used for population screening. One wonders what other malignancy detection could be amenable to this methodology? Are there other cancers which could be candidates for what might be termed a “liquid screening biopsy”? Is this the next screening frontier?

HPV in the spot-light

The Human Papillomavirus (HPV) is a double-stranded DNA virus which is implicated as a risk factor in numerous malignancies. The virus exclusively infects epithelial cells, interrupts the normal cell cycle, and triggers uncontrolled cell division. HPV infection is usually efficiently cleared by a person’s immune system – in the case of cervical infections within a few months – and no residual danger remains. However, in some individuals, possibly because of repeated infections with oncogenic strains or because of reduced immunology robustness the virus penetrates the normal defences and neoplastic changes occur.

Reductions in immune responses can be due to illnesses, smoking, chemotherapy or drugs. As populations age cancers form a proportionally larger section of the pathology spectrum and more patients are given medications which inhibit immunity so HPV may not be effectively eliminated and thus give rise to epithelial malignancies. Transplant patients receiving chemotherapy may become susceptible to any viral infections and can develop multiple cancers ([Chang et al JAMA Netw Open](#) 2020;3:e2022107). These situations will become commoner and people who have been vaccinated may well be at an advantage downstream.

Publications show that the HPV vaccine is safe as far as cerebral side effects are concerned ([Hviid et al BMJ](#) 2020;370:m2930) and efficient in preventing invasive cervical cancer ([Lei et al NEJM](#) 2020.383:1340-8). The reduction in invasive lesions following any vaccination is 53% and if administered before the age of 17 the reduction rises to 88%. However, the data were derived from women followed to their 31st birthday and there is still a possibility of malignancies appearing later therefore adult-life screening should be recommended together with early vaccination.

Screening starts at 30 years in most countries with both HPV plus cytological investigations, the so-called co-testing approach. Where the tests match, there are clear algorithms as how to proceed but where they are discordant advice is less straight-forward so expert opinion should be sought (See [Sawaya et al JAMA](#) 2020;324:1557-8).

The case for early universal vaccination is compelling for boys and girls but those most at risk are least likely to be informed or have access to vaccination ([Russell et al SAfrMJ](#) 2020;110:887-93).

There is a need for screening to detect other epithelial dysplasias, such as oropharyngeal cancer which is also HPV driven. Oral-rinse testing has been researched in Australia and the technique has proved successful in identifying occult cancers that can be eradicated while still amenable to surgery ([Tang et al Front Oncol](#) 2020;10:408). These malignancies will hopefully also be prevented by HPV vaccination adding impetus to national programmes.

Incidentally, the 2020 Nobel prize for Medicine has been awarded to Alter, Houghton, and Rice for their work in discovering the Hepatitis C virus so it seems appropriate to highlight virology as an old discipline with a new lease of life ([Burki Lancet](#) 2020 396;1058).

Chronic pelvic pain – is gabapentin the answer?

During their reproductive careers, up to a quarter of women suffer from chronic pelvic pain. It is described as continuous or recurrent pain that lasts longer than 3 months – with or without dyspareunia or dysmenorrhoea – and has no discernible pathology as excluded by laparoscopic investigation.

As with dysmenorrhoea, both absenteeism and presenteeism from chronic pelvic pain result in a loss of productivity, social and relationship stresses and frequent consultations to the medical profession and alternate therapists. Because a reliable and safe medication is desirable to offer assistance to these women, a trial was conducted in the UK involving 39 hospitals and women were randomised to receive a titrated daily dose of gabapentin or placebo for 4 months ([Horne et al Lancet](#) 2020; 396:909-17). Subjective pain scores (between 1 and 10) were reduced from baseline by a mean -1.1 points in the active ingredient group and -0.9 in the controls suggesting minimal medicinal or placebo effect and no statistical evidence of benefit. Those receiving gabapentin had more adverse effects.

The investigators conclude “Given the increasing reports of abuse and evidence of potential harms associated with gabapentin use, it is important that clinicians consider alternative treatment options...” An article comparing electroacupuncture and sham treatment for low back pain showed no difference in analgesic properties but improved mobility so some benefit may be derived through alternative options ([Kong et al JAMA Netw Open](#) 2020;3:e2022787).

