O&G MAGAZINE

THE OVARY

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The College

The ovary

Women's health

The College

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From the President

Dr Vijay Roach
President

This issue of *O&G Magazine* addresses a critical gland, the ovary. The ovary provides oocytes for reproduction and critical hormones for female health. An understanding of the basic physiology and endocrinology of the hypothalamic-pituitary-ovarian axis underpins all obstetric and gynaecological assessment, diagnosis and management, in both physiological and pathological conditions.

Ovarian cancer remains a significant cause of morbidity and mortality and, while salpingectomy is a method of risk reduction and surgical management that has improved survival rates, late diagnosis remains the norm and an effective screening tool remains elusive.

Ovarian and egg freezing are new frontiers for fertility preservation, opening up opportunities for women and creating choice. We live in an era of rapidly emerging technologies and ethical and legal frameworks are often inadequately developed and then struggle to keep up.

The College coat of arms also recognises the importance of older women and management of the menopause as the ovary ages. This complex endocrinological phase often coincides with a period of significant social transition. Management of the menopause is a large and important responsibility for our members and one that deserves more attention, both in training, and in practice.

The College looks ahead to 2020 with much excitement. College House has been sold and, while we reflect on a special place with special memories, we look forward to finding our new home and taking RANZCOG into its next phase. The training year in Australia has just begun (December in New Zealand) and we wish all trainees a stimulating and successful year ahead. We hope that you enjoy your learning and, rather than trying to achieve the impossible concept of work-life balance, you make your lifelong ambition work-life integration. It cannot be overemphasised that self-care is paramount. Look out for each other and always be confident that the College, your College, cares about you and is there to support you.

The RANZCOG Board met for the first time in 2020 on 31 January to discuss the College strategy for the year ahead. We'll be travelling to Darwin for the Regional Fellow's Meeting in April, emphasising our genuine commitment to advancing training and clinical services to better serve women in rural and remote Australia. We're a bi-national College, so we also look forward to joining our New Zealand colleagues in Wellington for their ASM in June. What's the weather like in Wellington in June, Dr Tait? Vase and I will be travelling around Australia and New Zealand and we're keen to meet with you in person or hear from you via email.

We have many ambitions and lofty goals for the year ahead. Alongside that, we remain committed to our responsibility of training our registrars, supporting our members with CPD and improving the standard of women's health in Australia and New Zealand, the Pacific and throughout the world. This will be actioned through education and advocacy. RANZCOG is the leading institution in women's health in our region. What we do, who we are and what we stand for, matters. You, our members, belong to a family that is highly regarded, respected and valued. Your participation in the College that trained you, and now includes you as a valued member, is what makes us strong and effective. Whatever your ideas, your reflections, the bricks and the bouquets – send them all. It's your College and we want your voice to be heard.

From the CEO

Vase Jovanoska
Chief Executive Officer

We are already three months into 2020, but I would like to take the opportunity to welcome everyone to a brand new year. A new year brings new opportunities for growth, development and improvement and I look forward to what 2020 will bring our College.

The end of 2019 and start of 2020 saw Australia devasted by some of the worst bushfires in our nation's history. I'd like to acknowledge and send thoughts and wishes to all those communities and our members that have been affected.

What has been humbling to witness are the acts of generosity and kindness from Australians who continue to support each other through this difficult time. This includes the RANZCOG community – our members, trainees and College staff – who have come together and helped in any way they can by donating money, goods or services to charities to help people and wildlife affected by the fires.

Looking ahead

Work across education and training, member and training support and wellbeing, ongoing professional development, standards setting, policy, advocacy and engagement is progressing well.

We are investing more into trainee and member wellbeing initiatives and have formed a Trainees and Members Wellbeing Working Group to further build on support services for our trainees and members and to take a proactive approach to health and wellbeing.

An O&G Workforce Working Group has been formed to analyse and assess the current state and trends, scope of practice and distribution of the O&G workforce. This working group will also undertake workforce modelling and deliver recommendations to the Department of Health and other regulatory bodies, to address the maldistribution of workforce in regional, rural and remote areas.

Work continues on a number of projects that will increase the breadth of services and educational resources offered to members and trainees. The College also plans to increase and build on last year's successful advocacy and engagement activities with our neighbours in the Pacific, and continue to provide leadership in the pursuit of excellence in women's health in Australia, New Zealand and the Pacific.

Following the sale of College House, the search for new College premises has commenced. The criteria briefed for the new premises is for a fit-for-purpose facility that is efficient and practical. The new location will future proof the College, be conveniently located to public transport, have easy access to the airport, accommodation, amenities and dining in close proximity, and we will aim to create an environmentally sustainable workplace, with a reduced carbon footprint.

Ready to take on challenges

Following a comprehensive review and realignment of College functions and staff in late 2019, we are better positioned to address our challenges, embrace new opportunities and maximise efficiency to meet the College's current and future needs.

We have welcomed several new staff including Dr Sarah Hanieh, commencing in the role of Executive Director, Women's Health and Engagement in February. Dr Hanieh brings a unique mix of leadership, extensive research, global health and indigenous health experience to RANZCOG.

College staff are very excited and ready to work alongside our members and trainees to achieve everything that we have planned for the year ahead.

See you in Darwin

We look forward to welcoming Fellows, trainees, Diplomates, PVOGS, midwives, medical students, allied health professionals and prominent guests from both federal and state government, to the RANZCOG 2020 Regional Fellows Scientific Meeting (RSM) being held in Darwin, Northern Territory, in April.

The theme of the meeting is Outback and Beyond, with sessions focussing on the day-to-day experiences and realities within regional obstetrics and gynaecology, as well as a focus on our nearest neighbours in the Pacific and give participants the opportunity to find out how to become involved in important activities within these regions.

The four-day program begins with two days of practical pre-conference workshops, including a dedicated Diplomates Day for general practitioners. The Friday and Saturday programs are designed for both specialists and generalists to encourage innovative solutions and applications.

I look forward to seeing many of you there.

Stay connected

As always, I would like to remind you that your feedback is crucial to ensuring that our College remains the leading voice for women's health in Australian and New Zealand. The College's ongoing success depends on the continued support and engagement from our valued members and trainees. There are many opportunities to get involved in College activities and I encourage you to do so.

The best outcomes will always be achieved by working together. All the best for 2020.

LEADERS IN FOCUS

Dr Nisha Khot
MBBS, MD, FRCOG, AFRACMA, FRANZCOG

This feature sees Dr Nisha Khot in conversation with RANZCOG members in a broad range of leadership positions. We hope you find this an interesting and inspiring read.

Join the conversation on Twitter
#CelebratingLeadership @RANZCOG @Nishaobgyn

Dr Lindsay Edwards FRANZCOG

Dr Lindsay Edwards is a true Tasmanian. She was born in Devonport (on the north west coast of Tasmania) and graduated from the University of Tasmania in 2003. She initially thought that a career in general practice with a focus on women's and children's health would be her preference. That changed, however, once she attended an ALSO course where she was thrown in the deep end with a simulated birth with shoulder dystocia and postpartum haemorrhage. From that moment on, she was hooked. She moved to Victoria to complete her training and subspecialisation in maternal-fetal medicine (MFM). She returned to Hobart in February 2017 to establish a MFM service for the women of Tasmania.

Dr Edwards is currently the Chair of the Tasmanian State Committee for RANZCOG as well as the Chair of the organising committee for the 2020 RANZCOG ASM, and co-chair for the 2020 ADIPS/SOMANZ ASM, both of which will be held in Hobart. She is the Tasmanian lead of the Australian Preterm Birth Prevention Alliance, spearheading a project to reduce the high rates of preterm birth in Tasmania using a targeted approach of education and evidence-based care planning. She has also teamed up with some researchers through the University of Tasmania to establish a placenta biobank, and will be studying the role of pericytes in the placenta of pregnancies complicated by fetal growth restriction.

What does a typical day look like for you?
A typical day starts at 6am with a walk or a run with Maggie, my energetic Australian Shepherd. This is much harder in Hobart in the winter months when it is dark and cold, but Maggie always manages to put me in the right frame of mind for work. My work day is a mixture of counselling, scanning, supervising and mentoring. The clinical work usually finishes at 6pm and then it is time to catch up with emails and all the paperwork. My day often ends the same way as it started, with a quick walk with Maggie (or sometimes Netflix on the couch).

Why did you choose MFM and what makes it special for you?
I really enjoyed obstetrics during my O&G training. Gynaecology, on the other hand, was not something I felt particularly drawn to. I was much more comfortable with an ultrasound transducer in my hand, rather than a laparoscope, and in 2016, I completed my Diploma of Diagnostic Ultrasound in O&G. I love that as an MFM subspecialist, I am often in a very privileged role of helping women and families negotiate difficult, life changing experiences. Though I currently work exclusively in the public system, I am able to provide continuity of care, and form relationships that continue throughout one pregnancy and into the next. I especially love this component of MFM.

How do you balance your personal and professional life?
Not very well! Having heard Vijay speak at the last ASM, my new mantra is work-life integration rather than balance. My work brings me joy and I think this is critical to personal wellbeing.

When and where is your next holiday (especially since 2020 is going to be a very busy year for you)?
I am looking forward to Disneyland in July with my husband, sister in law, and niece. It really is the happiest place on earth! I fell in love with rollercoasters when I got on one for the very first time in 2018 in Disneyland. Before then, I wasn't very brave.

If you could, would you do anything differently in your career?
I moved back to Tasmania in 2017 almost immediately after completing my MFM training. If I could, I would have liked to stay in Melbourne for a bit longer to consolidate my experience, or perhaps travelled overseas to gain experience of how MFM services are organised in different countries. I'm looking to do this via a sabbatical in the near future.

What advice would you give to a trainee starting their career?
Be passionate. Training in O&G can be all-consuming but your passion will keep you going.

Take every opportunity offered; you never know where it may lead.

Dr Lindsay Edwards with her husband, Andrew Allison,after being presented with her certification for maternal-fetal medicine in 2019 .

What words best describe your life?
Chaotic but thoroughly enjoyable.

Are you willing to be contacted by trainees for career advice/mentoring?
Yes, I would be very happy to advise trainees as well as mentor them, especially local Tasmanians. I would love to see Tasmanian medical graduates return to Tasmania and join the healthcare workforce.

What have been your career-defining moments?
The ALSO course that I attended as a resident medical officer put me on the path to O&G training. Hearing Prof Sue Walker speak at a MRANZCOG revision course in 2010 was truly inspiring. As I sat in the audience, I thought to myself, I want to work with her one day. It is so important to have strong role models to aspire to early in your career.

Returning home to Hobart in 2017, and finally receiving my Certification in MFM at the ASM in Melbourne last year.

Where did you learn your leadership skills?
At home! I am the eldest child and so I was always very organised and highly motivated (or bossy, as my siblings might say). I feel my leadership skills, however, are still a work in progress.

Does the current training program prepare trainees for leadership?
Yes and no. Yes because as trainees, we get to experience both the positive effects of good leadership as well as the negative effects of poor leadership.

We don't have a structured way of learning or teaching leadership. This is something that would be a good investment for senior trainees to prepare them to take on leadership roles.

What do you see as the challenges for current RANZCOG trainees?
The challenge of acquiring surgical skills is one that will have long-term effects on trainees and on women's health service provision in the future.

There is increasing awareness of the high levels of burnout and mental health issues among trainees as well as consultants. We know that this has implications not only for the doctors themselves but also for the patients we care for. This is an issue that we as a profession have to address urgently.

What would you tell your younger self if you had the chance to go back in time?
Trust your instincts and don't worry too much about what anyone else thinks. And where you can, choose to be kind.

Thank you to Dr Kirsten Connan for establishing the Leaders in Focus column as a regular feature in *O&G Magazine*. Her shoes are hard to fill but, fortunately, I can always rely on her for guidance. I have taken my lead from Kirsten by featuring Dr Lindsay Edwards, the first MFM subspecialist and an emerging leader from Tasmania, Kirsten's home state. I am truly excited to continue this column and look forward to celebrating all the rich diversity that exists among the Fellows and Diplomates of our College.
– Dr Nisha Khot

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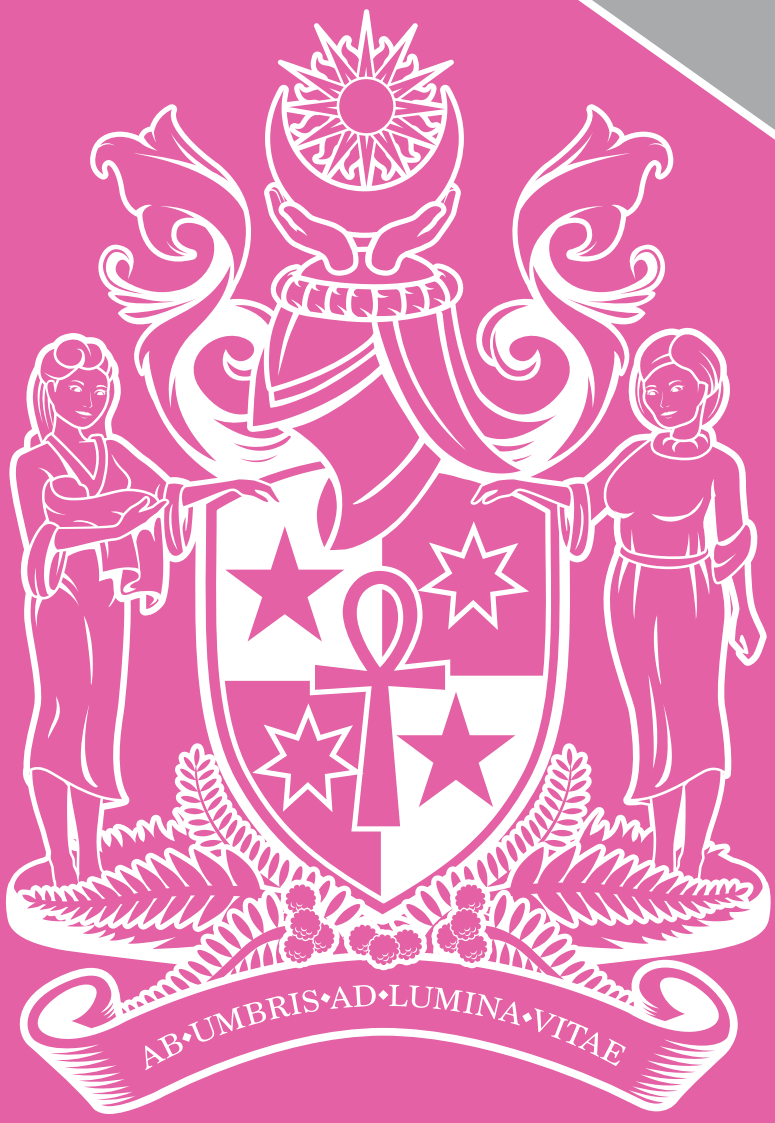

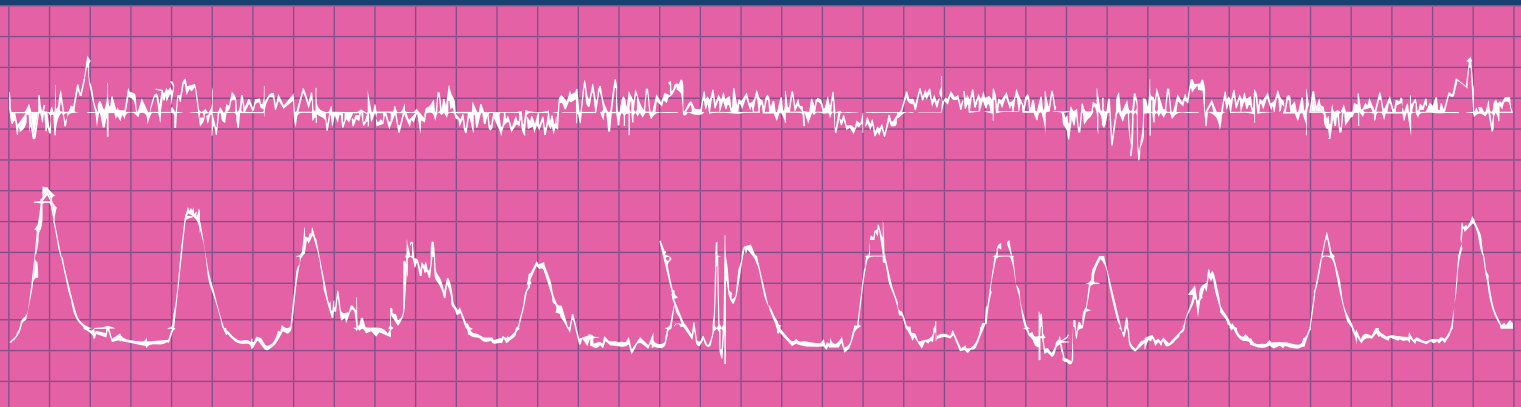

Editorial

Dr Sue Belgrave
FRANZCOG

The *O&G Magazine* Advisory Committee has devoted this issue to the ovary in recognition of its particular importance to our specialty.

I imagine most adults would have some understanding of what an ovary is and what it does but probably only think of it when it is associated with a problem such as menstrual disturbance or pain.

It is an undervalued and underrated structure that has such a central role in women's lives. For such a small structure, it exerts phenomenal power over women's bodies and their psychological wellbeing. It's oocytes and the hormones produced by the ovary are essential for reproduction.

The first known use of the word ovary was in 1658 and is derived from the New Latin word ōvārium, meaning egg or nut. It has only been in the last hundred years that the function of the ovary has been understood. Scientific interest and progress in understanding ovarian function and chemistry began early in the 20th century.

Prior to this, there were interesting theories about conception. Clara Pinto-Correia, the author of *The Ovary of Eve,* gives a fascinating account of seventeenth- and eighteenth-century efforts to understand conception. In the early years of the Scientific Revolution, people struggled to come to terms with the origins of new life, and one theory – preformation – sparked an intense debate that continued for over a hundred years. Preformation theory proposed that organisms develop from miniature versions of themselves.

Oestrone was the first female hormone to be discovered and was isolated from the urine of pregnant women, in 1929, by Edward Doisy from St Louis. In 1935, oestradiol was isolated from the ovary and, soon after, chemists had produced ethinyl oestradiol and diethylstilboestrol. Progesterone was discovered in 1933 and by 1941, Premarin was being manufactured.

Most literature on the ovary are medical texts, papers and dissertations on ovarian function and physiology, as well as conditions of the ovary such as PCOS and cancer, and a number of women have written memoirs about their experiences with conditions such as ovarian cancer and infertility. There is the odd exception, such as *Madame Bovary's Ovaries* by David and Nanelle Barash, which is described as a Darwinian look at literature.

The ability to exert control over the ovary has given women freedom over conception and this has coincided with massive social and political changes for women.

In this issue of *O&G Magazine*, we present an interesting collection of articles, rather than a complete review of the ovary in relation to obstetrics and gynaecology.

There is an overview of basic biology and current research as well as the ovary in early pregnancy and details of an IVF cycle.

'Exercise and the ovarian hormones' looks at both the effect of exercise on the ovary and of the ovary on exercise. It is not surprising that most studies on human physiology and sport have been on men.

'The Pill: a short history' alludes to the massive social change and improvement in the status of women that was associated with the means to control decisions on fertility and childbirth. Newer and safer versions have followed the original pills and we have a better understanding of the benefits and risks.

Cancer screening and risk-reduction surgery is topical and has received wide media coverage, especially when Angelina Jolie decided to have bilateral mastectomies to reduce her genetic susceptibility to develop breast cancer. The ovary can be seen in a similar light. Genetics of cancer is a developing and rapidly changing area and is discussed in 'Ovarian cancer risk and how to manage it'.

The article on 'How to manage a complex ovarian cyst' is of particular interest to me and discusses the questions most gynaecologists need to consider when receiving such an ultrasound report. Ideally, the reporting sonologist understands the clinician dilemmas, the decisions that will follow such a report and the implications for the women about whom the report is written.

There are also surgical articles on preventing adhesions and a step-by-step guide on laparoscopic ovarian cystectomy.

'Ovarian cancer and life after surgery' puts a lot of emphasis on quality of life after surgery and the need to counsel women carefully and individualise care and advice taking into consideration factors such as her age and stage of disease.

We hope you find this issue on the ovary both informative and interesting.

Basic biology and current research

A/Prof Sarah J Spencer
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The ovaries are a key organ of female reproduction, necessary for the storage and release of the oocytes – the egg cells that in adulthood may be fertilised by sperm to develop into an embryo. The ovaries also produce and secrete female sex hormones that are essential for the development of secondary sex characteristics and for regulation of the menstrual cycle.

Ovarian development

The ovary begins to develop at approximately 6–7 weeks of gestation. By 20 weeks, each ovary contains a peak of around 5 million oocytes.[1] This oocyte population starts to decline precipitously from this time, with around 1–2 million oocytes at birth, each stored inside a single cell layer envelope, known as a follicle, inside the ovary. Immediately after birth, this population of oocytes continues to decline so that by the onset of puberty a girl retains around 180,000.[1] While the diminution of this initial population is necessary to eliminate those with DNA damage or dysfunctional mitochondria[2] and to allow the surviving oocytes to be supported in a healthy condition, several genetic and environmental factors can influence how many oocytes survive to this stage. Genetic perturbations in such genes as Nobox, Figla and Taf4b, have been implicated in primary ovarian insufficiency.[3] Likewise, maternal smoking reduces the number of oocytes in the fetal ovary[1] and endocrine disruptors, including synthetic oestrogens (such as bisphenol A [BPA], found in plastics), and the phytoestrogen genistein (a key ingredient in soybeans), can impair follicle formation and contribute to abnormal oocyte retention.[3]

The immune system also plays an important role in the multifaceted process of the establishment of the initial follicle pool and subsequent follicle development. Interactions between cytokines, growth and transcription factors mediate the assembly and development of the primordial follicle pool.[4,5] In our preclinical work, we have shown that an early life immune challenge during the final stages of primordial follicle pool formation results in upregulation of intraovarian cellular pathways associated with immune signalling, leading to increased follicle apoptosis.[6,7] Since the number of primordial follicles is finite, a smaller primordial follicle reserve is typically associated with a shorter reproductive lifespan and reduced fertility.[1] Our current research utilises CRISPR/Cas9 targeted genome editing in animal models to investigate the role of the major immune cells in ovarian development and function.