Editorial opinion: While on the topic of pain, we may be called upon to prescribe medications for the relief of acute pain but evidence-based data are difficult to assess. A systematic analysis indicates little, if any, advantage of opioids for recurrent situations and comes down in favour of topical and oral non-steroidal anti-inflammatory agents and acetaminophen (paracetamol) with or without diclofenac ([Busse et al Ann Int Med](#) 2020.doi.10.7326/M19-3601).

Paracetamol is one of the most widely used analgesics but a few months ago NICE revised the recommendation of its use for chronic pain relief and Switzerland showed an increase in poisonings with the introduction of 1 000mg oral dosages ([Martinez-De la Torre & Weiler JAMA Netw Open](#) 2020 3:e2022897). For children under the age of 2 years ibuprofen was found to be superior to paracetamol for pain and pyrexial relief ([Tan et al JAMA Netw Open](#) 2020;3:e2022398).

There are also significant questions being asked about paracetamol’s safety in pregnancy with associations being found between fetal levels (as measured in meconium) and the risk of ADHD in later life ([Baker et al JAMA Pediatr](#) 2020 doi. 10.1001/jamapediatrics.2020.3080).

The use of NSAIDs in pregnancy has again been under reconsideration in the US where the FDA has issued a [Safety Communication](#) warning of fetal renal damage if used in the second half of gestation.

What factors dictate a woman’s cardiovascular health? A heartfelt meander

Women enjoy better cardiovascular health than men up to middle age, after which the difference becomes less apparent, but what factors influence their advantage?

Reproductive physiology – A woman with a normal hypothalamic-pituitary-ovarian axis will experience menstrual cycles that are regular chronologically and consistent in duration. Deviations from such regularity have been empirically recorded to be associated with higher instances of cardiovascular disease (CVD) and premature death, arbitrarily determined as younger than 70 years of age ([Wang et al BMJ](#) 2020;371:m3464).

The length of a woman’s reproductive life-span, judged by the number of years between her menarche and menopause, is also an indicator of subsequent CVD risk. Large-number statistical calculations have shown that having fewer potential child-bearing years is correlated with a higher burden of CVD and abbreviated longevity, especially if associated with an early menarche. In actual numbers the definition of a short reproductive span was found to be less than 33 years ([Mishra et al JAMA Cardiol](#) 2020 doi. 10.1001/jamacardio.2020.4105). The exposure to high levels of circulating estrogen during these years is thought to be central to a woman’s lowered CVD risk.

Age at menarche – The most clearly defined aspect of puberty in girls is menarche which has been occurring at progressively younger ages over the last few decades. The mean age has decreased with the latest figures for the US showing a median age of 11.9 years compared with 12.1 some 5 years earlier ([Martinez 2020 Nat Health Stats Rep](#)). The maturation of the central endocrine axis is thought to be a function of body habitus related to fat and weight ratios with environmental factors mediating the process.

But there are psychological factors at play as well. Adverse factors in the early life of children can have an effect on their development and this can find expression in accelerated maturation in adolescents. There are studies linking early-life adversity, in particular actual or threat-related physical abuse, to premature menarche. The sociological observations were backed by the finding of greater telomere attrition which is an indication of rapid biological aging ([Sun et al *JAMA Netw Open* 2020;3:e2013588](#)). It has even been speculated that this response to stress in the form of abuse, assault, neglect or poverty is part of an adaptive model for early reproductive capacity in the face of adversity. This supposition is supported by the demonstration of a later age of menarche being associated with higher socioeconomic status.

So early menarche, which until recently was thought to be an indicator of a better nourished population, may have a darker aspect with its inexorable decrease chronologically bringing detrimental effects in its wake. Among these are rising rates of depression, eating disorders and substance abuse together with later adult obesity, type 2 diabetes, breast cancer and earlier onset of the menopause. It also requires “addressing dysmenorrhea, facilitating HPV vaccination, and providing effective contraception” as early menarche is strongly linked to a lowered age of sexual debut.

Gynaecological disorders – Factors exclusive to women (including pregnancy related issues) can also influence a woman’s subsequent CVD risk and an umbrella review on the topic indicates how women are not improving their cardiac prognoses as rapidly as men ([Okoth et al *BMJ* 2020;371:m3502](#)).

Polycystic Ovarian Syndrome (PCOS) has been implicated in “premenopausal cardiometabolic dysfunction” and this translates into the conferring of an increased risk of CVD postmenopausally ([Christ & Neal-Perry *ASRM V Conf* Oct 2020 Ab O-35](#)).

Obstetric outcomes – The outcomes of pregnancy as judged by maternal and fetal criteria can indicate a woman’s future CVD risk. Two large retrospective studies from US and Sweden looked at the CVD histories of postmenopausal women and matched their status with their obstetric and perinatal histories ([Søndergaard et al *JAMA Cardiol* 2020 doi. 10.1001/jamacardio.2020.4097](#) and [Crump et al *BMJ* 2020;370:m2533](#)).

Both investigations showed strong correlations, particularly between preterm deliveries, light for dates infants and hypertensive disorders and future atherosclerotic events. A more at-risk prognosis of CVD status was associated with shortened gestational age births, growth restricted fetuses and more serious hypertension with complications. The bottom line was the more complex the obstetric history the greater the risk of premature CVD disability or death and preventative measures should be advised accordingly.

It may be worth noting that in the obstetric literature preterm and term are being defined as:

<u>Delivery nomenclature</u>	<u>Gestational age in weeks</u>
Extreme preterm	22 – 27
Very preterm	28 – 33
Late preterm	34 – 36
Early term	37 – 38
Full term	39 – 41
Post term or post-dates	42 onwards

General factors – Apart from factors relating to exclusively female physiology, the elements that predict CVD incidence are genetic and lifestyle.

Genetic – The genes inherited from one's parents can now be sequenced to give any individual's risk of CVD affliction. Such a Genetic Risk Score (GRS) can be measured for a host of pathological conditions and is used where there is a strong family history of a disorder. In the case of CVD prediction a GRS has, as yet, not superseded more traditional methods of assessing risk in the clinical setting. The Framingham Risk Score has practical utility as does the biochemical measurement of Lipoprotein(a) and more complex genetic laboratory measures add little to atherosclerotic predictions ([Trinder et al JAMA Cardiol](#) 2020 doi. 10.1001/jamacardio.2020.5398).

Just a reminder about women who suffer from migraine with aura. A study of female health professionals in the US showed that the incidence rate of CVD for this type of migraine sufferers was 3.4 per 1 000 v 2.1 per 1 000 for those without migraine ([Kurth et al JAMA](#) 2020;323:2281-9).

Lifestyle – This is the most amenable aspect of CVD risk manipulation. The 3 most important factors are diet, drugs and exercise and it is beyond the scope of this meander to delve into these in depth. A few points are:

- In the broadest of terms, a healthy diet decreases the chances of CVD and 3 major studies have shown strong correlations ([Shan et al JAMA Intern Med](#) 2020;180:1090-100)
 - In the last 5 years 5 countries Chile, Israel, Mexico, Peru and Uruguay have introduced legislation that foods with high levels of unhealthy nutrients must carry health warnings ([Hall & Grummon JAMA](#) 2020 doi: 10.1001/jama.2020.18941)
 - Smoking reduces life expectancy by 10 years on average
 - Smoking and diabetes affect women's CVD risk more than men
 - Drugs – both prescription and illicit must be legislated judiciously into submission rather than continuing with the farcical "war on drugs"
 - Along with climate change a healthy built environment should be mandatory
 - Physical inactivity costs the US more than \$100 billion in health costs per year
- Virtual advisors are non-inferior to human advisors so new methods of nudging people can be popularised ([King et al JAMA Intern Med](#) 2020 doi. 10.1001/jamainternmed.2020.4143).

If a woman (or man) is in a high-risk category then action should be advised which includes regular medical checks, lifestyle modifications as required and judicious drug management, for example the consideration of aspirin use prophylactically, which remains the centre of debate ([Cainzos-Achirica & Greenland JAMA Cardiol](#) doi. 10.1001/jamacardio.2020.4961) as do statins.