In the adult, ovaries are egg-shaped structures approximately 4 cm long. They lie on either side of the uterus, against the pelvic wall, in a region known as the ovarian fossa. They are attached to the uterus by the ovarian ligament and to the fallopian tube by the infundibulopelvic ligament. The ovary is not directly attached to the fallopian tube, but releases the oocyte into peritoneal fluid produced by fallopian tube fimbriae, with the oocyte picked up by cilia on the fimbriae.[8] The oocyte then travels down the fallopian tube where it can be fertilised before moving to the uterus to implant in the uterine wall (Figure 1).

Follicle maturation and oocyte release

Which oocytes from the initial pool end up being fertilised depends upon which follicles make it through to the appropriate maturation stage at the correct phase of the menstrual cycle. The initial recruitment of the primordial follicles into the developing pool is regulated in part by anti-Müllerian hormone (AMH), which inhibits activation. This, and each additional stage of follicle development, requires the contribution of a host of different hormones and growth factors and the expression of different receptors on the cells of the follicle and on the oocyte itself.[9] As the follicle matures, the single cell layer enclosing the oocyte divides rapidly and the follicle becomes progressively larger. The maturation of each ovarian follicle from the primordial to the pre-ovulatory stage takes several months and follicles undergo folliculogenesis at all stages of the menstrual

cycle, so that follicles of all developmental stages are present at all times.[9] There is relatively high attrition during this process, with only a small portion of follicles that commence maturation progressing to ovulation. Midway through each menstrual cycle, gonadotrophin-releasing hormone (GnRH) is released from GnRH neurons in the hypothalamus, stimulating the pulsatile release of follicle stimulating hormone (FSH) and luteinising hormone (LH). These hormones circulate in the bloodstream and act on the ovary to stimulate ovulation.[10] In response to high pulsatile levels of LH, the ovary releases an oocyte from the most mature of the follicles into the reproductive tract, where it can be fertilised. The empty follicle becomes the corpus luteum that releases progesterone to stimulate uterine development in preparation for a potential pregnancy. Due to the high attrition of ovarian follicles through the maturation process a woman only ovulates around 400–500 oocytes, giving her a mean reproductive lifespan of approximately 35 years.[3]

The ovary and sex hormones

In addition to being the storehouse for oocytes, the ovary also produces the major female sex hormones oestrogen, particularly 17β-estradiol, and progesterone. These play a role in follicle growth, but are also important for secondary sex characteristics such as breast development, hip and thigh fat deposition, as well as for regulating the menstrual cycle. 17β-estradiol is produced by granulosa cells of the ovary, increasing in circulation from the start of the menstrual cycle until the pre-ovulatory phase where it acts at the hypothalamus to stimulate GnRH-mediated pulse generation, culminating in LH release, which in turn triggers ovulation. Progesterone is produced by the corpus luteum and so is low in the preovulatory phase of the menstrual cycle, increasing after ovulation where it supports the pregnancy should fertilisation occur.[11] Oestrogen and progesterone are not only important in regulating menstruation and preparing the uterus for pregnancy, both have a host of additional functions.[12] For example, oestrogen plays a role in cognitive function in women. When oestrogen levels are decreasing and progesterone rising, in the luteal phase of the menstrual cycle, women preferentially use a spatial strategy to solve a navigation task. At early stages of the menstrual cycle they (with the same success levels) preferentially use a response strategy in the same task[13] (Figure 2). These adjustments may be achieved by oestrogen-mediated differences in the density of synapses, which, at least in animal models, can differ by up to 30% across the ovarian cycle.[14]

Ovarian dysfunction

Most women naturally undergo reproductive senescence at around the age of 50. This occurs due to a combination of the depletion of the follicle pool and a decline in the production of sex hormones. As a woman ages, the remaining oocytes can also accrue double-strand DNA damage due to a decline in the expression of key genes normally involved in DNA repair. Therefore, fertility becomes increasingly less likely as we age. Genetic and environmental factors interact to contribute to the rate of ovarian ageing. Latest genome-wide association studies identify at least 44 gene loci that influence when a woman undergoes menopause. Added to this, poor diet, environmental toxins, stress and illness can all lead to ovarian inflammation, oxidative stress and premature follicular atresia.[15] An integration between the environment and genetic background may be achieved via non-coding RNAs, explaining why some women are more susceptible to these influences than others.

A further major cause of ovarian dysfunction is polycystic ovary syndrome (PCOS). This condition affects 5–10% of women of reproductive age and is more common in obese women. In this condition, the follicles mature to the antral stage but fail to progress further and the oocyte is not ovulated. These follicles appear as eponymous cysts on the ovary under ultrasound examination. The condition is associated with a number of complications and is thought to be caused by an imbalance in ovarian hormones, with contribution from other hormones, such as insulin. Lifestyle factors, including prenatal hyperandrogenism and diet at any life stage, can exacerbate PCOS.[16]

Infertility also occurs in relatively young healthy women for whom causes are difficult to define. Stress may be one of these causes. Stress is fairly ubiquitous in all our lives, making it difficult to ascertain the full impact on ovarian health; and, certainly, women with significant life stress do usually have functional ovaries and normal fertility. However, evidence suggests that the interplay between stress and other lifestyle and physiological factors may contribute

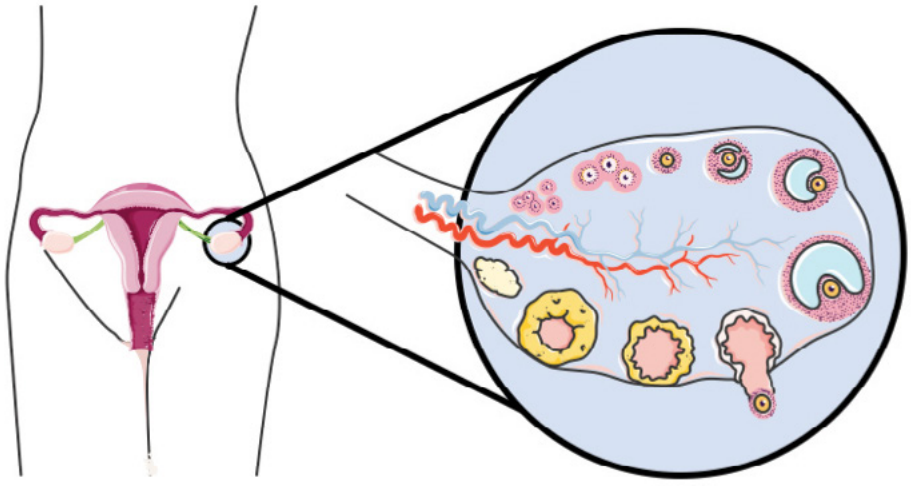

Figure 1. Position of the ovary in the body (circled) with a magnification of the ovary showing all stages of follicular maturation. Clockwise from smallest: primordial to attrition of the corpus luteum.

to ovarian dysfunction. As one example, stress in conjunction with a dysregulation in the signalling of the satiety hormone, ghrelin, may lead to impaired ability of the ovary to synthesize sex hormones and to premature follicular development and attrition.[10] Our preclinical work has shown the ability of the ghrelin receptor antagonist to attenuate stress-induced depletion of primordial follicles.[17] This work suggests there may be a link between eating, stress and ovarian dysfunction. While adequate nutrition and energy balance are essential for reproductive function at all stages of life, it is particularly important during early development, with both insufficient and excess dietary intake altering reproductive development and ovarian function, and impeding adult fertility.[18] Our group and others have shown that early life under- or overnutrition in rodents alters the timing of puberty,[19] impairs ovulatory capacity and accelerates the depletion of the primordial follicle reserve.[20] These studies indicate that a poor early life nutritional environment can cause lasting and deleterious effects on the development of reproductive circuitry, including the ovary, increasing the potential to experience lifelong reproductive dysfunction.

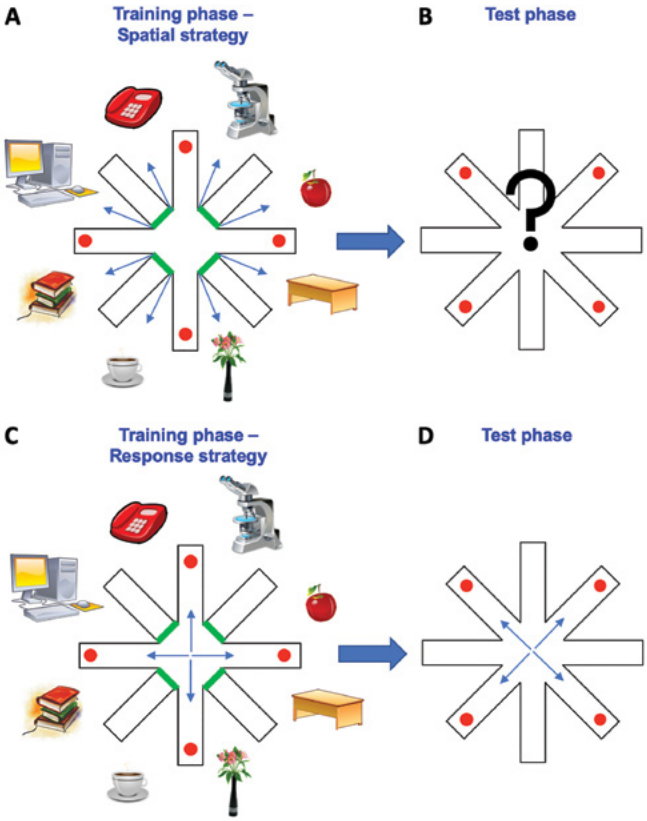

Figure 2. Illustration of decision-making strategies in cognitive tasks during the different stages of the menstrual cycle. During the training phase of the task, participants are introduced to a radial arm maze, consisting of eight arms with objects at the end of four accessible arms. Participants are required to remember which arms they visited in the training phase in order to avoid these arms and collect objects from different arms in the test phase. In the luteal phase of the cycle, high levels of progesterone boost a reliance on landmarks in the environment leading to implementation of a spatial strategy (A). This strategy relies on associations between landmarks, creating a cognitive map of the environment. If these landmarks are removed in the test phase (B), this will result in an increase in errors. In the pre-ovulatory and ovulatory phases of the cycle, rising and high oestrogen levels, respectively, drive a response strategy that relies on stimulus-response specific associations. Therefore, a removal of landmarks in the test phase (D), results in minimal errors.

Future research

The aetiologies of PCOS and premature ovarian insufficiency are still not well understood and our capacity to remedy these is currently poor. We are also in want of strategies for preventing and reversing the effects of ageing on the oocyte. New research into the capacity for oogonial stem cells to generate healthy eggs and offspring is an exciting direction for the field in this regard.[21] Perhaps most important is the need to identify markers for an early diagnosis of ovarian dysfunction, not only for therapy management, but so that women can make informed reproductive choices.

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Exercise and the ovarian hormones

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The ovary has two primary functions: ovulation, and the synthesis and secretion of female sex steroid hormones.[1] Ovarian function is controlled by the hypothalamic-pituitary-ovarian (HPO) axis, as outlined in Figure 1.

Oestrogens

Oestrogens include oestradiol, oestrone and oestriol. Oestradiol is produced by the granulosa cells of the developing follicle and also by the corpus luteum. Oestrogen can also arise from peripheral conversion of androgens to oestrogen in skin and adipose tissue. Its production is stimulated by follicle stimulating hormone (FSH) and lutenising hormone (LH). Once released, it is bound to albumin and sex hormone binding globulin (SHBG), allowing steady release. To act upon a cell, it interacts with a receptor that stimulates protein synthesis and a cellular response. Cells release oestradiol by converting it to estrone and estriol, which are less potent and subsequently removed from the body via urine and bile.[2] The mechanisms of action of oestrogens outside of pregnancy and lactation include:[1]

- The development of secondary sexual characteristics in addition to the maturation and maintenance of the female reproductive organs
- Contributing to the pubertal growth spurt and closure of the epiphyses
- Promotion of breast development and deposition of subcutaneous fat
- Proliferation and development of ovarian granuloma cells
- The upregulation of oestrogen, progesterone and LH receptors
- Negative and positive effects on secretion of LH and FSH from the anterior pituitary during the menstrual cycle
- Decreasing LDL cholesterol and increasing HDL cholesterol
- Inhibition of differentiation of osteoclasts, thereby reducing bone resorption (oestrogen deficiency is common in female athletes)

Progesterone

Progesterone is secreted from both the adrenal glands and the ovary. Pregnenolone is synthesised in the ovarian tissue compartments by entry of cholesterol into the cell through a receptor for LDL.[2] It is then converted to 17-α-hydroxyprogesterone and androstenedione (an androgen) in the granulosa cells of the corpus luteum.[3]

The mechanisms of action of progesterone outside of pregnancy and lactation include:[1,3]

- Promotion of breast development
- Negative feedback on the production of FSH and LH by the anterior pituitary
- Maintaining the secretory activity of the endometrium during the luteal phase of the menstrual cycle
- Increasing basal body temperature during the luteal phase of the menstrual cycle through mild thermogenic action

Androgens

Dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA) and androstenedione are pro-androgens that require conversion to testosterone and dihydrotestosterone to be active at androgen receptors.[4] In the female, testosterone,

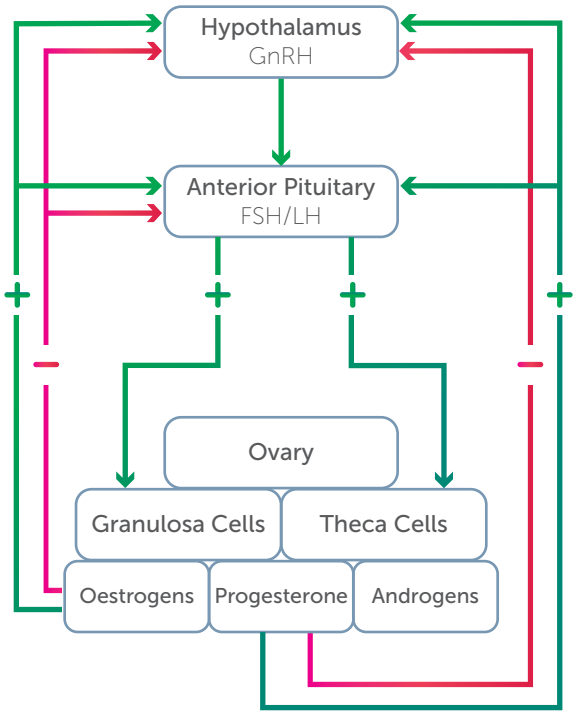

Figure 1. Hypothalamic-pituitary-ovarian axis.

dihydrotestosterone and androstenedione arise from the ovary and adrenals. DHEA and DHEAS are derived from the adrenal glands. LH promotes the secretion of androgens within theca cells of the ovary. Androgens are precursors to oestrone and oestradiol. Polycystic ovarian syndrome (PCOS) is characterised by hyperandrogenism and will be discussed in greater detail. It has been demonstrated that ideal levels of ovarian androgens optimise the process of ovulation, whereas excess levels reduce ovulation and follicle health.[4] Hyperandrogenism is a significant cause of menstrual irregularity in female athletes.

The effect of exercise on the ovary

Exercise in obese and overweight women

Moderate exercise has been demonstrated to restore ovulation and improve fertility in overweight and obese women, independent of weight loss.[5] A mechanism for this has been purported to be increased insulin sensitivity caused by reduced visceral fat and increased uptake of glucose by skeletal muscle.[5] There is less evidence regarding improved ovulation with exercise in women with a healthy weight range.

Relative energy deficiency in sport

The HPO axis is exquisitely sensitive to energy deficiency and elevated stress. Functional hypothalamic amenorrhoea is a diagnosis of exclusion and associated with suppressed GnRH pulsatility.[6] A systematic review by Hakimi and Cameron, outlined how vigorous exercise reduced fertility in women, except for those who were obese and overweight.[5]

Endurance athletes complete high volumes of training in order to realise new physical and psychological limits. This constant state of overreaching and recovery walks a fine line, often disrupting the HPO axis in the female athlete. Oligomenorrhoea is common, as is primary and secondary amenorrhoea. The prevalence of secondary amenorrhoea in collegiate female athletes ranges from 2–5% and is as high as 69% in dancers[7] and 65% in long distance runners.[8]

Energy availability refers to the difference in dietary energy intake and all energy expenditure required to support homeostasis, hormonal health, activities of daily living, growth and repair, in addition to that required to train and compete in sporting activities.[9] Low energy availability is common in athletes and is associated with disordered eating, eating disorders and energy restriction in an attempt to maintain low body fat percentage. This may be imposed by the sport (such as weight restricted categories in rowing, combat sports and power lifters) or for performance or aesthetic purposes (power to weight ratio in runners, gymnasts, divers).

The term 'female athlete triad'[10] was defined by the IOC as the combination between disordered eating and irregular menstrual cycles eventually leading to reduced bone mineral density (BMD).[11] It has been replaced by the term relative energy deficiency in sport (RED-S), created in 2014[12] to describe the syndrome where an athlete of any gender is operating in a state of relative energy deficiency. This occurs where energy is used for physical performance and sporting output to the detriment of physiological function including metabolic rate, menstruation, bone health, immunity, protein synthesis, cardiovascular health, psychological health, libido and mood. Low levels of leptin, found in athletes with RED-S, are thought to downregulate GnRH in the hypothalamus, thereby reducing LH and FSH secretion and stimulation of the ovary.[5]

A significant consequence of RED-S is that of reduced BMD. This can result in bone stress injury, which can be season- or career-limiting in athletes. Oestrogen inhibits the activity of osteoclasts that promote bone resorption. Suppression of the HPO axis and subsequent low levels of oestrogen are detrimental to the achievement of peak bone mass. High training loads are often undertaken in the crucial period where BMD is being optimised (that is, up to the age of 25). Exercise is osteogenic and athletes in weight-bearing sports should have BMD 5–15% higher than non-athletes.[13] Mitchell et al found the trabecular BMD to be greater at the weight-bearing distal tibia in athletes versus non-athletes, and also found that young amenorrhoeic athletes have lower BMD and an increased prevalence of fracture compared with eumenorrheic athletes and non-athletes.[14] Failing to achieve peak BMD and subsequent relatively low BMD is not only a risk to their athletic career but increases long-term osteoporosis and fracture risk.[15]

Functional hypothalamic amenorrhoea due to RED-S is a diagnosis of exclusion.[12] Oligomenorrhoea or amenorrhoea in an athlete is not normal, and is a red flag to investigate imbalance in training load/stress and energy availability, as well as a prompt to screen for other causes of menstrual irregularity.

Exercise and PCOS

PCOS is characterised by menstrual irregularities, hyperandrogenism and metabolic abnormalities, including hyperinsulinemia. The prevalence of PCOS in the general population is approximately 6–15%,[16] but is thought to be present in approximately 30% of female athletes.[17,18] Females with higher circulating androgens are naturally stronger, faster and recover better. Hyperandrogenism associated with PCOS may improve physical performance[18] and attenuate the negative metabolic effects of reduced oestrogen.[17]

Exercise can be used to induce ovulation in obese and overweight women with PCOS.[5] This is purported to be a result of increased insulin sensitivity secondary to exercise.

The effect of the ovary on exercise

Just as exercise has been demonstrated to affect ovarian function in ways that have been well described, ovarian function affects exercise. Human physiology and sport science research has largely been conducted on untrained males who are, hormonally, more simple to study. A review of 1382 papers from 2011–2013 comprising over 6 million participants in sports science research showed 39% to be female.[19] The major barrier to inclusion in research studies was hypothesised to be the menstrual cycle.[20]

The menstrual cycle and performance considerations

The literature suggests that oestrogen may promote endurance performance by altering carbohydrate, fat and protein metabolism, with progesterone often appearing to act antagonistically.[21]

During the follicular phase, where progesterone is at its lowest circulating levels, a female may have the more favourable hormonal profile for athletic performance. While significant research still needs to be undertaken, we know female athletes subjectively feel stronger, leaner, less bloated, have improved thermoregulation and higher plasma volume. When planning strength and conditioning sessions, females may achieve greater strength and hypertrophy gains by training with high frequency in the follicular phase of their menstrual cycle.[22] The late follicular phase, characterised by the pre-ovulatory surge in oestrogen and suppressed progesterone concentrations, tends to promote improved performance in a cycling time trial.[21]

The luteal phase is associated with a prolonged surge of both oestrogen and progesterone and poses challenges for female athletes. Anecdotally, athletes report feeling as though they have less energy, feel bloated, retain fluid and experience pelvic pain and abdominal cramping. During short explosive exercise, oestrogen promotes contraction-stimulated glucose uptake into type I muscle fibres, which should be beneficial for performance in higher intensity aerobic exercise, but in the late luteal phase, progesterone antagonises this action.[23]

The high-performance sporting world is currently examining ways to periodise training and nutrition for female athletes to maximise performance around the menstrual cycle. Areas of interest include:

- Thermoregulation through the cycle with pre-cooling in the luteal phase and a longer warm up in the follicular phase
- Different nutritional substrate utilisation throughout the cycles and prescription to better match metabolism
- Injury prevention around the time of ovulation
- Fluid retention tracking across the cycle, relevant for weight-restricted sports

Hormones and injury risk

There is an association between hormonal levels and injury risk, particularly of the anterior cruciate ligament (ACL). Laboratory studies have shown that exposure of the ACL to oestrogen results in a dose-dependent reduction in fibroblast and collagen synthesis and that this effect is attenuated by the addition of progesterone.[24,25] It has been postulated that Relaxin may have the same effect on the ACL in non-pregnant women as it does in pelvic ligaments in pregnancy.[26] A quantitative meta-analysis concluded there is most likely increased ligamentous laxity around ovulation compared to the follicular phase.[27]

The luteal phase is the safest phase. Recent studies suggest oral contraceptives may offer up to a 20% reduction in the risk of injury, although the strength of the evidence is low.[27]

Hormonal contraception

Hormonal contraception has long been prescribed to female athletes to manage the timing and severity of menstrual symptoms around their competition schedule, in addition to standard indications. Currently, approximately half of female athletes take hormonal contraception.[17] The effect of hormonal contraception is difficult to study due to significant variation in baseline ovarian hormones and cycle length in female athletes, in addition to the variation and dosages of various types of hormonal contraceptive. The type of hormonal contraception, as well as the type and dose of oestrogen and progestogen within, will have varying effects on exercise.[28]

Combined oral contraceptive pill

There are mixed conclusions around the use of the combined oral contraceptive pill (COCP) in athletes, but at the moment, the resounding message from sports physicians is that where an athlete has a disrupted menstrual cycle due to RED-S, the COCP will only mask this. Rather than prescribing the COCP to manage menstrual dysfunction in this population, efforts should be made to restore energy balance in the short term, with both performance and long-term health in mind.