Premature menopause

Primary ovarian insufficiency or premature menopause, is a rare condition in young women but increases in incidence with age, afflicting 1 in 10 000 aged 20 years, 1 in 1 000 aged 30 years, 1 in 250 aged 35 years and 1 in 100 aged 40 years. The definition is oligo- or amenorrhoea for 4 months before the age of 40 years with 2 follicle stimulating hormone levels in the menopausal range 2 months apart ([Jiang Menopause](#) 2020;27:1101-3).

The condition carries a myriad of consequences, one of which is decreased bone mineral density and the treatment possibilities include low- or high-dose replacement hormone therapy or combined oral contraceptives. In a comparative trial the contraceptive pill consisting of ethinylestradiol 30 µg plus levonorgestrel given continuously was superior in terms of increased bone density measures ([Gazarra et al Menopause](#) 2020;27:1110-6).

Gallstone disease in pregnancy

- Increased levels of estrogens increase cholesterol secretion
- Increased levels of progesterone delay gall bladder emptying
- These conditions increase the risk of acute cholecystitis
- It occurs in more than 1 in 2 000 pregnancies
- It is the second commonest indication for surgery in pregnancy
- Most gallstones are asymptomatic and should be left alone if discovered incidentally.

The commonest presentation of gallstones is biliary colic which classically is post-prandial right upper quadrant pain. Conservative management consists of analgesia (avoiding non-steroidal anti-inflammatory drugs) bowel rest and IV fluids but the resort to surgery should have a low threshold. In any trimester the laparoscopic approach is advised and results are excellent for mother and fetus if preterm labour can be circumvented ([Schwulst & Son JAMA Surg](#) 2020 doi. 10.1001/jamasurg.2020.3683).

Aortic aneurysms in pregnancy

Despite the high profile attention it attracts when it occurs, dissection of an aortic aneurysm is a rare event in pregnancy. One third of aortic dissections occur in women and those that are chronologically related to pregnancy represent 0.3% of all recorded acute aortic emergencies ([Braverman et al JAMA Cardiol](#) 2020 doi. 10.1001/jamacardio.2020.4876). When it does present it is usually in women who have a genetic predisposition in the form of Marfan or Ehlers-Danlos syndromes but ironically it is often the aortic event that leads to the more generalised disorder diagnosis ([McNally JAMA Cardiol](#) 2020 doi. 10.1001/jamacardio.2020.4884). It may occur in the puerperium when oxytocin receptor sensitivity remains high.

Cystic fibrosis in pregnancy

One of the spin-offs of the UK Obstetric Surveillance System (UKOSS) is its collective ability to record sufficient cases of rare disorders to give a statistically-likely picture of outcomes. Such an example is cystic fibrosis of which UKOSS retrieved the records of 70 pregnancies over 2 years ([Ashcroft et al BJOG](#) 2020 doi. 10.1111/1471-0528.16423). With compromised lung function being the most critical parameter, it transpired that outcomes were generally good even with FEV1 readings below 60%. Overall there were no maternal deaths, one perinatal demise and the main adverse outcome was preterm delivery (mean age 36.2 weeks) and growth restriction commensurate with falling maternal lung function measurements.

Genetic investigations pre- and postnatally

Nonimmune hydrops fetalis is a sinister sign on ultrasound that warrants diligent investigation. It is associated with a wide range of structural, genetic, metabolic and infectious disorders but the contribution of exome sequencing to diagnostic accuracy is unknown. To evaluate the usefulness of genomic protein-coding tests a series of more than 100 fetuses were investigated and diagnostic variants identified in a third of cases ([Sparks et al NEJM](#) 2020 doi. 10.1056/NEJMoa2023643).

As with cerebral palsy diagnostics, there is about a one third positive yield using genetic sequencing and if extended into childhood diagnostics, similar results can be anticipated. Children with unexplained medical complexities, even after routine karyotyping should undergo sequencing and again, a third of previously undiagnosed genetic disorders can be uncovered ([Costain et al JAMA Netw Open](#) 2020;3(9):e2018109).

Snippets

Urinary incontinence therapy

In the previous issue of JASS the data from individual and group therapy treatment of urinary incontinence were presented. The work showed equally satisfactory results with pelvic floor muscle training at one year either singly or as group participants ([Domoulin et al JAMA Int Med](#) 2020 doi. 10.1001/jamainternmed.2020.2993). But what about adding electromyographic biofeedback?

Research from 23 centres in the UK used adjunct biofeedback both in formal classes and for patients at home in a randomised trial and assessed any differences after 2 years ([Hagen et al BMJ](#) 2020;371:m3719). Using standardised questionnaires the outcomes were disappointing with the authors concluding “routine use of electromyographic biofeedback with PFMT for women with stress or mixed urinary incontinence does not provide additional benefit.”

Male infertility

About 15% of couples experience infertility and half of these involve a male factor. It is well documented that sperm counts have decreased in the last half century but there is no consensus as to the reason for this decline with lifestyle and endocrine-disrupting chemicals being the most frequently cited potential causes. The majority of studies on semen analysis involve men attending fertility clinics rather than the population at large so an investigation from Denmark in healthy young men is interesting ([Jensen et al JAMA Netw Open](#) 2020;3:e1919462).

Army recruits supplied semen samples and information about their intake of fish oil supplements and a correlation between the two sought. It transpired that those using supplements had better testicular function as measured by total sperm counts, concentration, morphology and motility. This tends to support the theory that diet is linked to sperm quality and echoes the practice of treating of low counts with polyunsaturated fatty acids ([Salas-Huetos JAMA Netw Open](#) 2020;3:e1919569).

Epidurals & autism

The increase in the number of children with autism spectrum disorders (ASD) has prompted widespread investigations into possible causes. Among these are modes of delivery and anaesthetic agents, with special attention given to those involved with caesarean sections (CS) and now a focus on epidural analgesia ([Qiu et al JAMA Pediatr](#) 2020 doi. 10.1001/jamapediatrics.2020.3231). There does appear to be a connection between the risk of ASD and the duration of epidural neuraxial analgesia in labour but this does not appear to be “temperature related”.

Quite how such a connection can be made aetiologically remains unclear but these findings “raise concerns” so more research is clearly indicated.

Hair dyes and cancer

Is there a relationship between the use of hair dyes and cancer?

In Western countries more than half of women use hair dyes that are classified as oxidative (permanent), direct (temporary) or natural dye with the oxidative type used by the majority of women. The exposure is through dermal contact but there is no evidence of carcinogenicity in a large cohort (more than 100 000 women) followed up for 36 years ([Zhang et al BMJ](#) 2020;370:m2942). Hair-colouring substances can be given a clean bill of health.

Appendicitis means surgery?

If a diagnosis of acute appendicitis is made, does that mean that the only correct management is surgical? It appears not according to a randomised trial conducted in the US in which more than 1 500 cases were treated surgically or with a 10 day course of antibiotics ([CODA Collective NEJM 2020 doi. 10.1056/NEJMoa2014320](#)).

The researchers claim non-inferiority of antibiotic therapy according to predetermined criteria but one third of the conservatively treated patients required surgical intervention within 3 months. They suffered more complications and had more emergency room consultations, while surgery (laparoscopic procedures in 96% of cases) offered swift and lasting relief.

Editorial comment: Although the criteria for non-inferiority were met according to the evidence-based outcomes, I wonder if a quick effective resolution is not preferable to the majority of patients. Yes, this trial suggests a viable medical alternative but if pushed, how many surgeons would recommend the antibiotic route? I side with Jacobs ([NEJM 2020 doi. 10.1056/NEJMe2029126](#)) who says that although it is an option and can be discussed, antibiotics should not be used as an opt-out for clear decision-making. I believe surgery is the method of choice.

Calcium intake – does it matter?

Intuitively, it feels logical to encourage osteopenic postmenopausal women to raise their dietary intake of calcium. Surely it is good for them to eat more calcium-rich foods or take supplements to prevent rapid or excessive bone loss? But is this deductive reasoning supported by data?

Evidently not, according to researchers who followed up a cohort 2 000 older women with hip T-scores between -1.0 and -2.5. They measured their bone mineral density a total of 3 times over 6 years and related bone loss to calcium intake ([Bristow et al J Clin End Met 2019 2019;104:3576-84](#)). Their conclusion was (quoted in full) “Postmenopausal bone loss is unrelated to dietary calcium intake. This suggests that strategies to increase calcium intake are unlikely to impact the prevalence of and morbidity from postmenopausal osteoporosis.”

and vitamin D supplementation?