The COCP reduces the following symptoms associated with menstruation, which may therefore assist with sporting performance: dysmenorrhoea, bloating and iron deficiency secondary to heavy menstrual bleeding.[29]

As previously discussed, there is a modest ligamentous injury protection risk provided by the COCP.[27] A database of 165 748 patients and the incidence of ACL tear and concluded 'OCPs have a protective effect on ACL tear, especially in the 15–19 age group'.[30]

Despite the theoretical metabolic and substrate usage improvement associated with oestrogen,[21] and the proposed effect of the COCP on circulating growth hormone,[31] the COCP has been shown to have no impact on skeletal muscle strength and no published data exists regarding the interaction between the COCP and muscle hypertrophy.[2] We are yet to prove a significant difference across COCP and non-COCP users across a menstrual cycle for VO2 max, heart rate, stroke volume or cardiac output at maximal exertion.[32] There is a possible decrease in VO2 max and increase in body mass for athletes on the COCP,[28] although this increase in body mass and fat-free mass was not significant in the small randomised control trial by Romance et al.[33] There is a possible decrease in muscle soreness after exercise and a blunted response to muscle damage.[34]

Progesterone-only contraception

Limited research has been undertaken on the use of progesterone-only contraception and its influence on exercise. A study by Armstrong et al (2005)[35] showed similar adaptations to heat and physical training in female athletes on the COCP and depot medroxyprogesterone acetate (DMPA). Loss of BMD using long term DMPA is a concern in young women (with already low levels of circulating oestrogen) especially where other risk factors for reduced BMD exist, such as RED-S.[36]

Opportunities for involvement

Sport Australia and the Australian Institute of Sport are currently looking to expand their research and connections in this area. Recently, a multisport workshop was held between athletes, coaches, health practitioners and physiologists, specifically looking at female athlete health and performance in regards to the menstrual cycle and hormonal contraceptive use. The project is looking to facilitate education and research as well as develop a network of preferred providers: sports physicians, gynaecologists and endocrinologists.

If you are interested in being involved, please contact Project Consultant, Dr Rachel Harris (drrachharris@gmail.com) .

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The Pill: a short history

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FRANZCOG

Its impact and importance are there in its name: there are many pills in our pharmacopeia, but for everyone, medical or not, the Pill is the oral contraceptive pill, which first became available for Australian women, in the form of Anovlar, in February 1961. The history books tell us that when it was first introduced, it was only available to married women, but I know that isn't true. I was prescribed Anovlar in 1964, when I was sixteen years old, by a kindly doctor at the Sydney University students' health clinic, where I had gone seeking treatment for acne. He breezily mentioned its contraceptive side effects. When I told some of my fellow female students about this, they all immediately developed acne.

The Pill is here in an *O&G* issue about the ovary because it suppresses the regular actions of the ovary. The combined oral contraceptive pill (COCP) contains both an oestrogen and a progestogen. It's the progestogen that is primarily responsible for preventing pregnancy. Progestogen negative feedback works at the level of the hypothalamus to decrease the pulse frequency of gonadotropin-releasing hormone. This then decreases the secretion of follicle-stimulating hormone (FSH) and luteinising hormone (LH), resulting in inhibition of ovarian follicular development, no LH surge and no follicle release; that is, no ovulation. The progestogen also acts on the endometrium to make it thin and unreceptive to a fertilised ovum, and on cervical mucus to thicken it and prevent sperm penetration. The oestrogen in the Pill has some effect in inhibiting follicular development through its negative feedback on the anterior pituitary, which slows FSH production. The progestogen-only pill (POP) may also suppress ovulation, increase cervical mucus preventing sperm reaching the upper genital tract, and induce endometrial atrophy.

The first generation of COCPs were developed by Gregory Pincus and John Rock in the years following World War II, but the ideas behind the science and the motivation for the research date back to the decades between the two World Wars. The American birth control activist, writer, and trained nurse, Margaret Sanger, had been championing the concept of a birth control pill for many years. In the 1930s, there were initial experiments to extract naturally-occurring steroids from plants, and Dr Carl Djerassi synthesised a progestogen from Mexican yams. Djerassi believed, correctly, that progestogens could inhibit ovulation, but he did not have the means to apply this knowledge to the development of an effective medication.

Rock was an O&G in Boston, educated at Harvard Medical School and very involved in early attempts in fertility research, including IVF and sperm freezing. He was also a committed Catholic who was nevertheless very supportive of Sanger's work to bring birth control to poor American women. He taught at Harvard in the 1940s and, radically, included birth control in his lectures. Pincus was an eminent American zoologist and physiologist who in 1944 established the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts, not far from Boston; he was very interested in steroid hormones and performed successful IVF in rabbits.

Between 1951 and 1953, Sanger brought these two men together, with others, to work on developing a contraceptive pill. She received funds for the work from her friend, wealthy US feminist, suffragette and philanthropist Katharine McCormick.

In 1954, Rock performed a clinical trial on fifty Boston women of the oestrogen/progestogen combination he and Pincus had developed, describing it as a 'fertility study'. There were no requirements in that era for informed consent or ethics approval, and the trial proceeded without these; its results were promising and further trials were planned. These took place in Puerto Rico, where there were a number of birth control clinics (which up until then were offering only limited barrier methods). Several hundred women took part, again without formal consent, including 200 in a trial in 1956. The contraceptive actions of the combined pill were confirmed, but a number of women reported side effects: nausea, headaches and thrombosis.

The side effects were not considered a problem, however, by the teams developing and administering the drugs, and in 1957 Enovid, consisting of 150 µg mestranol and 9.85 mg norethynodrel, was approved by the US Food and Drug Administration (FDA) for use as a 'menstrual regulator'; in 1960 the FDA approved Enovid as a contraceptive.

Sanger famously wrote that 'No woman can call herself free who does not own and control her own body. No woman can call herself free until she can choose consciously whether or not she can be a mother.'

The Pill was both a part of the changes, and a contributor to the changes, that brought about many improvements in the status of women and the lives of women in the second half of the 20th century, as women strove to attain the freedom glimpsed by Sanger. It was part of a global movement by women (supported by some men) for the right to work, have

Photo of Margaret Sanger from George Grantham Bain Collection (Library of Congress).

careers and have equal pay with men; for better healthcare, especially reproductive healthcare; for the right to control one's own fertility; for better childcare arrangements for working women; and for freedom from sexual harassment and violence. I feel privileged to have lived through this time, seen the changes this movement has brought about, and been a small part of it.

However, the first-generation Pills were far from perfect. By the late 1960s, it was clear that the side effects could be significant for some women. The importance of informing both women wanting contraception and women agreeing to take part in trials, was beginning to be realised, largely due to the vocal demands of the women's movements in most Western societies. 'Our Bodies Our Selves' published in 1971 by the Boston Women's Health Book Collective became the go-to book for women who wanted to know about, and control, their own fertility; Barbara Seaman's book 'The Doctor's Case Against the Pill' exposed the lack of informed consent and the concealment of details around the earlier Pill trials.

Moreover, there was strong opposition to the Pill from the Catholic Church. Rock had always championed birth control and he had hoped that his Church would embrace it; he was well aware of the difficulties women – especially poor women in Boston – faced with years of unwanted childbearing. He saw no problem with inhibiting ovulation so that women could choose how many children they wanted to bear; he regarded it as a way of understanding and managing a natural process. Pope Paul VI saw otherwise. In 1968, he stunned many Catholics around the world, including Rock, with the papal encyclical Humanae Vitae, Of Human Life, in which he called artificial birth control 'intrinsically wrong' and therefore sinful. Subsequent Popes have confirmed these views. However, birth statistics and research over the 50 years since clearly demonstrate that many Catholics, probably a majority, do not follow this directive.

Work continued in many centres, resulting in the development of newer and safer versions of the original.

In 1972, Gough Whitlam removed the 27.5% 'luxury tax' on the Pill in Australia, and put it on the PBS at a total cost to the woman of one dollar (this, obviously, has since increased)! Currently, about 44% of women in Australia who use contraception use the Pill. There has been a subtle shift in recent years to hormonal implants and IUDs, particularly among younger women, but this is still not much more than 10%. First-generation Pills contained as progestogens either norethynodrel, norethisterone or dionogest, together with an oestrogen, mestranol; doses were relatively high and side effects such as nausea and vomiting, and risks including thromboembolism, were a cause for concern.

Second-generation Pills contain as progestogen norgestrel, levonorgestrel, norethisterone or norgestimate, and as oestrogen ethinyloestradiol. These were developed in the 1970s. Doses of both synthetic hormones were very much lower than in the first-generation Pills; risks and side effects were therefore fewer, and much work was done on tailoring hormonal effects to suit particular women's needs.

Third-generation progestogens are desogestrel, gestodene and cyproterone acetate, together with an oestrogen. Third-generation Pills, which first appeared in the 1990s, have been demonstrated to have a higher risk of thromboembolic events than second generation, although this increased risk is very small. The rather excitable public announcement of this fact in the UK in 1995 led many women to stop the Pill altogether, instead of transferring to known safer options. An estimated 20,000 extra unintended pregnancies and 10,000 abortions were the result. The cost to the National Health Service, the British Pregnancy Advisory Service reported, was enormous; in future, the BPAS said, the level of risk should be more carefully assessed and advice more carefully presented to doctors and women, in the interests of good public health.

Fourth-generation Pills contain drospironone, homogestrel acetate or dienogest as progestogens, and ethinylestradiol, estradiol hemihydrate or estradiol valerate as oestrogens.

We now know a huge amount about oral contraception. If used correctly, it is very effective at preventing conception, while fertility returns quickly on discontinuing it. The risks are well understood and should be considered carefully for every woman it is prescribed for. Cycles can be manipulated and, indeed, dispensed with altogether if the woman wishes. As well as its contraceptive effects it can manage heavy menstrual bleeding, dysmenorrhoea, and symptoms of endometriosis. It can reduce the risks of endometrial, ovarian and bowel cancer, and benign ovarian cysts, and can be useful in managing polycystic ovarian syndrome, premenstrual syndrome and perimenopausal symptoms. And, as my friendly university doctor told me in 1964, it can improve acne! The pill has made an incalculable difference to women's lives in terms of their ability to manage their own fertility and must be considered one of the greatest advances of the twentieth century.

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The impact of endocrine disrupting chemicals

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Endocrine disrupting chemicals (EDCs) are agents that may interfere with the production, secretion, metabolism, action and the excretion of hormones within the body. The most widely recognised are bisphenol A (BPA), and metabolites of the phthalate diesters. These agents have been prevalent within the environment for decades; however, it is only recently that their potential for harm has been widely acknowledged. For instance, the European Food Safety Authority banned the use of BPA in baby bottles in 2011 and restricted the use of phthalates. BPA is widely used in plastics and epoxy resin and confers on plastics an exceptional strength and stability on heating. Phthalates are a class of chemicals that are widely used in industry, household goods and personal care products (such as makeup and hairspray) and possess EDC properties.[1]

There are believed to be in excess of 800 chemicals within the environment that may possess some endocrine disrupting or modulating effects, and consequently, it is impossible to avoid exposure. Indeed, one study of phthalates suggested that 95 per cent of participants analysed in a study in the US had measurable levels of phthalates, and BPA, in their urine. EDCs can enter the body through the skin, via inhalation, and commonly within food. Consequently, we are constantly exposed to EDCs, which may have synergistic actions with other EDCs, and their effects do not follow typical dose response curves; hence, they may be agonistic and antagonistic at the same receptor at differing concentrations and may have their maximal effects at very low concentrations. Measurable levels of phthalates and BPA are not only detectable in serum and urine, but also breastmilk, cord blood and amniotic fluid. This suggests the fetus, and the newborn, are at risk of exposure and in some instances, may receive greater exposure than the parents. Evidence from human epidemiological studies, collected by the WHO, link EDCs with a wide variety of health effects such as reproductive, neurobehavioral and neurodevelopmental changes, metabolic syndrome, bone disorders, immune disorders, and cancers;[2] although, whether these are causal effects or associations is not clear from observational data.

In recent times, there has been an increasing awareness of the potential for the environment to affect reproductive health. An example of the concern that these chemicals have generated is the conflicting evidence regarding the belief that sperm counts have been diminishing over the last few decades. Despite it not being clear whether sperm counts are decreasing, it is established from registries that the incidence of undescended testis, hypospadias and testicular cancer, are increasing in some countries. These clinical findings are believed to have a potential unifying early-life origin related to a lack of fetal androgenisation. Evidence from animal studies suggest that if oestrogenic EDC exposure was to occur during a vulnerable period of male fetal development, correlating to human 8–14 weeks of gestation, a lack of male androgenisation may ensue, characterised by a shorter anogenital distance (AGD), impairment of sperm production, hypospadias and cryptorchidism.[3]

Reproductive effects of BPA exposure

Unconjugated BPA binds as a weak agonist at the oestrogen receptors, and evidence from animal studies suggest that in-utero exposure to environmental concentrations of BPA may impair adult spermatogenesis, leading to reductions in semen parameters and serum testosterone.[4] Adult exposure leads to a central hypogondal picture, with testicular damage and impaired semen parameters.[4] Human studies of prenatal exposure to EDCs are challenging due to the inherent difficulties of long-term follow-up studies, and the complicating fact that we are exposed to numerous EDCs at any one instant, compounded by exposures over a lifetime. Hence, deriving associations from a particular agent is problematic.

As AGD is now a recognised marker of prenatal androgenisation,[5] with a longer AGD being a marker of greater prenatal androgen exposure, this offers a potential approach to assess prenatal androgenisation. A Chinese study showed that boys (whose mothers had detectable levels of BPA in their urine at 12–16 weeks of gestation) were more likely to have shorter AGD than boys with undetectable levels of maternal BPA.[6] A further study demonstrated an inverse relationship between cord blood BPA concentrations and male newborn anoscrotal distance, suggesting a potential loss of androgenisation from fetal BPA exposure.[7]

With respect to deriving associations of in-utero exposures to BPA with adult male reproductive function, we recruited men from the Raine cohort at 20 years of age to undergo a thorough testicular assessment.[8] The result of the analysis after adjustment interestingly demonstrated that

maternal BPA exposure, from stored maternal blood, was positively associated with some of their sons' sperm parameters in adulthood. These may be chance findings, in view of the lack of any other associations being identified with testicular volume or any hormone measured. Human studies relating concurrent exposure to BPA with semen parameters have been conflicting, although most studies suggest a negative influence on male reproductive parameters.[9]

The data on female exposure to BPA is less clear. BPA exposure has been associated with the development of endometriosis and PCOS, and adverse outcomes for women undertaking IVF treatment, although no long-term studies have been performed.[9]

Reproductive effects of phthalate exposure

Studies in humans and rodents have demonstrated that male newborn AGD was negatively associated with maternal phthalate exposure during pregnancy, suggesting a reduction in prenatal androgenisation.[10] Subtle associations have been demonstrated between phthalate monoester concentrations in breastmilk and reproductive hormones in three-month-old boys.[11] Our analysis of men within the Raine Study suggests a potential negative association of antenatal exposures to phthalate metabolites on adult testicular function, with a reduction in testicular volume and an increase in serum testosterone concentration in adulthood.[8] Although our findings are of borderline significance, and our study is small, they are plausible and consistent with numerous experimental data.

With respect to female reproductive outcomes, concurrent urinary phthalate concentrations have been associated with girls with premature thelarche, and women with endometriosis – findings consistent with an oestrogenic influence, and an increased time to conception, reductions in serum Anti-Müllerian hormone (AMH) and less oocytes being retrieved in an IVF cycle.[1] However, limited data exist with respect to any associations of antenatal exposure to phthalate metabolites on adult female reproductive outcomes. When we performed a reproductive assessment of girls within the Raine cohort at 15 years of age, and related the measures to maternal serum phthalate concentrations, maternal metabolite MCiOP was positively associated with her daughter's uterine volume, MEP was negatively associated with her daughter's antral follicle count and AMH, and there was a tendency towards an earlier menarche in relation to exposure to DEHP metabolites.[12]

Conclusion

EDCs are ubiquitous within the environment, so preventing our exposure to them is impossible; however, it is important to take steps to minimise our exposure to EDCs, and this is particularly relevant at vulnerable stages of development, during pregnancy and when attempting to conceive. Due to the limitations of space, this review was limited to BPA and phthalates, the most widely recognised EDCs, although many more chemicals exist in the environment that may influence reproductive development.

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How to manage a complex ovarian cyst

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Gynaecologists are frequently confronted with the quandary of an ultrasound report stating that there is a 'complex ovarian cyst', especially when the ultrasound has not been performed by a specialist with a certificate of obstetric and gynaecological ultrasound (COGU). Complex is a very vague term that does not adequately guide further management. The questions the referring gynaecologist wants answered by an ultrasound can be broadly described as:

1. Is the cyst likely to resolve on its own?
2. Am I able to remove the cyst laparoscopically?
3. Is the risk of cancer sufficiently high that I should refer the patient to a gynaecological oncologist to perform the surgery?

Until recently, answers to these questions have been difficult to obtain, as much of the data on the ultrasound appearance of different types of cysts has been empirical and based largely on expert opinion. The International Ovarian Tumour Analysis group (IOTA) has, over the last two decades, proposed standardised definitions for adnexal lesions and has conducted a great many retrospective and prospective trials with extensive surgical and pathological follow up. The IOTA methodology has also been prospectively evaluated by other centres with good correlation. This has enabled IOTA to propose rules (IOTA Simple Rules) and a computer-based model (ADNEX) to more accurately identify the risk of malignancy of an adnexal lesion. The IOTA group is a multinational collaboration, membership is obtained by attending a workshop and then successfully passing an examination. It is possible to check if your preferred ultrasound specialist has passed this examination via www.iotagroup.org/certified-members.

The IOTA models have been shown in several studies to perform much better at the detection of malignancy than the older risk of malignancy index (RMI) or OVA1 algorithms.[1]

Many national bodies have recommended using the IOTA models, including the Royal College of Obstetricians and Gynaecologists,[2] American College of Obstetricians and Gynecologists[3] and, most recently, the American College of Radiology through their Ovarian-Adnexal Reporting and Data System ultrasound risk stratification and management system (O-RADS).[4]

Classical ovarian lesions

The IOTA technique of assessing an ovarian mass begins with identifying several classical ovarian lesions, referred to as 'simple descriptors'. These are:

1. Simple cyst: unilocular, no internal material (anechoic), thin walled and avascular.
2. Corpus luteum: unilocular with peripheral vascularity ('ring of fire'), second half of the cycle and associated with a secretory endometrium (unless there is a Mirena insitu). These often appear haemorrhagic.
3. Haemorrhagic cyst: unilocular, reticular pattern of fine thin intersecting lines (fibrin strands).
4. Endometrioma: homogeneous low-level internal echoes 'ground glass', minimal vascularity, smooth walled. Often bilocular, often bilateral.
5. Dermoid/teratoma: avascular, usually unilocular but with variable internal structure due to the differentiating cell types, most commonly hair (fine linear dots and dashes) and fluid levels (due to different fluid types). Classically dermoids have shadowing echogenic areas due to calcification.
6. Invasive malignancy: large irregular solid mass, highly vascular, usually no visible normal ovarian tissue remaining, ascites (defined by IOTA as fluid above the level of the uterine fundus to differentiate from physiological pelvic fluid commonly seen after ovulation).

These classical lesions do not usually cause much uncertainty about the management pathways once they have been correctly identified on ultrasound.

Haemorrhagic cysts often resolve spontaneously. A repeat ultrasound in two–three months can be considered to ensure cyst resolution. Ideally, this ultrasound should be performed just after a period to prevent confusion with a new corpus luteum. Endometriomas and dermoids, if not removed, should have annual follow up as there is a risk of malignant transformation, especially post menopause.[5]

Unfortunately, there are many ovarian lesions that do not fit these classical descriptions. For these less straightforward lesions, IOTA propose using Simple Rules or the ADNEX algorithm to guide further management.

IOTA Simple Rules

The Simple Rules technique highlights five features most associated with a lesion being benign and five features most associated with a lesion being malignant (Table 1). The rules are that if the lesion has only benign features then it can be considered benign or if the lesion has only malignant features

Table 1. IOTA features used for the Simple Rules.

Benign features	Malignant features
Unilocular cyst	Irregular solid lesion
Solid components present, but < 7 mm	Ascites (fluid above the top of the uterus)
Acoustic shadows	At least 4 papillary structures
Smooth multilocular lesion with largest diameter < 100 mm	Irregular multilocular-solid tumour with largest diameter ≥ 100 mm
No blood flow	Abundant blood flow

then it can be considered malignant. If none of the 10 benign or malignant features are seen or if there are both benign and malignant features present, then the lesion is unclassifiable. After exclusion of the 'classical lesions' (dermoid, endometrioma, simple cyst, etc) about 75% of lesions can be classified in prospective studies for a 95% sensitivity and 91% specificity.[6] The 25% of unclassifiable lesions could be sent for second opinion from an expert (such as a COGU) or have the ADNEX model applied. This technique has been validated prospectively by imaging specialists with no specific gynaecological experience with similar accuracy.[7]

The IOTA Assessment of Different Neoplasias in the Adnexa (ADNEX)

The ADNEX algorithm is available online[8] or via a phone app. By entering specified ultrasound parameters, the imaging specialist can come up with a percentage risk of malignancy. IOTA have proposed that if the percentage risk is greater than 10%, further management should be performed by a gynaecological oncologist. The ADNEX model has been prospectively shown to have 92–95% accuracy for a 10% false-positive rate.[9] CA 125 can also be incorporated into the ADNEX model and is mostly used to help distinguish stage 1 ovarian cancer from stage 2–4, borderline or metastatic cancer to the ovary. CA 125 has only minimal contribution to determining if the lesion is benign or malignant as it is often in the normal range with stage 1 ovarian cancer. This highlights that CA 125 in isolation is not a good screening test to identify stage 1 ovarian cancer.[10]

Other considerations in evaluating ovarian lesions

Transvaginal ultrasound generally provides much more accurate assessment of a lesion than transabdominal, especially when looking for blood flow. There are, however, instances where transvaginal ultrasound cannot be performed, such as virgo intacta or patient refusal. There are also circumstances where transvaginal accuracy is reduced, such as increased BMI and greatly enlarged fibroid uterus (which often elevates the ovaries high into the abdomen).

Most simple cysts in the reproductive age range are functional and will resolve within two–three cycles. Simple cysts less than 3 cm should be considered physiological (a follicle) and reported as such with no follow up required. Cysts more than 10 cm in diameter are more difficult to fully assess with ultrasound; particularly, blood flow and small projections may not be seen in the deep aspect of a large cyst, leading to erroneous classification. Repeat ultrasound in three months, pelvic MRI or surgical removal can be valid management options.

Many simple cysts over 2 cm in the postmenopausal patient are small cystadenomas and review should be considered. The exact interval has not yet been determined, but review in three months[11] and, if no change, six months, and then yearly if the cyst remains stable, could be considered.

Septations are common in benign cystadenomas but also in malignant tumours with borderline tumours frequently having more than 10 septations.

Papillary projections are wall projections that are at least 3 mm in height, perpendicular to the wall. Four or more projections, or projections involving more than 50% of the internal cyst wall, are suspicious features for malignancy. The larger the projection or solid area is compared to the overall cyst size, the greater the risk of malignancy.

Vascularity demonstrated within a solid area, papillary projection or in a septum is a concerning feature. Vascularity is measured with colour or power Doppler. Resistance index (RI) has been used historically, with a level less than 0.4 considered high risk for malignancy, but is no longer recommended due to very poor sensitivity and specificity. RI is still occasionally used to demonstrate that the flow is arterial rather than ultrasound artefact.

Solid masses with no vascularity, especially with irregular calcifications, are often fibromas, which are almost always benign. Solid masses with increased vascularity are almost always malignant, sometimes secondary tumours to the ovary (Krukenberg tumours).

Secondary metastases to the ovaries are always vascular and often, but not always, bilateral. They originate most commonly from the stomach, but also from other bowel and biliary sites and the breast. They can be solid tumours (gastric, breast, lymphomas) but can also be large multilocular with solid areas (colon, rectum, pancreas/biliary tract). Additional investigations to consider if a secondary tumour to the ovary is suspected (to find a possible primary) may include PET-CT, MRI whole body diffusion, gastroscopy, colonoscopy and x-ray mammography.

Tumour markers that may be of use include CA 125, but as previously stated, a low CA 125 level does not exclude stage 1 ovarian cancer. CA 125 also has many false positives including, but not limited to, adenomyosis, endometriosis and diverticular

disease. CA 19-9 may be raised in mucinous tumours including cystadenocarcinoma, borderline tumours and secondaries from the bowel. Germ cell tumours may have raised αFP or βHCG.

Conclusion

When evaluating an ovarian lesion, it is important the ultrasound is performed and reported by clinicians able to assess and describe the lesion appropriately. Some lesions are classical and easily described (such as endometriomas and dermoids) but many are less certain. Using IOTA Simple Rules and/or the ADNEX model has shown good value to identify the risk of malignancy and both are more accurate than RMI. CA 125 is useful to identify advanced cancer, but has a limited role in the detection of stage 1 ovarian cancer due to significant false positive and false negative rates.

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Laparoscopic ovarian cystectomy: step-by-step

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Ovarian cysts are a common cause for presentation to emergency departments and gynaecology clinics. Up to 10% of women will have surgery during their lifetime for the presence of an ovarian mass.[1] The majority of benign ovarian cystectomies can be performed laparoscopically. Basic investigations are completed to stratify risk of ovarian malignancy. These will include a transvaginal ultrasound scan and tumour markers such as Ca125, HE4 and LDH, α-FP and HCG in women under age 40 to rule out germ-cell tumour.[1] CEA and Ca19.9 are also commonly requested; however, their clinical value is less clear.[2] If there are concerns of malignancy, a gynaecological oncologist should be consulted.

The aims of a laparoscopic ovarian cystectomy are to have minimal blood loss, to perform efficient surgery and to preserve ovarian tissue. It is important to keep the cyst intact to avoid inadvertent spread of undiagnosed malignancy and, in the case of a dermoid cyst, to avoid chemical peritonitis. Endometriomas are an exception and can be ruptured.

Surgical Consent

There are several risks that are specific to performing an ovarian cystectomy that should be discussed with the woman prior to her procedure:

- Risk of oophorectomy
- Risk of spread of undiagnosed malignancy
- Risk of ongoing pain if pain is a primary symptom
- Risk of recurrence of ovarian cysts

Procedure

- Patient is placed in lithotomy position. Routine skin preparation using alcoholic chlorhexidine for skin and aqueous povidone-iodine for vagina and vulva.
- A uterine manipulator is placed.
- Pneumoperitoneum is achieved by the surgeon's preferred method of entry.
- A 5 mm port is inserted on the patient's left side. The port is placed 1 cm lateral to the surface landmark of McBurney's point – one third of the way between the anterior superior iliac spine (ASIS) and umbilicus. This is done to avoid the inferior epigastric vessels running along the anterior abdominal wall. Port sites may vary depending on size of the cyst, previous surgeries and surgeon preference.

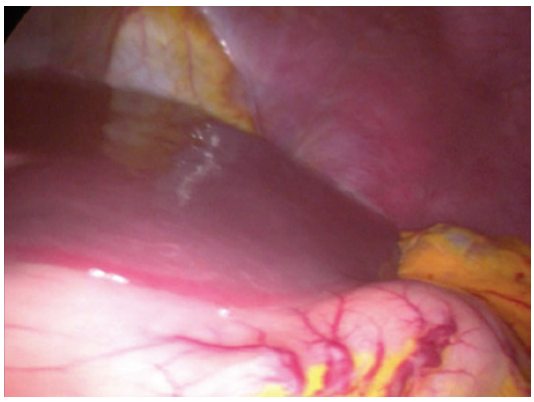
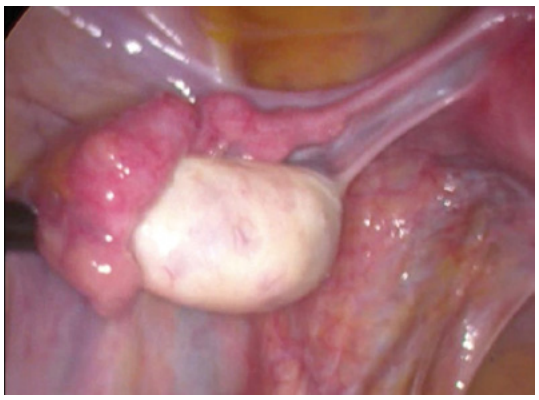
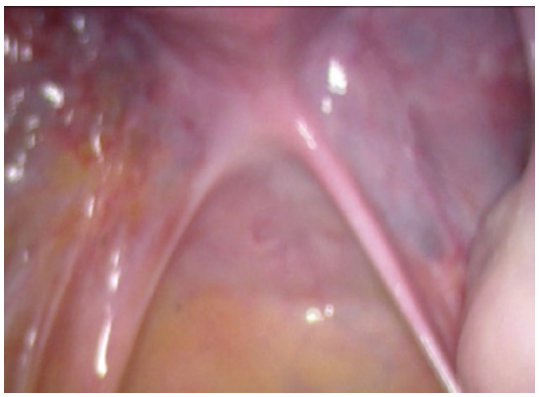


Figure 1. An abdominal survey is performed starting in the right and left upper quadrants looking at the liver and diaphragm.





Figures 2 and 3. Both fallopian tubes and ovaries, as well as bilateral ovarian fossae, pouch of Douglas and the bladder peritoneum are inspected. The appendix is also visualised to rule out any pathology and potential cause of abdominal pain. Pictures are taken documenting each anatomical area.

- Two further 5 mm ports are placed – one on the right side and the other in the high-suprapubic position.

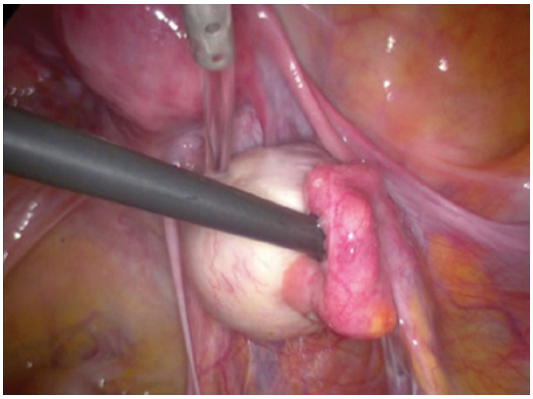


Figure 4. If there are any concerns regarding malignancy, peritoneal washing should be performed.

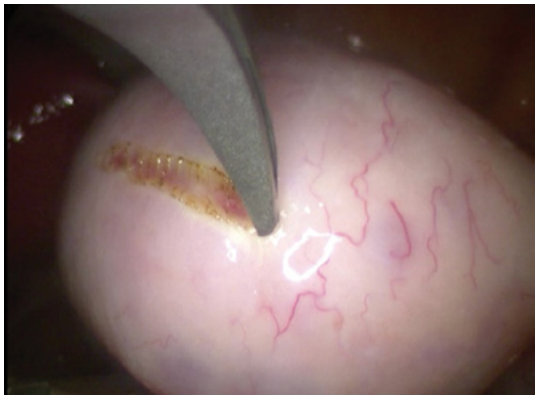
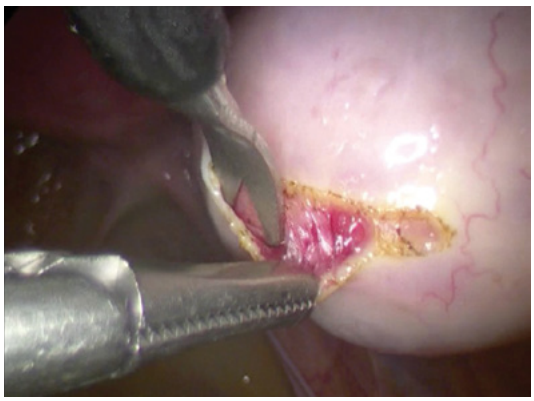
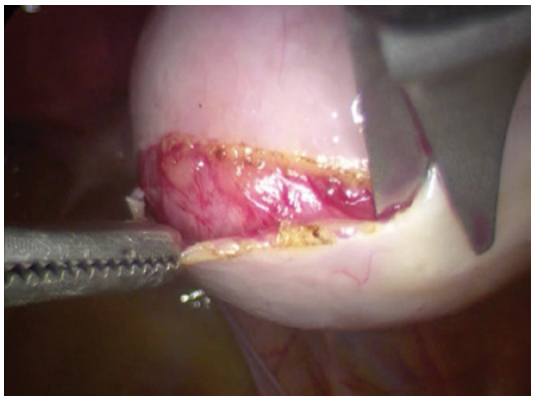


Figure 5. The ovarian cyst is scored using monopolar scissors or hook at a setting of 30–50W of pure cut. Incision is made on the thinnest part of the cyst. Avoid making the incision close to the fallopian tube or fimbrial end. Short bursts of energy are used. It is important not to inadvertently cut through the cyst wall.





Figures 6 and 7. Plane between the ovarian capsule and cyst wall is developed using a mix of blunt and sharp dissection.

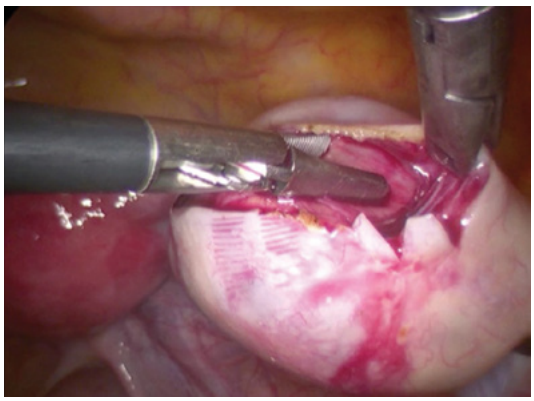


Figure 8. It is important to keep your instruments close to each other. The back of the scissors provides a useful dissection tool. Ensuring the scissors are facing away from the cyst minimises the risk of inadvertent rupture. Slowly work your way around the entire cyst.

- Particularly when dealing with a large and heavy cyst (such as a dermoid cyst), holding the body of the ovary above the cyst allows gravity and the weight of the cyst to help with the dissection.
- Once the cyst has been detached, the ovary can be repaired. Preference is to use a monofilament suture, such as Monocryl®. It is important to include the base of the ovary to achieve haemostasis. Alternatively, haemostasis can be achieved with bipolar energy or with haemostatic agents such as Surgicel®. Haemostasis by bipolar energy appears to have the greatest reduction in ovarian reserve.[3]

- Check haemostasis. Consider use of adhesion barriers – although evidence is limited.[4] Remove ports under vision and close skin wounds.

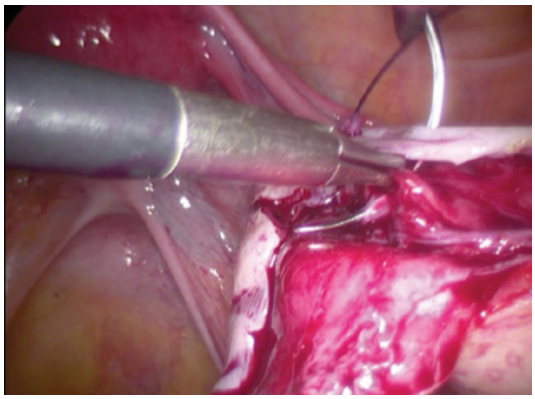


Figure 9. Suturing the ovary has the added benefit of reducing the likelihood of the ovary adhering to the pelvic side wall.

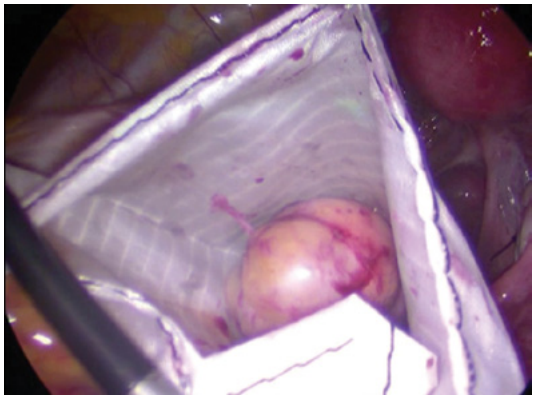


Figure 10. Cyst is removed using a specimen bag. Pictured is a small Espinar E-Sac®. Other popular alternatives include the Endocatch®.

Deviations from routine practice

- Ovarian cysts in pregnancy: procedure should be performed by an advanced laparoscopic surgeon. Procedure is best performed in early second trimester; however, timing of surgery will also depend on symptoms.
- With increasing age, and if there are any concerns regarding risk of malignancy, consider performing a laparoscopic oophorectomy over a cystectomy.
- Extremely large ovarian cysts: consider obtaining pneumoperitoneum at Palmer's point.

Pro Tips

- When dissecting the cyst from the ovary, keep instruments close to each other
- Point scissors away from the cyst
- Include base of the ovary when suturing to close dead space and achieve haemostasis

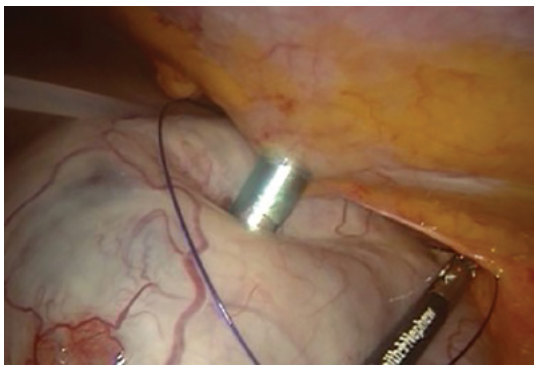


Figure 11. With simple cysts, a 5 mm Applied balloon port can be used to insert directly into the cyst and drain the cyst. If desired, an Endoloop® can be placed on to the ovary and the Applied balloon port placed through the loop.

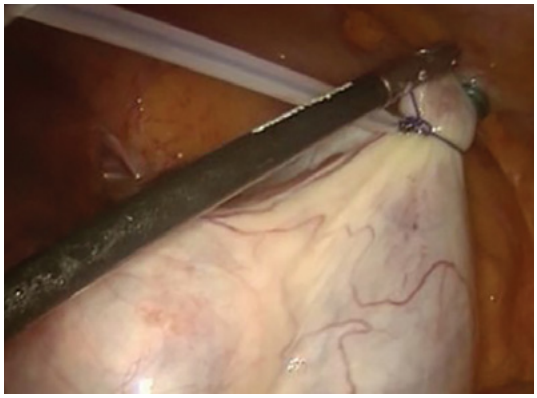


Figure 12. After the cyst is drained, the loop can be tightened to seal the cyst wall defect.

Effect of cystectomy on ovarian reserve

- Ovarian cystectomies performed for endometriomas have greatest reduction in ovarian reserve, as measured by serum AMH levels.[5]
- Excessive diathermy appears to be more detrimental.[3,6]

All pictures courtesy of Dr Michael Wynn-Williams.

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Preventing adhesions: a practical guide for pelvic surgery

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The formation of peritoneal adhesions following surgery is a common problem that can have significant implications both to the individual and to the healthcare system.

The need for effective adhesion prevention strategies has been extensively reported in the literature. This article provides a summary of the available evidence, as well as a practical guide towards better strategies for adhesion prevention.

Clinical significance

Adhesions may occur after both laparotomy and laparoscopy. Postoperative adhesions have been reported in 60–90% of women who underwent extensive open gynaecological surgery.[1]

Although often asymptomatic, adhesions can be associated with significant morbidity, including bowel obstruction (adhesions account for 30–41% of all cases of intestinal obstruction and 65–75% of small bowel instruction requiring further surgery),[2,3] chronic pelvic pain, deep dyspareunia and female subfertility[4] (up to 15–20% of infertility in women is secondary to adhesions).[5]

A Scottish study that followed 8489 women who underwent open gynaecological surgery showed that 34.5% were readmitted one or more times over the following 10 years because of adhesion-related complications. The highest rate of readmission (48%) was in women whose primary site of surgery was the ovary.[6]

In addition, adhesions may increase the risk of complications during subsequent surgery, including difficult surgical access, increased risk of injury to bowel and genitourinary tract, blood loss and increased duration of surgery.[7,8,9]

Pathophysiology

Adhesion formation is triggered by injury to the peritoneal mesothelium, which initiates a peritoneal repair response. Adhesions can develop within the first few hours after surgery, depending on the fine balance between pathways that promote fibrin deposition and others that cause degradation (fibrinolysis). Factors that favour the deposition of fibrin over its degradation will lead to the formation of fibrinous bridges between adjacent peritoneal surfaces. The two main factors associated with surgical injury that escalate the organisation of fibrin into adhesions are inflammation and tissue ischaemia.

At a biomolecular level, the injury to tissue triggers the release of cytokines, growth factors, cell adhesion molecules and histamine, mediators of the local inflammatory response that promote fibrin deposition. This inflammatory reaction involves processes such as coagulation and the recruitment of leucocytes (macrophages and neutrophils) and fibroblasts. In particular, macrophages are involved in the recruitment of adjacent mesothelial cells and fibroblasts, which migrate to the site of peritoneal injury and re-epithelialise the injured peritoneal surface over 3–5 days. Adhesion formation usually occurs within this 3–5-day window, which has clinical implications for the efficacy of anti-adhesion agents that must also be active over this period.

Tissue damage associated with ischaemia also promotes the formation of peritoneal adhesions as a maladaptive response. The response is an attempt to revascularise areas of relative ischaemia following

surgical procedures such as ligation, fulguration or crushing, which disrupt tissue vasculature.

Lastly, contamination of the peritoneal cavity with materials such as sutures, talcum powder, starch, faeces or bacteria may induce further inflammation, which inhibits fibrinolysis and increases the likelihood of adhesion formation. Hence the importance of measures that reduce contamination.

Strategies to prevent adhesions

Adhesion-prevention strategies can be broadly categorised into injury minimisation via meticulous surgical technique and reduced tissue trauma, placing a physical barrier between peritoneal surfaces and the use of pharmacological agents to modulate the cellular response to tissue injury.[10,11]

Meticulous surgical technique / careful tissue handling

The treatment of adhesive disease is very difficult and most patients who undergo surgery for adhesiolysis develop adhesions to a similar degree. The best strategy is to avoid, as much as possible, initial adhesion formation. All measures that reduce epithelial damage should be routinely employed. Precise and meticulous surgical technique, which includes gentle handling of tissue and meticulous haemostasis, reduces adhesion formation.

The method of surgical approach is also important; laparoscopic techniques involve smaller incisions and reduced exposure to foreign materials leading to reduced injury. Nevertheless, adhesions can still occur depending on the type and extent of the surgery performed as well as individual patient characteristics. Copious irrigation is recommended to minimise contamination.

Adhesion barriers

Physical barriers aim to reduce the formation of fibrinous attachments between injured peritoneal surfaces by keeping them apart, particularly for the first 72 hours. Physical barrier agents in either solid or liquid forms have been developed and there is randomised trial data showing some evidence of benefit.

Figure 1 demonstrates the classification and types of physical barrier agents and Table 1 summarises the advantages and disadvantages of commonly used types.

Pharmacological agents

Corticosteroids have been considered as a way to prevent adhesions based on their anti-inflammatory properties. At present, there is no evidence to support their use. A meta-analysis of five RCTs that investigated the efficacy of steroids in preventing adhesions showed that neither adhesion formation nor pregnancy rates improved, with the potential for an increased risk of infection in the perioperative setting.[12] Similarly, studies that used heparin to try to prevent adhesions have also not shown benefit, either alone or in combination with barrier methods.