Most advocates of vitamin D supplementation suggest 400 IU per day for people who are vitamin D deficient. But many people hope “more is better” and doses of 1 000 IU or even 4 000 IU per day are taken by those who believe in supplements, despite enjoying a healthy diet and normal serum levels of vitamin D. In women these high doses are detrimental to bone health ([Burt et al JBMR 2020 doi. 10.1002/jbmr.4152](#)). Bone density loss increased as the doses of vitamin D rose and the effect was much more marked in women. Primum non nocere.

Dare one think that the whole **calcium – vitamin D edifice** for “quality aging” in healthy older people is built on sand?

 **JOURNAL ARTICLE
SUMMARY SERVICE**

October 2020

Dear Colleague

Brave new medical world.

We have been exposed to “liquid biopsies” through our introduction to the topic using “Non-Invasive Prenatal Tests (NIPTs)” in which fetal DNA is analysed by sequencing molecules from the fetus shed into the maternal circulation. Add to that machine learning technology plus cheaper laboratory methods and molecular medicine is on our doorsteps.

This has set us up to accept technologically advanced screening but are we going to see liquid biopsies being used to search for a range of cancers as a means of screening?

I have my doubts as there is the danger of such investigations becoming “fishing trips”. They could cause all sorts of reactions if an otherwise healthy person turns out to have a “potential malignancy”. We deal with abnormal variations in our cellular reproduction all our lives and our immune system eradicates these non-identical (non-normal self) deviants – so when do we or our health systems go on the hunt for a supposed primary? Am I being a Luddite?

Two areas where science is poised to assist us, and they are in Covid diagnostics.

By identifying a protein specific to SARS-CoV-2 researchers have pin-pointed antibodies that are created against Covid and the method holds promise. It is published in Science but sensitive readers are warned about the density of the scientific language used in the article ([Schrock et al Science 2020 doi. 10.1126/science.abd4250](https://doi.org/10.1126/science.abd4250)).

Another approach to Covid diagnosis has become available using CRISPR technology that is “as specific as and more sensitive than qRT-PCR for detecting SARS-CoV-2 from clinical samples” ([Brandsma E et al J Infect Dis 2020 doi. 10.1093/infdis/jiaa641](https://doi.org/10.1093/infdis/jiaa641))

If you wish to be authoritatively updated about Covid by Tony Fauci then click on

<https://www.youtube.com/watch?v=3MH-3ICY-N4&feature=youtu.be>

Kind regards

Athol Kent

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JASS questions for October 2020

- | | True/False |
|---|------------|
| 1. Metabolomics is the study of serum-borne metabolites that can potentially screen for tissue malignancies | _____ |
| 2. Human Papillomavirus is implicated in initiating malignant change only in epithelial cells | _____ |
| 3. Gabapentin is the analgesic of choice for women with chronic pelvic pain | _____ |
| 4. Non-steroidal anti-inflammatory drugs are safe to use in the second half of pregnancy | _____ |
| 5. The more regular a woman's menstrual cycles in terms of duration and chronologically, the lower her risk of CVD in later life | _____ |
| 6. Early menarche is associated with a lowered risk of cardiovascular disease in later life | _____ |
| 7. Primary ovarian insufficiency is associated with a lowered risk of cardiovascular disease in later life | _____ |
| 8. Gallstones discovered in pregnancy should be definitively treated surgically even if asymptomatic | _____ |
| 9. Diets high in calcium or calcium supplements reduce the likelihood of osteoporosis in otherwise healthy women postmenopausally | _____ |
| 10. Vitamin D supplementation – even at high levels is harmless | _____ |

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Please request the current CPD Annual Answer Sheet if you do not have a copy.

You are advised to fill in your answer sheets each month but to return the CPD Annual Answer Sheet (only) to JASS administration early in 2021.

You are NOT required to send back each month's questionnaire – just the CPD Annual Answer Sheet – by scanned email, fax or post to JASS's South African office to be sent your CPD point's certificate.

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