Oophoropexy

Ovarian adhesions are a common consequence of surgery for the removal of ovarian cysts and, most importantly, surgery for the treatment of endometriosis. The main implications of ovarian adhesions are infertility and chronic pelvic pain. In addition to the several techniques described in this article, authors have proposed suspending the ovaries with the use of sutures to keep them away from the pelvic sidewalls during the first few days after endometriosis surgery.

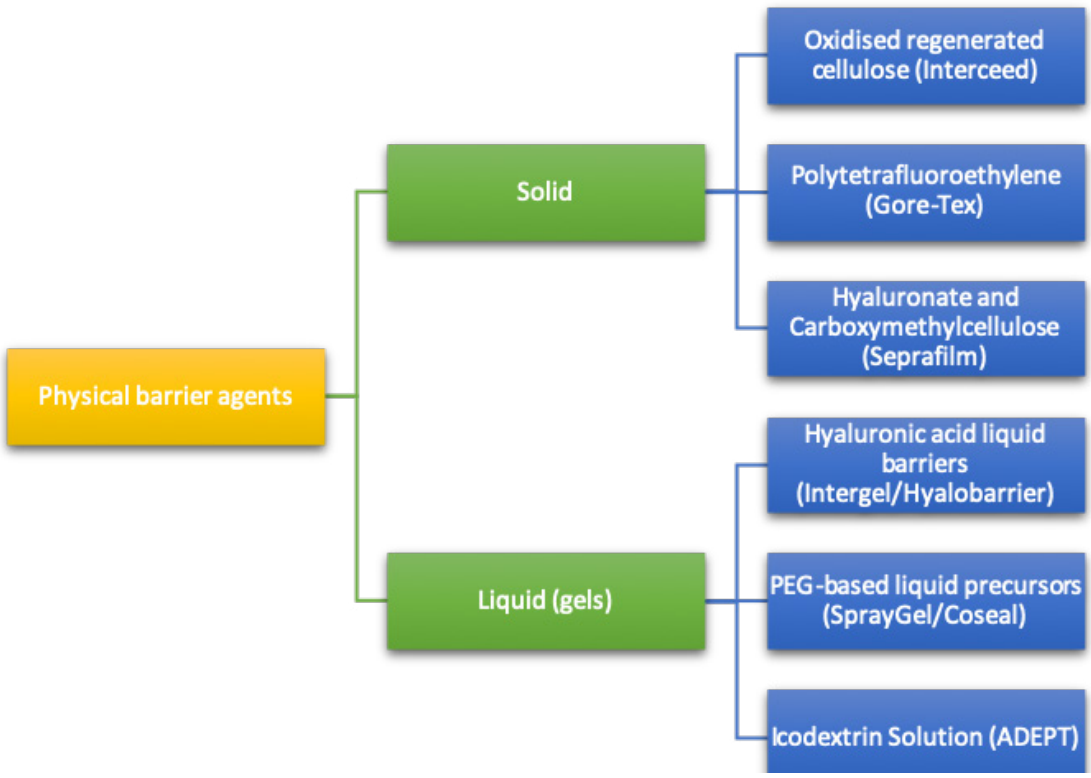

Figure 1. Classification of adhesion barriers.

Table 1. Summary of adhesion barriers.[11]

Agent	Trade name and manufacturer	Cost	Description	Advantages	Disadvantages
Oxidised regenerated cellulose (ORC)	Gynecare Interceed™ **Johnson & Johnson**	$175	Absorbable synthetic sheet applied directly onto peritoneum Transforms into gel that coats surface	- May be cut, permitting use in laparoscopy - Absorbed within 2 weeks - No adverse effects reported - Demonstrated in RCT to reduce incidence and recurrence of adhesions compared with no barrier treatment	- Mixture of blood with ORC increases fibrin deposition and may increase adhesions if adequate haemostasis not achieved prior
Polytetrafluoro-ethylene	Gore-Tex® **W.L. Gore & Associates, Inc.**	Unable to be sourced	Flexible non-absorbable material		- Must be sutured onto peritoneum, leading to surgical delay - Requires secondary surgical procedure for removal - No evidence for use in laparoscopy
Chemically modified sodium hyaluronate / Carboxymethyl-cellulose	Seprafilm® **Genzyme Corporation**	$345	Hyaluronic acid sheets composed of two synthetic polysaccharides Forms gelatinous barrier within 24–48 hours	- Absorbed within 7 days - RCT demonstrated reduction in incidence, extent and severity of adhesion formation at second look laparoscopy compared to no treatment - No adverse effects reported	- Sheets unsuitable for laparoscopic surgery as membrane is brittle
Hyaluronic acid liquid barriers	**Intergel/ Hyalobarrier®** Anika Therapeutics	$240 per 10mL	Liquid hyaluronic acid barrier	- Significant reduction in adhesions in meta-analyses - No effect on subsequent pregnancy rates	
Polyethylene Glycol (PEG)-based liquid adhesion	**SprayGel®** Confluent Surgical Inc. **Coseal sealant** Baxter Healthcare	$300 per 2mL (Coseal)	Synthetic hydrogel sprayed onto target tissues	- Absorbed after 30 days	- Conflicting data on efficacy
Icodextrin solution	**ADEPT®** Baxter Healthcare Corporation	$250 per 1500mL	Iso-osmolar surgical irrigant that persists on the peritoneal surfaces	- Absorbed via lymphatic system over 4 days	- Conflicting data on efficacy

A meta-analysis of several clinical trials published last year concluded that the procedure carries very low risk and was shown to be beneficial for adhesion prevention.[13] The limitations of the review include the fact that it is a relatively new procedure (most studies included in the analysis were published after 2011), there were only two RCTs and the studies used different techniques for the oophoropexy (for example, permanent or absorbable sutures, intra or extra abdominal tying) and for the assessment of postoperative adhesion formation (transvaginal ultrasound, second look laparoscopy, etc).

Initial evidence suggests that ovarian suspension can be an effective strategy in preventing postoperative ovarian adhesion formation in women undergoing laparoscopic surgery for stage III–IV endometriosis. The authors have been doing this consistently with a quick absorption polyglactin 910 suture (2-0 vicryl rapide, Ethicon, US) used to suspend the ovaries to the ipsilateral round ligament whenever the surgery requires extensive dissection of the pelvic sidewalls or the removal of endometriomas.

Conclusion

Postoperative adhesions are a significant source of patient morbidity and place a considerable burden on the health system. Aside from meticulous surgical technique, few agents have a solid evidence base of efficacy, with little long-term data on safety. Progress has been made in recent years, with some products showing some success in reducing adhesion formation. Much work and further research is still required to develop new products that can more effectively reduce the formation of surgical adhesions to improve clinical outcomes, reduce the health implications to individuals and the overall impact to the health system.

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Tumour pathology and classification

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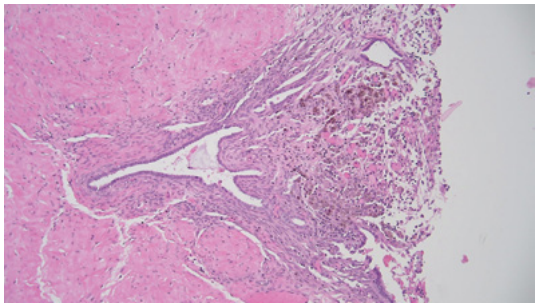


Figure 1. Endometriosis showing endometrial stroma, endometrial glands and haemosiderin-laden macrophages, confirming evidence of old haemorrhage.

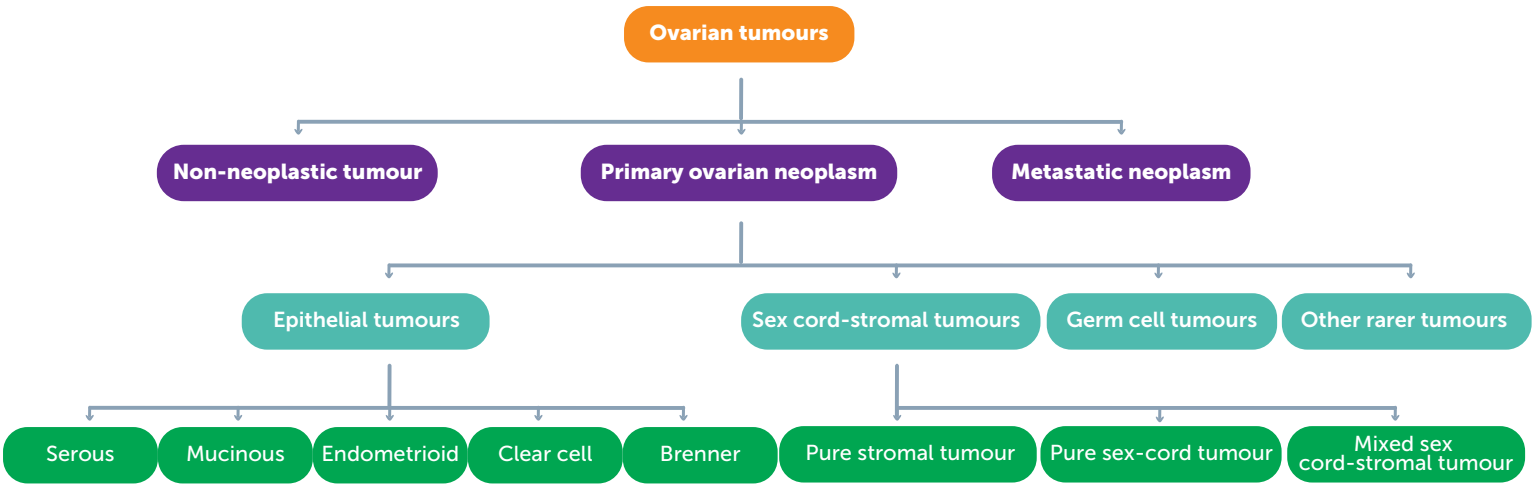
Understanding the pathological basis for ovarian tumour classification is important for providing informed and comprehensive treatment and management of ovarian disease. The World Health Organization 'blue book' *Classification of Tumours of the Female Reproductive Organs* is the gold-standard classification system, which underpins the diagnosis of these tumours worldwide.[1] Ovarian tumours can be conceptualised in three broad areas: non-neoplastic tumours, primary ovarian neoplasms and metastatic neoplasia to the ovary. This article aims to provide a brief overview of ovarian tumours and their classification, concentrating on the more common tumours while highlighting some of the most recent changes and developments.

Non-neoplastic tumours

Benign ovarian tumours or tumour-like lesions can cause ovarian enlargement, potentially mimicking a malignancy and causing diagnostic problems, especially in younger patients of reproductive age.[2] Common benign mass forming ovarian lesions include benign follicle cyst, endometriotic cyst (also known as endometrioma), corpus luteum cyst and tubo-ovarian abscess. Ovarian endometriosis is a common pathological specimen, which is usually a simple histological diagnosis requiring the confirmation of at least two of the following four histological features: endometrial stroma, endometrial epithelium, new haemorrhage or old haemorrhage (hemosiderin).[2] The risk of malignant transformation is very rare in endometriosis, occurring in only 1% of cases;[3] however, the absolute risk of developing epithelial ovarian cancer increases two- to three-fold in women with endometriosis.[4]

Primary ovarian neoplasms

Primary ovarian neoplasms can be subdivided into three major categories: epithelial, germ cell and sex cord-stromal tumours. Other tumours,



Graph 1. Summary of the classification of ovarian tumours.

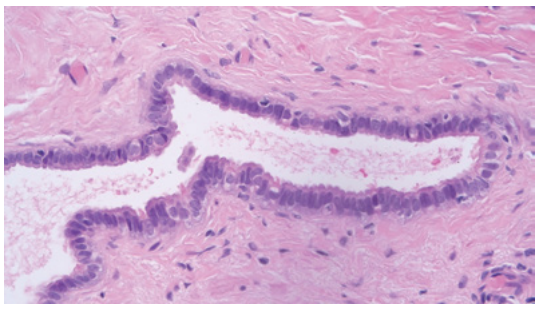


Figure 2. Benign serous cystadenoma characterised by cysts lined by benign cuboidal to columnar cells with focal ciliated cells. High power image.

such as mesenchymal tumours, mixed epithelial and mesenchymal tumours, mesothelial tumours, lymphoid tumours and other rare and miscellaneous tumours, may also occur in the ovary.

Epithelial neoplasms

Epithelial tumours make up the bulk of the primary ovarian neoplasms, and are classified into benign, borderline (variably termed low malignant potential [LMP]) or malignant. The nomenclature for epithelial tumours is based on their cellular origin. They include, in order of most to least prevalent: serous, mucinous, endometrioid, clear cell, and Brenner tumours; mixed Müllerian tumours may occur. Seromucinous tumours are a separate tumour type included in the 2014 WHO classification;[1] however, these will now be mentioned as a subtype of endometrioid tumours in the new, fifth edition of the WHO classification, due for release later in 2020.

Benign tumours are lined by simple non-stratified cells consistent with their cell of origin. Borderline tumours show increased cytological and architectural atypia compared to benign tumours, but do not

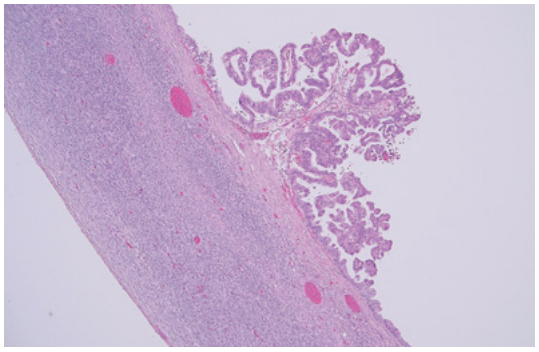


Figure 3. Serous borderline tumour showing focal hierarchical branching papillae covered by stratified serous cells showing moderately enlarged and hyperchromatic nuclei. There is no invasion present.

demonstrate invasion. Malignant tumours show invasion of the ovarian stroma, with variable degrees of cytological atypia.

A key development in the classification of serous tumours has been the clear separation of low-grade serous carcinomas (10%) and high-grade serous carcinomas (90%).[1] These two tumours do not actually represent a morphological spectrum, but rather that they are mostly different types of tumours and develop via different pathways. Low-grade serous carcinomas may contain KRAS and BRAF mutations, which may occasionally be actionable with targeted therapy. High-grade serous carcinomas are distinguished by a high level of genetic instability and harbour TP53 mutations[1] in the vast majority of cases. This can be highlighted with the immunohistochemical stain p53, which shows either strong nuclear staining or complete absence of staining.[1] Generally, however, low- and high-grade serous carcinomas can be reliably separated based on routine light microscopy.[3] They may be associated with BRCA mutations and genetic testing is recommended for all high-grade serous cancer patients. A combination of low- and high-grade serous adenocarcinoma in the same tumour is very rare.

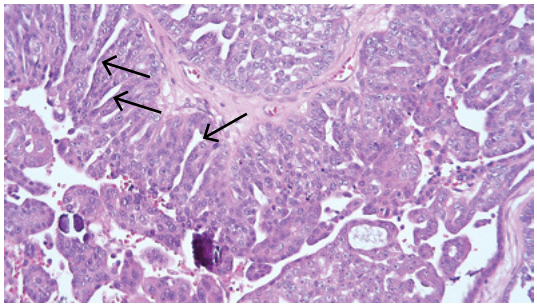


Figure 4. High-grade serous carcinoma demonstrating sheets of cells with slit-like spaces (arrows). The tumour cell nuclei are pleomorphic with prominent nucleoli. Psammoma bodies are also present.

Ovarian germ cell tumours

The classification system of ovarian germ cell tumours includes dysgerminoma, yolk sac tumour, embryonal carcinoma, choriocarcinoma, teratoma (immature and mature) and mixed germ cell tumour. Mature teratomas, also referred to as a 'dermoid cyst' or 'mature cystic teratoma', are the most common ovarian germ cell tumour. These tumours are benign, unless somatic-type malignant transformation occurs, such as squamous cell carcinoma in skin components, which is extremely rare.[5] Unlike mature teratomas, immature teratomas have malignant potential and tend to be more solid than mature teratomas.[2] Grading is based on the amount of immature neuroepithelial tissue present

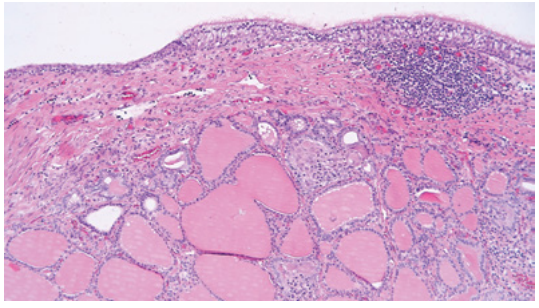


Figure 5. Mature teratoma showing a cyst lined by respiratory type epithelium with underlying thyroid tissue; often termed struma if constituting more than 50% of the lesion.

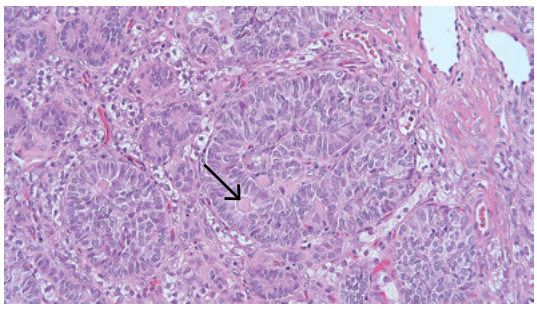


Figure 6. Adult granulosa cell tumour demonstrating a microfollicular pattern with classic Call-Exner bodies (arrow).

microscopically.[5] Macroscopically, neural tissue typically appears soft and fleshy showing a yellowish to grey colour.[2]

Sex cord-stromal tumours

The classification of sex cord-stromal tumours can be divided into pure stromal tumour, pure sex cord tumour or mixed sex cord-stromal tumour. Included within pure stromal tumours are benign fibroma, Leydig cell tumour, microcystic stromal tumour and other rare tumours. Pure sex cord tumours include adult granulosa cell tumour (AGCT), juvenile granulosa cell tumour (JGCT), Sertoli cell tumour and sex cord tumour with annular tubules. Tumours composed of variable proportions of Sertoli cells and Leydig cells constitute mixed sex cord-stromal tumours and are graded as well, moderately or poorly differentiated. Apart from fibromas, all of these tumours are rare, and show a vast range of histological appearances. The recent discovery of FOXL2, DICER1 and CTNNB1 mutations in AGCT, Sertoli-Leydig cell tumours and microcystic stromal tumours respectively,[6] can be helpful in the diagnosis of difficult cases. Determining DICER1 mutation status can also assist with the risk assessment for DICER1 syndrome in Sertoli-Leydig cell tumours.[6]

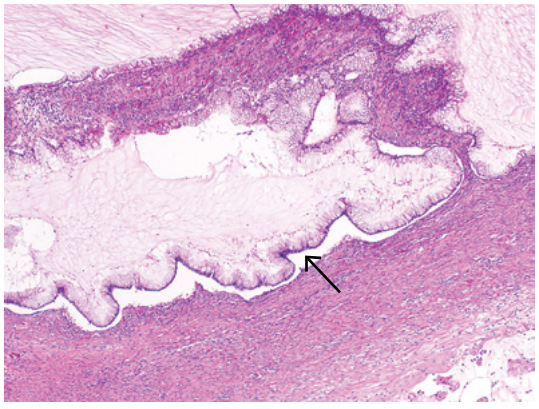


Figure 7. Metastatic low-grade appendiceal mucinous neoplasm demonstrating scalloped glands and subepithelial clefts (arrow).

Picture courtesy of A/Prof L Anderson.

Metastatic tumours

It is estimated that 3–15% of ovarian malignancies are metastatic in origin and may be the presenting sign of a non-ovarian primary.[1] One of the most challenging diagnostic dilemmas is differentiating primary mucinous ovarian tumour from metastatic mucinous tumour. Macroscopic features that favour metastases include small size (often less than 10 cm), bilateral tumours, surface involvement, and extensive intra-abdominal spread.[7] Additional microscopic features may also raise suspicion of metastases. For instance, in a low-grade appendiceal mucinous neoplasm, the mucinous glands are scalloped and show subepithelial clefts.[8] Common primary mucin producing neoplasms that metastasise to the ovaries include the gastrointestinal tract, pancreas, breast and other gynaecological sites such as cervix.

Metastasis occurring from other gynaecological sites to the ovary represents a unique and fascinating situation where the clinical behaviour in a significant amount of these cases is more aligned with that of a low-stage, organ-confined disease.[9,10] In the case of low-grade endometrioid endometrial carcinoma, with secondary unilateral ovarian metastases, there is evidence that these could potentially be classified as FIGO stage IIIA endometrial carcinoma, with the possibility for more conservative management options.[9] It is anticipated that the staging of these tumours will evolve as molecular testing becomes more prevalent.[8]

Summary

The classification of ovarian tumours is extensive, with a large range of morphological appearances. These histological features, however, still form the backbone of this highly reproducible classification system[10] and in the vast majority of cases, accurately predicts whether tumours will be benign, borderline or have malignant potential.

I wish to thank A/Prof Lyndal Anderson for proofreading and editing this article.

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Treating ovarian cancer and life after surgery

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Ovarian cancer (OC) is common and, in 2015, 1365 Australian and 366 New Zealand women were diagnosed with OC, accounting for 938 and 228 deaths in 2016 respectively. Unfortunately, no effective screening strategies exist, and most women present at an advanced stage, with an 80% risk of recurrence, usually followed by multiple courses of chemotherapy and, ultimately, life-limiting disease.

For the past two decades, standard primary therapy has consisted of surgery combined with a chemotherapy regime of platinum and taxane. More recently, improvements in the management of OC include access to tertiary level care, a more radical approach to surgery, targeted agents such as PARP-inhibitors and bevacizumab and a more aggressive approach in managing recurrence. As such, women are living longer, and in 2011–2015 the estimated five-year overall survival in Australia was 46% compared with 36% in 1986–1990; for those with early-stage disease five-year overall survivals are around 80%. Given this, OC fits the criteria of a chronic disease and it should be managed as such, where focus of treatment includes both the initial presentation of disease and survivorship care.

With this in mind,one of the current challenges in OC management is to not only extend life expectancy but to also improve quality of life (QoL). This involves the careful personalisation of treatment ensuring patients have access to therapies that will benefit them while avoiding interventions that will be of little benefit but reduce their QoL. For most patients, there are many such decisions around this that have to be made over the course of their disease. Unfortunately, in many of these situations, it is difficult to predict the outcome of individual interventions and these uncertainties need to be carefully discussed.

Regarding primary treatment, surgical resection aiming for no residual macroscopic disease is the gold standard as residual disease after surgery significantly effects prognosis.[1] With this in mind, in recent years neo-adjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) in advanced disease has been proposed as an alternative standard of care as it significantly reduces surgical morbidity.[1]

This is based on the findings of two randomised controlled trials showing comparable progression free and overall survival in women with upfront versus IDS. However, the jury is still out for some as questions raised, specifically in relation to the surgical quality of these studies, make some clinicians dubious about whether this should be considered standard of care for all patients with advanced disease just yet. This question is hoped to be answered by the TRUST study (trial on radical upfront surgery in advanced ovarian cancer), which has finished recruitment with results expected in 2024.

Other important considerations surrounding primary surgery include preoperative counselling regarding the radicality of surgery, as this is increasing on the global stage and more radical surgery is associated with greater morbidity and longer recovery times, and may not be appropriate in some patients. Important factors to discuss include bowel resection and stoma formation and in some cases, women may flatly refuse to have a stoma, which can lead to suboptimal resection. More recently, ultraradical peritonectomy surgery is gaining popularity, which when coupled with heated intraperitoneal chemotherapy has shown promise, but is associated with significant morbidity. It should also be noted that while on average women who have surgery do better than those who do not, some women for whom optimal debulking will not be achieved may not benefit and hence careful patient selection for surgery is imperative.

Other important considerations for primary surgery are those surrounding younger women with early-stage disease, as traditional surgery has huge impacts on QoL including a loss of fertility. Pleasingly, research has shown that fertility sparing surgery (FSS) is safe and feasible for select patients (serous stage IA grade I or II and stage ICI grade I) and this should be discussed with this cohort of women.[2] Other considerations include surgical approach (minimally invasive versus laparotomy) as the risk of cyst rupture and the subsequent consequences on adjuvant therapy recommendation need to be weighed up against the known consequences on body image that a midline laparotomy scar carries, in addition to increased surgical morbidity.

Following on from surgery comes recovery and the consideration of recovery times when planning a woman's surgery and its radicality, particularly in the setting of advanced disease, is an important aspect of treatment planning for several reasons. Firstly, prolonged recoveries will translate to more of a woman's limited life expectancy being medicalised, which understandably reduces QOL. In addition to this, the commencement (or recommencement) of chemotherapy may be delayed by prolonged recoveries and subsequently impact prognosis. This reiterates the point that if a surgery will not improve a woman's prognosis, survival or QOL, it is inappropriate, and comprehensive discussions need to be had with women and their caregivers in these situations.

Unfortunately for most women with OC, primary treatment is just the tip of the iceberg of their journey and, following its completion, women are likely to experience a wide range of sequalae that often persist throughout their lives and negatively impact their QoL. Additionally, the increasing use of maintenance therapies to improve disease free survival, which in themselves have side effects (which may include a financial burden) now need to be considered. Hence, implementing individualised survivorship programs is a crucial component of managing women with OC.

Key to any survivorship program are regular clinical reviews assessing for treatment side effects, general and psychological wellbeing, in addition to looking for evidence of recurrence. Additionally, regular surveillance enables us to address general health promotion including maintaining a healthy BMI, regular exercise and tobacco cessation; all of which are associated with better outcomes for gynaecological cancer survivors.[3]

Treatment side effects often include lymphoedema, bowel and bladder dysfunction, pain and chemotoxicity (particularly cognitive impairment and neurotoxicity) and fatigue.[3] When considering neurotoxicity specifically, it is common and occurs in up to 57–83% of women treated with paclitaxel.[4] It can be very debilitating, manifesting with acute pain syndromes, numbness, tingling and sensory disturbance. Sadly, we do not have strong evidence regarding effective prevention strategies and treatment is very challenging, which is compounded by the fact that it not only negatively impacts QoL, but is a common reason for chemotherapy dose reduction, which in turn can worsen prognosis, making it a significant challenge for women and their caregivers.

Not surprisingly, psychological distress is also very common, with depression and anxiety present in 25% and 40% of women respectively.[3,5] Additionally, post-traumatic stress disorder affects up to one third of women with advanced gynaecological cancers.[3]

Exacerbating these problems are stressors such as feelings of isolation, strains on intimate relationships and worries about passing on a genetic predisposition to disease.[3] Additionally, the financial sequelae of a cancer diagnosis coined 'financial toxicity' can be crippling, with 25% of cancer survivors in Europe being quoted to live in poverty two years post diagnosis compared with just 14% of the general population.[3] Given OC commonly effects women who are still working, and a diagnosis often heralds the end of their working lives, the financial toxicity of the disease should not be underestimated as it perpetuates its psychological sequalae.

From this, it is clear that being aware of, and screening for, psychological stressors in survivorship programs is essential and initiating interventions via a multidisciplinary approach (with the support of psychologists, social workers, sexual and spiritual health consultants) in addition to addressing any treatable contributing physical symptoms, is prudent in these women's follow-up. Interventions include things such as optimising a patients physical health (exercise, BMI and tobacco cessation) and utilising pharmacological agents (SSRIs and SNRIs) where appropriate.[3]

In addition to, and often exacerbating, the negative psychological sequalae, an OC diagnosis often has negative psychosexual consequences, inclusive of a loss of 'womanhood', infertility, iatrogenic menopause, body image disturbance and sexual dysfunction (encompassing arousal, sexual interest, pain and orgasm).[6]

Infertility is obviously a devastating consequence of treatment for some women and fertility-sparing options should always be considered in treatment if possible. In addition to this, iatrogenic menopause can be more abrupt, intense and prolonged than the natural menopause and, if not appropriately managed, leads to reduced QoL, physical function and sexual desire.[7] Compounding the issue is the pharmacological limitations in its management, often limited to lifestyle modifications, cognitive behavioural therapy and non-hormonal therapies.[6]

Sexual dysfunction and a loss of 'womanhood' should not be underestimated as it is reported in up to 90% of gynaecological oncology patients.[7] Surprisingly, despite the staggering prevalence, 64% of patients have never had these issues addressed, although 74% of women have a strong desire for these discussions; which, ideally, should start prior to treatment.[7] Potential reported barriers include time and financial resources, physician discomfort and the belief that older women may not see sexual health issues as an important component of their care; which is categorically untrue, given published data shows the majority of older adults (57–85 years) are sexually active and regard sexuality as an important part of their QoL.[7]

Sadly, the conclusion of many women's OC journey is relapse and most will succumb to their disease,

making the provision of palliative care an important aspect of their journey. Common problems facing women at the end of life include pain, nausea and vomiting, hydration and nutrition, constipation and bowel obstruction, ascites and breathlessness. Managing these physical symptoms and providing support for psychological and spiritual needs is important and should extend to the woman's family. Timely discussion regarding the role of palliative care with patients and their families is essential in order to minimise distress and empower the patient.

In conclusion, a diagnosis of advanced OC is essentially one of a chronic and life-limiting disease. Given this, we must consider not only its initial treatment but also a woman's journey after surgery in its management. For myself and my colleagues, we find that one of the most humbling and privileged aspects of our job is supporting these brave and resilient women throughout their journey, as despite the huge physical, psychological and psychosocial stressors, many women find that their spirituality and connection with loved ones strengthens throughout. It is our job to support and care for these women and their families and to address as best we can the multifaceted consequences that a diagnosis of OC has on their lives.

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Fertility preservation

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The incidence of new cancers has stayed static in children, adolescents and young adults (AYAs) over the last three decades and advancement in medical therapies has led to increasing five-year survival rates for all cancers, meaning many more are surviving into adulthood and having the opportunity to have children. Many consider fertility to be a fundamental right and although the option of donor gametes exists, due to technological advancements in cryopreservation techniques, many more now desire to preserve their own gametes to use to conceive later in life. Many cancer therapies can be irreversibly gonadotoxic, so consultation with a fertility specialist for any individual regarding their fertility preservation options, prior to their chemoradiotherapy, is integral to the standards of care for AYA Cancer Network Aotearoa. Due to the evolution of oocyte and ovarian tissue cryopreservation techniques and increasing demand, fertility preservation is a rapidly evolving area in the field of reproductive endocrinology and infertility.

Oocyte cryopreservation

More than 3000 babies have been born worldwide from cryopreserved oocytes and with the advent and refining of the method of vitrification, oocyte freezing has shifted from an experimental to realistic option for future fertility preservation.

New Zealand Assisted Reproduction Technology (ART) providers are governed by the HART Act 2004, which initially did not include oocyte and ovarian tissue cryopreservation as established and permissible procedures, as both were still experimental at that time. The Advisory Committee on Assisted Reproductive Technology (ACART) was formed to hold public consultation, assess risks and advocate for new emerging technologies to amend ART legislation over time. ACART submitted a letter to the health minister for oocyte cryopreservation and utilisation in 2008 and legislation was amended to permit and allow oocyte cryopreservation and utilisation in 2009.

Oocyte freezing is currently permissible in NZ in women 16 years and older, with storage for a maximum of ten years, although storage after 10 years is usually permitted on a case-by-case basis. Publicly funded fertility preservation is inclusive of oocyte cryopreservation but only for AYA's and women up to 40 years with cancer necessitating gonadotoxic treatment. Otherwise, non-medical indications are deemed elective and are privately funded. The utilisation of these frozen gametes later is only publicly funded if the woman or her partner has proven infertility, is under 40 years, has a BMI below 32, is a non-smoker and has no children.

Cryopreservation of oocytes involves ovarian stimulation for 10–14 days, oocyte collection and cryopreservation prior to gonadotoxic treatment, then later utilisation with a male partner's sperm or sperm donor through intracytoplasmic sperm injection (ICSI). Oocytes are frozen at Metaphase II (MII) stage when both nuclear and cytoplasmic maturation has occurred, and ovarian stimulation medications are only able to recruit and mature small cohorts of 10–30 primary and secondary follicles to MIIs in post-pubertal ovaries.

Cryopreservation halts all biological and physiological activity of the cells and efficacious cryopreservation methods aim to preserve intracellular structures, DNA integrity and restore normal cellular function after the freeze-thaw process. Pregnancies from frozen sperm were first reported in the mid-1950s and from frozen embryos in the 1980s. Oocyte cryopreservation has been more difficult due to several inherent oocyte issues, requiring new technological advancements in ART to overcome. Cryopreservation of oocytes creates hardening of the zona pellucida, causing failure of fertilisation with conventional in-vitro fertilisation (IVF). ICSI overcame this and was a major evolutionary step in ART in the late 1980's. Oocytes are one of the largest cells in the human body with a high water content. The older slow-freeze method is a slow, stepwise reduction in temperature, whereas vitrification is an ultra-fast, sudden reduction in temperature. When undergoing slow-freeze cryopreservation, intracytoplasmic ice crystals form within oocytes and confer poorer survival (45–75%) and fertilisation rates (54-67%) compared to vitrified oocytes (82–91% survival, 77–83% fertilisation rates).[1-3]

Cryopreserved oocytes have lower chances of pregnancy compared to embryos, but higher chances compared to ovarian tissue. So, many more

oocytes, compared to embryos, need to be frozen to give a reasonable chance of a livebirth later in life, and there are no guarantees that any cohort of oocytes will achieve a child. The younger the woman at the time of egg retrieval and freezing, the higher the chance of pregnancy per oocyte. Livebirth rates per oocyte have been reported as 7.5–10% in women 30 or younger, 7–7.5% in 35-year-olds and 5% in women of 40 or older.[4,5] The largest retrospective observational study compared pregnancy outcomes in 6362 women and found no significant difference in oocyte survival or cumulative live birth rates between those who froze oocytes for cancer or electively.[6] Reassuringly, the largest report on neonatal outcomes in more than 1000 children born from frozen oocytes has shown no increase in perinatal and neonatal morbidity.[7]

Low utilisation rates and, therefore, cost effectivity are the more controversial aspects to oocyte cryopreservation. Utilisation rates are the proportion of women returning to use their frozen gametes and are lower (5%) for cancer indications[8] compared to 6–13% for non-medical, elective indications.[5,9] This probably mostly relates to the younger age of those undergoing egg freezing for cancer, compared to non-medical indications, where they have yet to reach the age where they are ready to have children, and less so from lack of gonadotoxicity from their cancer treatment or non-survival from their cancer.

Ovarian tissue cryopreservation

Prepubertal girls or those with insufficient time to undergo 10–14 days of ovarian stimulation, oocyte retrieval and cryopreservation before starting their gonadotoxic therapy, are by default left with ovarian tissue cryopreservation to preserve their fertility using autologous tissue.

The first baby born from reimplanted cryopreserved ovarian tissue was reported in Belgium in 2004 and more than 100 babies have been born worldwide from this method since, so it is no longer considered experimental. Ovarian tissue freezing is permissible by legislation in NZ but is not a publicly funded fertility preservation option. Surgical excision typically occurs in the public hospital where they receive their oncology treatment, so only ovarian tissue preparation and cryopreservation needs to be privately funded. There are more than 50 ovarian tissue samples currently stored in NZ and usage via autologous ovarian tissue reimplantation is currently not permissible in NZ. However, a letter to the health minister was submitted by ACART to amend legislation to allow ovarian tissue reimplantation to be a permissible therapy in 2017 but at the time of writing, legislation has yet to be amended.

Surgical removal of ovarian tissue is usually performed laparoscopically at the time of a peripheral long- or central-line placement under general anaesthesia. Our embryologists collect and transport the tissue back to the laboratory where they prepare the ovarian cortex tissue into strips, insert them into cryostorage devices and then slow-freeze them. Various reimplantation techniques are being explored globally in order to optimise graft survival and restore hormonal production and reproductive function. Dr Dror Meirow, former President of the International Society for Fertility Preservation (ISFP), advocates reimplantation of the ovarian tissue back into the ovarian bed or remnant (orthotopic transposition) to utilise the existing vasculature and ovarian infrastructure, to permit physiological ovulation and natural conception, and not necessitate IVF as does heterotopic transposition (that is, forearm site). Meirow describes promising reproductive outcomes in the largest series of 21 women under 35 years of age undergoing ovarian tissue reimplantation; 21 (100%) had restored endocrine function and 10 (47.6%) had conceived at least once, half of which were natural conceptions.

Another concern regarding ovarian tissue reimplantation is potentially reintroducing cancer into the individual. Meirow's group describes using all available technologies to investigate for residual malignancy cells in cryopreserved ovarian tissue before autologous reimplantation, including light microscopy and immunohistochemistry for cancer cells, cytogenetic analysis for any previously identified oncological gene mutation, next generation sequencing for common gene mutations implicated in the malignancy and xenotransplanatation into several mice with later sacrificing to ensure no malignancy cells are found in their tissues or blood.[10]

Controversially, consent for ovarian tissue cryopreservation more often than not is given by the parents/caregivers and not the individual, who is typically under the age of consent. It is akin to parents taking out a fertility insurance policy for their daughter; however, given use is so far untested in NZ, controversy also surrounds whether this should be a publicly funded fertility preservation procedure in NZ.

Conclusion

Advancements in cancer therapies, improved cancer survival and more women choosing to delay having their children is increasing the demand for fertility preservation and this is a rapidly evolving area of reproductive endocrinology and infertility. Legislation needs to be current with emerging ART techniques so as not to disadvantage NZ women and their right to reproduction.

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Ovarian cancer risk and how to manage it

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Epithelial ovarian cancer (EOC) is a highly lethal malignancy and the most common cause of gynaecological cancer death. In Australia in 2019, there were an estimated 1510 new diagnoses and 1046 deaths from EOC, representing the sixth leading cause of cancer-related death in women.[1] Most cases are diagnosed at an advanced stage and have a poor prognosis, with a 46% chance of surviving five years.[1] EOC is a heterogenous disease composed of multiple histologic subtypes with unique genomic features.[2] The most common histotype is high-grade serous carcinoma (Box 1). The disease has a major heritable component, which provides opportunities to identify women at increased risk and to reduce risk.[3]

In Australia, the lifetime risk of EOC is 1.2% by the age of 80 years.[4] Family history is an important risk factor, with an approximate three-fold increase in relative risk to all first-degree relatives. For a woman with a first-degree relative with EOC and no known genetic susceptibility, the lifetime risk of EOC is 2–3%[5] and guidelines do not recommend risk-reducing surgery.[3] Women with two first-degree relatives with EOC have a lifetime ovarian cancer risk of 8%, provided that a BRCA1 or BRCA2 mutation has been excluded in a relevant family member.[5] In families with a strong history of both breast and ovarian cancer, and no known genetic susceptibility, the ovarian cancer risk may be as high as for BRCA mutation carriers. Discussion with a clinician with relevant expertise is essential when making decisions about the role, if any, of risk-reducing surgery for an individual woman.

Most women diagnosed with EOC do not have a family history of ovarian cancer. One third of women with EOC with a BRCA1/2 mutation will have no known family history of breast or ovarian cancer.[6-8] Ashkenazi Jewish populations have a high BRCA1/2 mutation carrier rate (1 in 40 compared to approximately 1 in 400 in the general population) and 30% of Ashkenazi Jewish women with EOC will have a BRCA1/2 mutation.[9-10]

The most common inherited mutations in EOC include:

- BRCA1 and BRCA2, which are inherited in an autosomal dominant pattern. EOC typically occurs at an earlier age and with greater frequency among BRCA1 carriers than among BRCA2 carriers.
- DNA mismatch repair (MMR) genes associated with Lynch syndrome are also inherited in an autosomal dominant pattern. There is an increased susceptibility to ovarian cancer, although less than 1% of patients with EOC have germline mutations in MMR genes.[11] Ovarian endometroid and clear cell histotypes predominate in Lynch patients. Patients will generally only be eligible for germline mutation testing, however, if there is loss of MMR expression on immunohistochemical staining of their tumour.
- Pathogenic mutations in RAD51C, RAD51D and BRIP1 confer an elevated lifetime risk of ovarian cancer and are now offered in conjunction with BRCA testing as part of next generation sequencing multigene ovarian cancer panels.
- Mutations in the PALB2 gene (partner and localiser of BRCA2) have recently been shown to be associated with a moderate increase in lifetime risk (5% to age 80 years) of EOC.[12]
- Other emerging genes in which mutations that may be associated with increased EOC risk include ATM, NBN and BARD1, but until there are more data they should not be routinely tested.

Box 1. Epithelial ovarian cancer histotypes.

There are several different EOC histotypes that behave and respond differently to treatment:

1. **High-grade serous carcinoma** account for the majority of EOC **(70%).** These are the most chemo-sensitive histology. Heritable BRCA1/2 mutations are found in approximately 17% of women with a high-grade serous EOC unselected for family history[6]
2. **Endometrioid (10%)** high-grade endometrioid ovarian carcinomas may be associated with germline BRCA1/2 mutations
3. **Clear cell (10%)** may be associated with germline BRCA1/2 mutations
4. **Low-grade serous (<5%)** are not associated with BRCA1/2
5. **Mucinous carcinomas (<5%)** are not associated with BRCA1/2

Table 1. Lifetime risk of ovarian cancer by gene mutation.

Cancer	BRCA1 mutation carrier	BRCA2 mutation carrier	MMR deficient	RAD51C RAD51D BRIP1 PALB2	General female population by age 85 years
Ovarian/fallopian tube	44% to age 80 years	17% to age 80 years	MLH1: 11% MSH2: 15% MSH6: low PMS2: no increased risk	5–10%	1.2%
Primary peritoneal carcinoma post RRBSO	<2%	<1%			<1%
Recommend RRBSO	35–40 years	40–45 years	40 years	45–50 years	

EOC risk is age dependent. The prevalence of BRCA1/2 mutations in women with ovarian cancer is highest for women in their 40s and 50s.[7] The median age of ovarian cancer diagnosis for BRCA1 mutation carriers is 54 years (43.5–62.5) and in BRCA2 mutation carriers is 59.5 years (53.3¬–64.7).[13] In one study, the incidence of ovarian cancer in BRCA1/2 carriers in the 30 and younger age group was 0%, and in the 31–40 age group was 1.8% and 0.3% in BRCA1 and BRCA2 carriers respectively.[13] There appears to be an increase in ovarian cancer incidence with age up to 61 to 70 years for both BRCA1 (29.4 incidence per 1000) and BRCA2 carriers (10.3 incidence per 1000).[6,7,13] Based on a small number of studies, the prevalence of BRCA1/2 mutations in women with ovarian cancer aged 70 years or over at diagnosis is less than 10%.[11,14-17]

Risk prediction tools such as Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), BRCAPro and the Manchester scoring system predict the probability of a BRCA1/2 mutation based on family and personal history, and breast cancer histopathology.[18-20] Some also estimate cancer risks, regardless of gene status. Sufficient information to guide genetic risk assessment is usually provided by age, histology and family history for women with ovarian cancer.

Screening in high-risk women

For asymptomatic women at high risk for EOC, transvaginal ultrasound and serum CA125 levels lack sufficient sensitivity and specificity. In the second phase of the UK Familial Ovarian Cancer Screening Study, of more than 4000 high-risk women undergoing four-monthly serum CA125 testing using the Risk of Ovarian Cancer Algorithm (ROCA) there was evidence of a stage shift (a higher proportion of EOC was diagnosed at earlier stages during screening compared to the period after screening had ceased).[21] The authors concluded that ROCA-based screening is an option for women at high risk of EOC who defer or decline RRBSO. However, whether this strategy would decrease mortality in screened high-risk women is unknown and current Australian guidelines recommend against the use of pelvic ultrasound and CA125 in this population.[4]

Risk-reducing bilateral salpingo-oophorectomy

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is the only evidence-based strategy to reduce EOC mortality in high-risk women.

Decisions about RRBSO should be individualised based on the residual lifetime risk, current health status, cancer anxiety and personal preference. The decision to undergo prophylactic surgery is highly personal and challenging for many women. Confronting personal cancer risk can be confusing and frustrating and undergoing these procedures can have profound effects on a woman's body and quality of life. Historically the prevalence of the use of cancer risk-reducing strategies among Australian BRCA1 and BRCA2 mutation carriers has been low. Prospective follow up of female carriers of BRCA1/BRCA2 mutations who had no personal history of cancer and were enrolled in a multiple-case breast cancer family cohort study (kConFab) found that 125 of 325 (38%) BRCA1 and BRCA2 mutation carriers underwent RRBSO during 2447 person-years of follow-up (median follow up nine years).[22] A psychosocial study conducted in the same patient cohort showed that factors predicting uptake of RRBSO included being parous (OR 3.3, $p = 0.015$); knowing one's mutation positive status (OR 2.9, $p < 0.001$) and having a mother and/or sister who died from ovarian cancer (OR 2.5, $p = 0.013$).[23]

Patient consultation with experts in cancer genetics and gynaecologic oncology is recommended to assist women in their decision-making regarding RRBSO. Implications of loss of fertility, surgical menopause, the safety of menopausal hormone therapy (MHT), the risk of diagnosing an occult tubal cancer (up to 6% of women undergoing risk reducing surgery), and the residual lifetime risk of primary peritoneal carcinoma (1–2% risk) need to be discussed. If risk-reducing bilateral salpingo-oophorectomy (RRBSO) is undertaken prior to menopause, MHT should be considered to minimise potential cardiovascular complications, bone loss and sexual dysfunction associated with surgical menopause, until the age of natural menopause (50 years). The use of MHT is generally considered safe[24] as long as there is no personal history of breast cancer or medical contraindications to MHT, and does not appear to negate the benefits of salpingo-oophorectomy in BRCA1 and BRCA2 carriers.[25] The reader is referred to an excellent patient resource published in English, Arabic and Chinese by the Royal Women's Hospital in Melbourne entitled 'Considering surgery to reduce the risk of ovarian cancer' available to download at: www.thewomens.org.au/health-professionals/clinical-resources/events-and-resources#a_downloads. Pink Hope, an

Australian not-for-profit organisation established for the education and prevention of hereditary breast and ovarian cancer is another excellent resource for high-risk individuals: pinkhope.org.au

The combined oral contraceptive pill (COCP) has been found to reduce ovarian cancer risk in BRCA1 mutation carriers. Although the COCP can reduce ovarian cancer risk, it is significantly less effective than RRBSO and is not recommended for cancer prevention.[4] There are no data on Implanon or Mirena in BRCA1 mutation carriers with regard to ovarian cancer risk; however, a recent population study with substantial numbers of users, showed a small increased risk of breast cancer in Mirena users, but no increased risk in users of progesterone implants.[7] We await the results of the prospective STICs and STONes study of Aspirin versus placebo for chemoprevention in high-risk women with BRCA mutations and women wishing to delay RRBSO (ClinicalTrials.gov Identifier: NCT03480776 and Australia and New Zealand Clinical Trials Registry no. ACTRN12619000520134).

In women at high risk, RRBSO remains the standard of care[4] and confers up to a 98% reduction in ovarian and fallopian tube cancer risk. Favourable effects of salpingo-oophorectomy include significantly reduced cancer-related worry in approximately 80% of BRCA1 and BRCA2 carriers and 95% satisfaction with their decision to undergo surgery.

RRBSO had previously been thought to reduce the risk of breast cancer in BRCA1 mutation carriers.[26] This has recently been challenged by a prospective study showing no protective effect of RRBSO on breast cancer risk in women with a BRCA1 mutation.[27] This study found that RRBSO reduces breast cancer risk in BRCA2 mutation carriers, but the effect of oophorectomy was only significant for breast cancer in BRCA2 mutation carriers diagnosed prior to age 50 years (age-adjusted HR=0.18, 95% CI=0.05 to 0.63, P=007).

The decision to perform hysterectomy at the time of RRBSO should be individualised. There are no data to support an increased risk of endometrial cancer in Australian BRCA1 mutation carriers, although there is limited evidence that serous histology may be more common.[28,29] Hysterectomy may rationalise subsequent MHT (by permitting oestrogen-only MHT), or the use of Tamoxifen for breast cancer chemoprevention or as adjuvant treatment of breast cancer, but it is not recommended for endometrial cancer prevention.[4]

Consideration needs to be given to the timing of RRBSO, even in the setting of elevated risk, given the potential harms of premature menopause. The NCCN and other guidelines recommend RRBSO once childbearing is complete: by age 35–40 years for BRCA1 and 40–45 years for BRCA2.[30]

Box 2. Referral guidelines for ovarian cancer risk assessment and consideration of genetic testing
(adapted from eviQ Referral guidelines for ovarian cancer risk assessment and consideration of genetic testing 2019 V.3).[35]

All of the people who fall into the categories below warrant a referral to a family cancer clinic for assessment.

Ovarian Cancer

- Untested adult blood relative of a person with an identified mutation in an ovarian cancer predisposition gene (e.g. BRCA1/2)

Tumour Pathology

Characteristics that warrant referral irrespective of other factors:

- Invasive grade 2/3 non-mucinous, epithelial ovarian, fallopian tube or primary peritoneal adenocarcinoma (regardless of age)
- Ovarian cancer that is MMR-deficient

For those with a personal history of cancer

- Individual characteristics that warrant referral irrespective of other factors:
- Invasive non-mucinous epithelial ovarian, fallopian tube or primary peritoneal cancer (regardless of age and grade) AND a close relative* with breast or ovarian cancer
- Invasive epithelial ovarian cancer (regardless of age, grade and subtype) including mucinous AND one of the following:
  - » a personal history of a second Lynch syndrome-associated cancer#
  - » a close relative with colorectal or endometrial cancer under the age of 50 years
  - » two or more close relatives with a Lynch syndrome-associated cancer#
- An individual with ovarian cancer in whom tumour testing has identified a somatic BRCA1 or BRCA2 mutation

For those with a family history of cancer

Characteristics sufficient to warrant referral irrespective of other factors:

- Close relative* with invasive epithelial ovarian, fallopian tube or primary peritoneal cancer AND an additional close relative* with one of the following:
  - » epithelial ovarian, fallopian tube or primary peritoneal cancer
  - » breast cancer or colorectal cancer under the age of 50 years
  - » endometrial cancer under the age of 50 years
- Three or more close relatives with a Lynch syndrome-associated cancer#

*close relative = 1st or 2nd degree

#Lynch syndrome-associated cancer includes adenocarcinoma of the colorectum, endometrium, small intestine, stomach, ovary or pancreas, urothelial carcinoma of the ureter or renal pelvis, cholangiocarcinoma, brain tumour, sebaceous gland tumour

Prior to RRBSO it is essential that women have been adequately counselled and have had sufficient time to consider surgery and its potential implications. In premenopausal women, referral to a menopause clinic prior to RRBSO is recommended. Informing the pathologist that the patient is at high risk for EOC is critical to ensure that the Serial and Extensive Sectioning of the FIMbrial end of the fallopian tube (SEE-FIM) pathology protocol is followed, otherwise occult carcinomas may be undiagnosed and untreated. Surgery by a gynaecologic oncologist who informed the pathologist that the woman was at high risk for EOC was independently associated with optimal RRBSO pathology in a prospective cohort study of women at high risk of pelvic serous cancer in the Australian kConFab cohort.[31] In this study, eligible women had RRBSO between 2008 and 2014 and their RRBSO surgical and pathology reports were reviewed. 'Adequate' surgery and pathology were defined as complete removal and paraffin embedding of all ovarian and extra-uterine fallopian tube tissue, respectively. Of 164 contemporary RRBSOs performed in 78 centres, 99% had 'adequate' surgery and 66% had 'adequate' pathology. Surgery performed by a gynaecologic oncologist rather than a general gynaecologist was independently associated with adequate pathology (OR 8.2, 95%CI [3.6–20.4], p < 0.001).

At the time of risk-reducing surgery, the following steps should be performed: a thorough inspection of the abdomen and pelvis to exclude macroscopic malignancy; peritoneal washings for cytology; at least 2 cm of the infundibulopelvic ligament resected to ensure that no residual ovary is left in situ; complete removal of tubes and fimbria; and the ovaries/tubes removed in separate Endo Catch bags in the event that an occult cancer is found. Histological examination should be according to the SEE-FIM protocol.[4,32]

The question of whether early bilateral salpingectomy alone with delayed bilateral oophorectomy may be an option for premenopausal women who want to delay surgical menopause has arisen following the discovery that most pelvic serous cancers originate in the fimbrial end of the fallopian tube.[33] Although this approach is increasingly being used, data regarding its safety and efficacy are lacking and bilateral salpingectomy with delayed oophorectomy should only be performed as part of a clinical trial. Microscopic tubal fimbriae adherent to ovaries were observed in three of 20 macroscopically-normal surgical specimens from high-risk women undergoing RRBSO.[34] If confirmed in larger studies, this finding challenges the concept of bilateral salpingectomy alone for risk-reducing surgery because the primary site of carcinogenesis may be left on the ovary and subsequently develop into a high-grade serous carcinoma.

Conclusion

Next-generation sequencing has led to the discovery of genes in addition to BRCA1/2 that are associated with increased EOC risk. However, the level of risk is not uniform, and knowledge of the cancer risks due to particular gene mutations is essential to provide appropriate advice and avoid inappropriate intervention. All women with non-mucinous high-grade EOC should be offered genetic testing. RRBSO is currently the only evidence-based strategy to reduce EOC mortality but may have negative effects on physical and psychosexual wellbeing. Decision making is complex, and patients require adequate time and psychological support to process information and consider their options. Discussion with a clinician with relevant expertise is essential when making decisions about the role, if any, of risk-reducing surgery for an individual woman.

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A full list of references is available online.

Basics of an IVF cycle

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The goal of ovarian stimulation in an IVF cycle is to obtain a certain number of oocytes that will enable the best probability of achieving a live birth, while minimising the risk of side effects to the woman, such as ovarian hyperstimulation syndrome (OHSS).[1,2]

This involves ovarian stimulation with gonadotrophins (recombinant or urinary forms) to recruit multiple dominant follicles. To prevent spontaneous ovulation cotreatment with some form of pituitary suppression is required such as a GnRH agonist or antagonist. When there are two or more leading follicles with a diameter 17–19 mm, an ovulation trigger is administered (hCG or GnRH agonist) and cumulus-oocyte complexes are collected transvaginally 36 hours later at the 'oocyte pick up' procedure. A fresh blastocyst (day 5 embryo) is transferred and any surplus embryos are then frozen for subsequent attempts.

Medications used for ovarian stimulation

Follicle stimulating hormone

The first recombinant human follicle stimulating hormone (r-hFSH) molecules received marketing approval in 1995 (follitropin alfa; trade name Gonal F) and 1996 (follitropin beta; trade name Puregon). These had better purity and less batch-to-batch inconsistency compared with urinary or pituitary derived FSH used prior.[1,3]

The recombinant forms of follitropin are produced using DNA technology. The main disparities between alpha and beta are in their chemical structure and the vectors of gene expression used. Despite the disparities between follitropin alfa and follitropin beta, results of head-to-head clinical studies and retrospective studies comparing the two products for ovarian stimulation in women undergoing IVF have shown no significant differences between the preparations in terms of efficacy or safety.

There are currently three forms of r-hFSH available: follitropin alpha, follitropin beta and follitropin delta (trade name Rekovelle). FSH has a relatively short biological half-life of about one day, necessitating daily administration. A biosimilar version of follitropin alpha, trade name Bemfola, is also available on the Australian Pharmaceutical Benefits Scheme (PBS).

There is a long acting r-hFSH preparation that is approved on the PBS, corifollitropin alpha or trade name Elonva. Due to its longer half-life, it can replace the first seven days of daily FSH therapy. In women receiving the 150 µg dose of Elonva, compared with daily administration r-hFSH, no significant differences in live birth rate were seen.[4,5] However, there was a higher cycle cancellation number due to overstimulation or under response in women with high ovarian reserve or poor responders respectively.

Human menopausal gonadotrophin

Human menopausal gonadotropin (hMG), which contains two components corresponding to FSH and LH, was first successfully extracted from the urine of postmenopausal women in 1950. Improved purification techniques with the use of FSH monoclonal antibody enabled the production of purified urinary FSH. In Australia, menotropins are available under the trade name Menopur, corresponding to FSH activity 75 IU and LH activity 75 IU.[6]

Luteinising hormone

Recombinant human LH (Lutotropin alpha, trade name Luveris) is available on the PBS. r-hLH is approved for use in women with severe LH and FSH deficiency, in combination with r-hFSH for instance in hypothalamic amenorrhoea. LH supports follicular recruitment and development in conjunction with FSH.[7] To improve convenience, a 2:1 fixed-ratio combination of r-hFSH and r-hLH has also been developed (trade name Pergoveris) which has been approved on the Australian PBS.

There is low-quality randomised controlled trial evidence in favour of adding LH in assisted reproductive technology (ART) therapy in patients of advanced age group to improve folliculogenesis.[7,8]

GnRH analogues

Pituitary down-regulation can be induced either with Gonadotropin release hormone antagonists (GnRHant) or agonists (GnRHa). GnRHant are short and immediate acting and have an antagonist effect on the pituitary GnRH receptor. This prevents premature ovulation by inhibiting the release of the FSH and LH surge that can occur as a result of positive feedback from rising serum E2 levels during the mid-follicular phase of an ovarian stimulation cycle. They can be started mid- to late-follicular phase and thereby reduce the total duration of stimulation required. There are two types, cetrorelix (brand Cetrotide) and ganirelix (brand Orgalutran) available on the PBS. They are administered in a subcutaneous injection.

GnRHa achieve pituitary down-regulation by continuous administration, which induces an initial flare effect due to gonadotrophin release followed by down-regulation due to the clustering and internalisation of the GnRH pituitary receptors. GnRHa long protocol requires a prolonged period of downregulation (usually two weeks) followed by FSH stimulation to induce multiple follicular growth. GnRH agonists can be administered as an intranasal spray (nafarelin, trade name Synarel) or subcutaneous injection (leuprorelin, trade name Lucrin or triptorelin, trade name Decapeptyl) or implant (zoladex).

Ovulatory trigger

Recombinant human chorionic gonadotropin (hCG) is used as a surrogate for the LH surge. It induces luteinisation of the granulosa cells, final oocyte maturation and resumption of meiosis prior to oocyte pick-up.

In the last few years, use of a GnRHa trigger in antagonist cycles has been increasingly used as a means to avoid OHSS. However, when GnRHa is used as a trigger, it causes a 'dysfunctional' luteal phase due to rapid luteolysis. This either warrants the need for cycle segmentation with a freeze-all-embryos approach or luteal phase rescue with hCG or high dose luteal support (intramuscular progesterone injections). This may be viewed as one of the downsides of using a GnRHa trigger.

Luteal phase support

The luteal phase in a standard cycle of IVF is 'dysfunctional'. The reasons for this are unclear, it is postulated to be related to destruction of granulosa cells during the oocyte pickup, administration of rhCG or supraphysiological E2 and P4 levels causing suppression of natural LH. It is therefore routine to supplement the luteal phase of an IVF cycle with progesterone. This is available in multiple preparations.

Vaginal progesterone pessaries are the mainstay because of their ease of use and equivalence to the intramuscular form. It is available in a tablet, suppository or 8% gel (Crinone).

Recently, a water-soluble injectable progesterone complex (Prolutex) has been developed for subcutaneous administration. A pharmacokinetic study of this compound demonstrated sufficient serum progesterone levels to allow clinical use in ART.[9]

There is no consensus on when to commence luteal phase support, it is administered anywhere between the day of oocyte retrieval to two days after.

Current protocols in ovarian stimulation

GnRH antagonist protocols

Currently in Australia, this is the most widely used stimulation cycle due to patient convenience as there is a shorter duration of stimulation. rFSH is commenced on cycle day 2. GnRHant is commenced on cycle day 6 when the leading follicle on ultrasound is 14 mm diameter. The trigger injection is given when two or more leading follicles measure 17–19 mm and oocyte pick up is performed 36 hours after trigger.

This cycle allows use of both rhCG and GnRHa trigger and has a significantly lower incidence of OHSS compared with the long agonist protocols.[10]

GnRH agonist protocols or 'long' protocol

Also called the long protocol, the pituitary is suppressed by commencement of a GnRha in the luteal phase of the preceding menstrual cycle. The agonist is continued until hCG trigger administration. The prolonged duration of treatment can be burdensome, but this cycle allows scheduling of IVF cycles with no adverse effects on pregnancy outcome.

GnRH agonist 'flare cycle' or 'short' protocol

In the short protocol, GnRHa is commenced on day 1 or 2 of the menstrual cycle. The aim is to use the initial flare effect of the GnRHa to increase recruitment of follicles, with commencement of rFSH day 3 of the cycle. A hCG trigger must be used prior to oocyte pick up. In practise, this cycle has been reserved for poor ovarian responders and is not suitable for those with high ovarian reserve due to the risk of OHSS.

Risk minimisation

The most important and potentially life-threatening complication of IVF remains OHSS. It comes with significant morbidity, including hospital admission and the need for invasive procedures such as paracentesis.[10] The use of a GnRHa trigger reduces the incidence of OHSS by more than 80% compared with a hCG trigger. The use of a GnRHant cycle compared to a GnRHa cycle also reduces the incidence of OHSS by 40%.[10,11]

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Early pregnancy

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Optimal ovulation is a sign of good health; not only of reproductive health but of all the body systems that contribute to reproductive function. Likewise, peak ovarian function contributes to optimal pregnancy outcomes.

A fully effective follicular and luteal phase relies on an intact hypothalamic-pituitary-ovarian axis which in turn acts on the endometrium, itself an endocrine-responsive organ. Under the influence of ovarian progesterone, the matured secretory endometrium allows for successful nidation of the blastocyst and placentation of the developing embryo.

Additionally, a complex interplay of many autocrine and paracrine factors (themselves mostly under the influence of pituitary or ovarian hormones) contribute to this highly refined implantation process [1] and remain the focus of ongoing research in the area of infertility, pregnancy loss, recurrent miscarriage and pre-eclampsia.

Luteal phase physiology

In the pre-ovulatory dominant follicle, the granulosa cells become enlarged and vacuolated (under the influence of adequate FSH, aromatisation of androgens and resultant rising oestrogens) later to become the large cells of the corpus luteum.

At ovulation the theca lutein cells, previously surrounding the dominant follicle, migrate into the developing corpus luteum and become the small cells in the steroidogenesis of the luteal phase.

In this two-cell theory, LH, and subsequently HCG, act on the small cell receptors to signal the large cells (devoid of LH and HCG receptors) through gap junctions to produce the bulk of progesterone, oestradiol, inhibin-A and PGF2a.[2]

Therefore, the large (granulosa-lutein) cells respond to auto- and paracrine-acting peptides ensuring a basal level of progesterone and the small (theca-lutein) cells respond to central LH stimulation. This may account for the apparent stability and reproducibility of integrated progesterone serum profiles drawn in subsequent and more recent studies describing the luteal phase profile of hormones.[3]

Ovarian production of vascular endothelial growth factor (VEGF) allows for potent angiogenesis, neovascularisation of the corpus luteum and dissemination of ovarian hormones systemically.

Luteal phase defect

The existence of a luteal phase defect is reported extensively in the ART literature, thought to be due to the supraphysiological hormonal levels and their impact on LH secretion. As a consequence, luteal phase support is routinely provided, usually as progesterone therapy in early pregnancy; the dosage, duration and method continue to be researched.[4]

Despite being described in infertile women by Jones in 1949, there remains no clear diagnostic criteria or validated clinical solution.[5] The only small RCT for progesterone support of the luteal phase in natural subfertile cycles was conducted in 1982.[6] Lower integrated serum levels of luteal progesterone have been reported in young women establishing regular cycles, PCOS, stress cycles, athletes, and perimenopausal women, all of whom have higher rates of adverse early pregnancy outcomes.

The hypothesis that some subfertile women have pre-existing ovulatory and/or luteal phase dysfunction and may benefit from early pregnancy supplementation is the topic of some of this author's randomised-controlled clinical trials.

Tubal transport

Tubal peristalsis and ciliary induced flow of secretory fluid and subsequent conceptus transport is dependent on ovarian progesterone, and prostaglandin F2a. Progestins, on the other hand, impair tubal transport. Ectopic pregnancies arise when embryonic transport is impaired by physical or hormonal factors.[7]

A recent case series was presented of 42 nulliparous women with a history of both miscarriage and ectopic pregnancy alone, of whom 28 underwent luteal hormone profiles. There was evidence of ovulatory dysfunction in 71.4% (n=20) of these women's cycles.[8]

Implantation

Progesterone is the primary endocrine requirement for a mature secretory endometrium, which is rich in glycogen and lipids for initial diffusion to the developing embryo. Additionally, progesterone creates a balanced pro- and anti-inflammatory cytokine environment through progesterone-induced blocking factor (PIBF),

it induces the formation of pinopodes aiding blastocyst attachment, and allows for IGF Binding Protein-1, which limits trophoblast invasion while simultaneously limiting endometrial growth.

Placentation

In early pregnancy, embryonic HCG and then maternal HCG 'rescues' the corpus luteum from its somewhat preprogramed demise. Along with local prostaglandin E2, HCG is luteotropic, allowing oestradiol and progesterone levels to rise above peak luteal levels further supporting the myriad of growth factors, cytokines and enzymes involved with trophoblast adhesion, invasion and limitation.

Placental hormonal shift

Progesterone is largely produced by the corpus luteum until about 10 weeks gestation. The placenta begins production at 7 weeks and continues to increase production surpassing the ongoing, but less significant, corpus luteal production. This shift is often seen as a slight initial fall in serum progesterone levels.

It is worth noting the location of the corpus luteum of any pregnant woman in her first trimester who may need laparoscopic surgery for a cyst accident, cystectomy, torsion or oopexy. Progesterone supplementation (100 mg daily as a minimum) should be given serious consideration if the ipsilateral ovary is impacted.

Miscarriage

Human experience and animal models show significant to universal miscarriage rates when the corpus luteum is surgically excised in early pregnancy, giving suboptimal progesterone levels.[9] Low serum progesterone has been shown to be an independent risk factor for miscarriage in women with no obvious risk factors for pregnancy loss.[10] A recent Cochrane review has found that giving progesterone supplementation early in a pregnancy of women with recurrent miscarriage of unknown aetiology may help.[11]

Threatened miscarriage

Women who experience a threatened miscarriage are at significantly increased risk of adverse pregnancy outcomes including antepartum haemorrhage, preterm delivery, perinatal mortality and low-birthweight babies. Whether hormonal support corrects these outcomes is unknown. A recent Cochrane review suggested progestogens are probably effective in the treatment of threatened miscarriage, but may have little or no effect on the rate of preterm birth.[12] This review did not include a very large study[13] that found progesterone made no difference except, upon subgroup analysis, in those with a prior recurrent miscarriage history.

For future awareness

Recent research has shown that some endocrine-disrupting chemicals (EDCs) can impair key processes in ovarian development and disrupt steroid hormone levels in women.[14] The EDCs with the most evidence are bisphenol-A (BPA), found in clear, tough plastics, and phthalates (plasticizers). Exposure to such exogenous compounds can mimic or antagonise ovarian function, particularly increasing follicular atresia/apoptosis and corpus luteolysis.

Additionally, BPA has been shown to attenuate steroidogenic gene expression in placental cells and decrease pregnancy progesterone levels.

Summary

Ovulation and continued corpus luteal function is critical for early pregnancy. The dominant luteal hormone, progesterone, orchestrates much of the early activity for the success of pregnancy. Luteal support by way of progesterone is required for ART pregnancies. Natural conception pregnancies may benefit from progesterone support, in some circumstances. Exposure to endocrine-disrupting chemicals may impact on ovarian function in the early pregnancy.

Further research needs to be given to inadequate function of the ovary at the crucial time point of early pregnancy and into the longer-term outcomes. Ovarian biology in early pregnancy is likely to have a role to play in the developmental origins of health and disease.

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The evolutionary paradox of PCOS

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In 1935, Irving Stein and Michael Leventhal first described a series of seven women sharing the features of a clinical triad of polycystic ovaries, hirsutism and irregular or absent menses.[1] In the 85 years since this publication, the condition which came to bear their name has become the commonest cause of anovulatory infertility globally, affecting one in every 7–17 of all women,[2] and is an important driver of the $32 billion global infertility treatment industry.[3] Renamed, the polycystic ovary syndrome (PCOS) is now the subject of more than 4000 scientific publications annually,[2] evidence of an intense effort to unravel the complex problems of definition, fundamental physiology and genetics, the effectiveness of treatment and the association of this condition with metabolic disturbance, cardiovascular disease and cancer.

PCOS has also attracted the close attention of evolutionary biologists, drawn to the exquisite evolutionary paradox that the condition represents – a very common and highly heritable condition that affects all human populations, and is an important global cause of infertility. They are also drawn to the curious phenotypic juxtaposition in PCOS of metabolic and reproductive traits. This is because in evolutionary biology, resource availability, procurement and allocation play a large part in shaping reproductive success and somatic evolution.[4-6] As Darwin famously said, this struggle for resources, and indeed existence, applies with 'manifold force to the whole animal and vegetable kingdoms.'[7]

RA Fisher, one of the architects of the modern synthesis of the theory of evolution, devoted an entire chapter of his seminal book, *The Genetical Theory of Natural Selection*,[8] to the power of fertility selection; selection based upon the differential effects of genes on fertility:

> 'The intensity of fertility selection is sufficient to produce considerable evolutionary changes in relatively short periods.'

Accordingly, fertility selection, if unimpeded, should act swiftly to reduce the prevalence of the genetic determinants of PCOS.

Speculation as to why this has not occurred and why PCOS is so common has been imaginative and agile, and the subject of several reviews.[9-12] These evolutionary hypotheses can be grouped as responses to fundamental questions about any biological trait: are they due to phylogeny, growth and development, or adaptation?[13]

Phylogenetic analyses of PCOS vulnerability are rare. Barnett has proposed that successful female reproductive adaptations to accommodate the growth demands of large-brained primate fetuses – pre-implantation endometrial proliferation and a rapidly invading placenta – have facilitated a particular vulnerability of higher primates to hypergonadotropic disruption of ovulatory function, as found in PCOS.[14] Another interesting analysis of global genotypic and phenotypic variation in PCOS has suggested that an intralocus sexual conflict, (that is, a fertility disadvantage in women balanced by a fertility advantage in men) may be present in humans and their hominid ancestors.[15]

Developmental programming of the hypothalamic–pituitary control of LH by in utero and prepubertal exposure to androgens enhances visceral fat distribution.[16] In challenging nutritional environments, this mechanism may confer survival and fertility benefits for the infant such as increased fat storage and increased follicular readiness in adulthood.[17]

Hypotheses that imagine the selective advantages in ancient times of the PCOS phenotype abound.[17-23] They include: kin selection,[23] delayed menopause,[20] increased muscularity and resistance to infection,[19] and, most commonly, the fertility benefits of insulin resistance and a relative hyperinsulinaemia.[10,17,18,21,24,25] These metabolic traits have been shown to foreshorten the duration of lactational amenorrhoea,[6] which was the most important determinant of lifetime reproductive success in hunter-gatherer and agrarian populations.[26]

Conversely, PCOS evolution need not have been driven by adaptive evolutionary mechanisms. Genetic drift due to a serial founder effect and population balance due to sexually antagonistic selection could equally account for contemporary PCOS patterns of occurrence.[9,11]

Notwithstanding this abundance of ideas, there is general agreement that whatever the genetic legacy of our pre-industrial past, the modern phenotype has come about because of a profound mismatch between traits that have evolved to optimise fertility and survival in ancient times with modern energetic and living conditions.[9] In the ancient world, average BMI of women was 18–21, total fertility rate was 6–7 births per woman and births were highly seasonal and tightly linked to rainfall, agricultural cycles and the price of grain. The unprecedented changes in

average body weight, fertility and mortality, caloric intake and average levels of physical activity began in Western Europe over 200 years ago and now apply to more than 80% of the world's population.[10,18]

There are two issues underpinning these hypotheses that need to be critically examined.

The first is whether there are ethnic differences in PCOS occurrence. Many of these hypotheses are premised on a view that prevalence is unvarying in human populations. Ethnic differences in disease incidence and prevalence have been used to infer adaptation to secular or geographic differences in environmental exposures or living conditions. The most pertinent example is the striking ethnic differences seen in the occurrence of type 2 diabetes with increasing body weight.[27,28] Explanations for this hierarchy of susceptibility, and in particular the comparatively low prevalence in people of European descent, have included the duration of exposure to an agrarian, rather than a hunter-gatherer, diet, the length of time elapsed since nutritional and demographic transition, and monsoon-driven agricultural cycles.

It is unclear whether PCOS mirrors this pattern of difference, and in particular, the relative steepness of the rise in prevalence with increasing body weight. A recent review concluded that PCOS prevalence was lower in Asians compared to Europeans and Africans, and that Indigenous Australians had a very high prevalence of the disease.[29] However, these comparisons are beset with the following problems of measurement error and bias:

- The paucity of population-based estimates of PCOS prevalence and referral bias in clinic-based studies.
- The inclusion of hirsutism as one of the diagnostic criteria potentially underestimates PCOS prevalence in Asian women.[30]
- The almost complete absence of estimates of prevalence in women with a BMI less than 20 limits any meaningful comparison with average body weight in the past.
- Changes in diagnostic criteria limit the ability to meaningfully compare prevalence studies over time.

The second is whether there is any evidence in contemporary populations of selection against the PCOS phenotype. Genetically based differences in lifetime reproductive success (LRS), or number of births per woman per lifetime, is a precondition for selection on the basis of fertility to occur. The cumulative probability of childbirth and the proportion achieving desired family size in women with PCOS over the longer term might be similar to that in women without PCOS;[31-33] however, there are differences in parity and LRS. A recent large study using linked population data in Sweden and a clinical diagnosis rather than self-reported symptoms enabled precise estimation of LRS.[33] Women with and without PCOS had an LRS of 0.8 births compared to 0.9 births per woman per lifetime, respectively. Furthermore, LRS differences were likely to be greater in women who did not undergo fertility treatment. While these differences may seem modest, they translate into a negative or purifying selection intensity of 10% per generation and, if sustained, would rapidly diminish the prevalence of the genetic determinants of PCOS. But even if rapid natural or purifying fertility selection against a PCOS phenotype had been happening over the last 1–200 years, it would have been tempered by the speed with which average body weight, and therefore expression of the PCOS phenotype, had been increasing.

Evolutionary medicine is a relatively new field that recognises that diseases need both proximate explanations of bodily mechanisms and evolutionary explanations of why natural selection has left the body vulnerable to disease. The insights gained have already contributed to important developments in the application of phylogenetics to biology of pathogen resistance and population genetics, and hold much promise in areas such as cancer and infectious disease control, reproductive medicine and public health.[34]

The puzzle of the evolutionary paradox of PCOS remains unsolved, but evolutionary speculation suggests that studies which elucidate the physiology and epidemiology of insulin resistance and fertility in natural fertility populations may point to a solution. These studies may also help to resolve the question as to whether prolonged breastfeeding mitigates the risk of the development of subsequent type 2 diabetes in women with gestational diabetes.

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A full list of references is available online.

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Q&A

For the broader *O&G Magazine* readership, balanced answers to those curly-yet-common questions in obstetrics and gynaecology.

Q Midway through a vaginal hysterectomy you are having trouble accessing the top pedicle due to uterine size. How can the uterus be safely morcellated to complete the procedure?

Dr Graeme Dennerstein
FRCOG, FRANZCOG

A

There is nothing new about vaginal hysterectomy (VH) with morcellation. It was widely practiced in Europe in the late 1800s because it was safer than laparotomy.[1] However, no one taught me how to morcellate a uterus at VH, so I had to develop the technique myself over the decades. My VH technique – or more correctly, that of the late AG Bond – I have already published in this magazine[2] and presented on Climate[3] and should be read in conjunction with this account. Box 1 is an extract of a pathology report on a recent, typical case of morcellation with VH. The patient could have gone home the next day had she not been living in a rural area. Fibroids and/or adenomyosis are the commonest causes of the need to morcellate.

As in the case in question, the usual indication to morcellate a uterus at VH is inability or difficulty reaching the third (and last) uterine pedicle (broad, ovarian and round ligaments and fallopian tube)

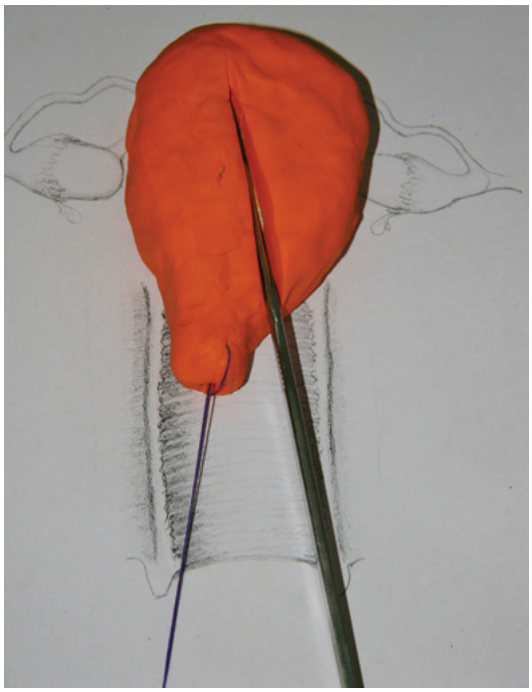

Figure 1. With the assistant pulling the cervix to the patient's right, make an incision to the uterine body to the left of the midline through to the back of the uterus and down to the vagina.

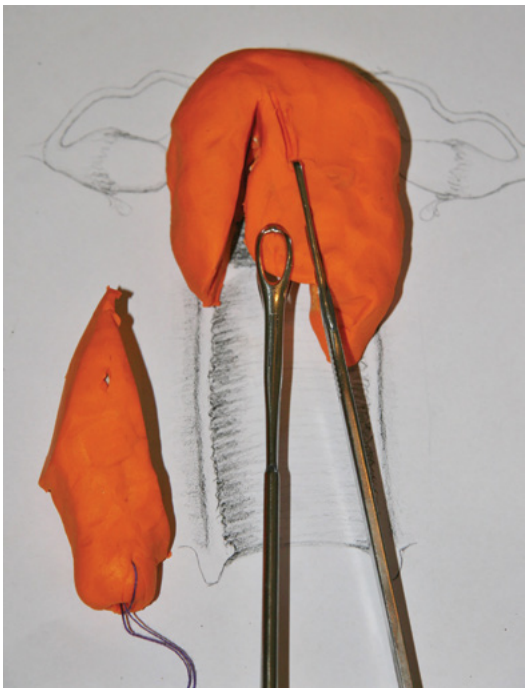

Figure 2. The cervix has been removed and the remaining uterus is pulled down with Morrison's forceps, enabling further excision towards the fundus.

Box 1. Extract of a pathology report on a recent, typical case of morcellation with VH

Macroscopy

Specimen received: uterus

- Integrity: piecemeal
- Size: 150 x 80 x 70 mm in aggregate
- Weight: 280 g
- Cervix: 35 x 30 mm with a narrow os 2 mm
- External gross description of uterus: difficult to assess
- Myometrium: 27 mm with multiple white whorled ovoid intramural, subserosal and submucosal nodules up to 45 mm, without areas of haemorrhage or necrosis
- Endometrial cavity: difficult to assess
- Endometrium: 1 mm

Conclusion

Uterus plus fibroid: Benign leiomyomata and adenomyosis

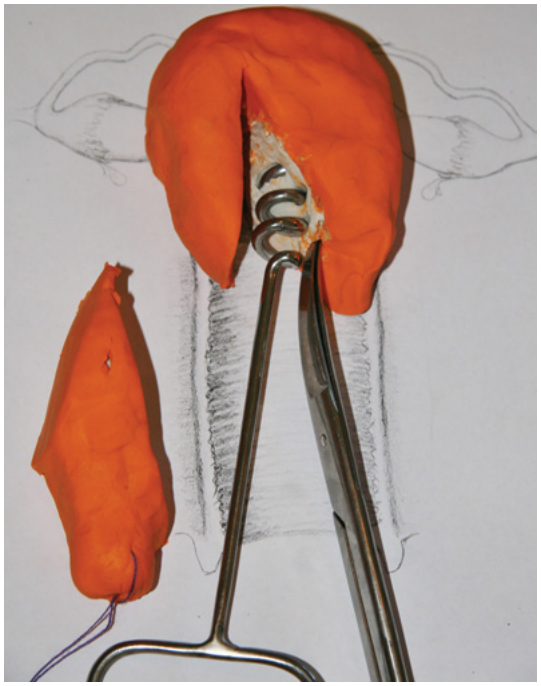

Figure 3. If a fibroid is exposed, a vaginal myoma screw can be used to enucleate the fibroid.

due to uterine size. Morcellation should not be considered until both uterine arteries (second pedicle) are ligated and divided. If this latter stage cannot be completed, an approach from above is the safest course of action.

With the assistant pulling the cervix to the patient's right, an incision is made in the uterine body to the left of the midline through to the back of the uterus and down to the vagina (Figure 1). The scalpel blade should be visible while in use – blind cutting is to be avoided. Next, with the assistant (or scrub nurse) pulling the cervix to the patient's left, a symmetrical incision is made through the uterus to the right of the midline. It is a bonus if this enables bisection of the uterus, because one side can be pushed up enabling easy access to the last pedicle. Failing bisection, accessible uterus can then be grabbed with Morrison's forceps (Figure 2) or, if a fibroid is exposed, a vaginal myoma screw (Figure 3) and the fibroid can then be enucleated. This enables excision of further uterine tissue and is repeated until the uterus is bisected and managed as above or the final uterine pedicle becomes accessible.

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ANZJOG: writing, reviewing and beyond

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Writing and researching

The *ANZJOG* Author Guidelines are freely available online. Please read these Guidelines, preferably before you start your research and certainly before writing up that research, if you are considering submitting to *ANZJOG*. We are looking for novel research findings, not necessarily complex or requiring massive laboratory or funding backup.

Please note that we do not publish case reports, and that most Reviews (systematic or short) are invited by the Editor – if you have a brilliant idea please send an email to the Editor before embarking on your review (if you plan to send it to us). We also publish Opinions and Letters – these are peer-reviewed and appear on PubMed and other databases.

Make sure you have appropriate ethical approval for your research, as per the Author Guidelines. Even if your research is likely to be low-risk or is an audit, a statement from an ethics committee confirming that formal approval can be waived is necessary. Consider, too, any conflicts of interest among your researchers.

Think carefully whether your topic is suitable for *ANZJOG*, which is a clinical journal (no rats, no complex biochemistry). We have an enormous backlog of obstetric original articles, so accepted articles on gynaecology, reproductive endocrinology and infertility, and sexual and reproductive health topics are likely to be published sooner (note this does not mean they are more likely to be accepted for publication – all submissions follow the same peer-review process). Likewise, Short Communications and Letters to the Editor are more likely to be published sooner.

A maximum of 2500 words and 25–30 references does not mean that these need to be achieved – less can be better. Consider whether you need tables and figures – are these clear? Think about your readers – clinical obstetricians and gynaecologists, GP obstetricians and trainees. Write in clear concise English, with UK spelling, correct grammar and full sentences. Consult our guidelines for abbreviations and references; we use the Vancouver system.

The Editorial Board consists of myself and 15 Associate Editors (AEs). I review all submissions, and make an immediate decision: reject, send for review by an AE, or doubtful (the latter is usually discussed with an AE). I also act as an AE.

If the manuscript is sent to an AE, it may be immediately rejected, but most are sent for review, blinded, to at least two reviewers. It can be very difficult and time-consuming to find reviewers – they are experts in their field, often very busy, and often asked to review.

Sometimes reviews are conflicting, or the AE disagrees, or the reviewer doesn't complete the review. While we aim to get a decision back to authors within six weeks, this is not always possible; sometimes up to 20 possible reviewers have to be approached before two suitable people are found and agree to timely review. If we are experiencing particular difficulty with finding reviewers, we will write to authors to tell them this.

You are able to indicate reviewers you are opposed to and we will observe these requests. You can also recommend reviewers, but these will not always be used by AEs who may consider them unsuitable. Reviewers are always blinded to authors and vice versa.

We are very grateful to those reviewers who review consistently for us and on time. They do this voluntarily, so all published authors should be prepared to review. And clinicians are as important as academics for this: remember that the majority of our readers are clinicians.

Good luck!

– Caroline de Costa

Reviewing

As AEs and reviewers, our roles are to facilitate and provide peer review, constructive feedback and publication recommendations for submissions. This is to ensure manuscripts are relevant and at the required standard for publication, while assisting authors to reach these standards where possible. When reviewing a manuscript, there are six key questions we need to answer:

1. Does this manuscript address a clearly focused issue or stated hypothesis, with the results relevant to the focus/hypothesis?
2. Do you have statistical concerns about this manuscript?
3. Do you have ethical concerns about this manuscript?
4. Is the referencing up-to-date and appropriate?
5. Are the conclusions drawn warranted from the data and its interpretation?
6. Is the language acceptable?

As mentioned, all AEs and reviewers are busy clinicians and/or academics. To assist them to answer these questions and increase the likelihood of your manuscript being accepted, there are a number of helpful strategies. Many of these strategies start at the early stages of planning the study and resulting manuscript prior to conducting the study:

- When you have an idea for a study, perform a rapid review of the literature, using keywords and literature search engines, such as Google Scholar or Pubmed, to help clarify your hypothesis, the question your study will attempt to answer and the need to answer this question. For most studies, the PI(C)O approach: Population, Intervention (+/- Comparator), Outcome, will help define your question. Keep a record of search terms and relevant papers to assist with referencing as you go.
- State your hypothesis and define a primary objective for your study.
- Consider and choose the most suitable study methodology, both from a scientific rigour and feasibility perspective, to assess your question, hypothesis and achieve your objective.
- At an early stage, seek advice from a statistician to develop a statistical analysis plan and, when appropriate, from a qualitative researcher to inform your methods and analysis. Such advice is enormously helpful in clarifying your question and ensuring the study design is able to answer that question.
- Discuss your study with your local ethics office to confirm whether an approval is required or waiver sufficient, prior to collecting data. If submitting for ethics review, waiver or quality audit approval, make full use of the quality audit or ethics submission processes, templates and checklists. Every institution will have a different form, but examples of templates are:
  - » Study protocol template: www.westernhealth.org.au/EducationandResearch/Research/Documents/LNR%20Protocol%20Template.doc
  - » Quality Assurance Project checklist: www.westernhealth.org.au/EducationandResearch/Research/Documents/WH%20QA%20Checklist%20and%20Site%20Specific%20Form.docx

  While the process may appear onerous, it will assist in designing the study, writing the protocol and ensuring your study has met the ethics approval standard required for publication.
- Start writing the manuscript at the beginning of the study design. As you progress through the question formulation (introduction and hypothesis), design (aims, methods and results format), approval (ethics statement), data collection and analysis (results) phases, you will be left with only the discussion and conclusions.
- The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network (www.equator-network.org) has reporting guidelines for the publication of most study types. These guidelines will inform the required elements of your study design and what to include in your manuscript.
- When writing the discussion, a suggested format is:
  - » Summary of key findings in relation to the objectives
  - » Discussion of interpretation and the implications of findings
  - » Statement of the strengths and limitations of the findings and study design
  - » Recommendations for future work
- In the conclusion, avoid overstating the significance and implications of your study results, keeping them consistent with the methods and limitations of the design.
- Be sure to reference any relevant papers as you go, to support statements made, acknowledge sources and minimise the risk of plagiarism.
- Asking a third party with a fresh pair of eyes to proofread your manuscript may help identify any issues prior to submission, including flow, terminology, grammar and punctuation. If English is not your first language, it will also help to have that third party be a native English speaker who works in the clinical field.
- Hopefully with careful planning, good advice and support, we can look forward to accepting your next manuscript.

– Oliver Daly

Communicating your research

While citations are an important metric of your research's impact, there are many other ways in which you can make sure your research gets read and informs practice. Altmetrics.com, for example, measures citations on Wikipedia and in public policy documents, discussions on research blogs, mainstream media coverage, and mentions on social networks, such as Twitter, to determine a journal article's impact.

Here are some alternative ways in which you can promote your research to a broader audience:

- **Do a conference presentation:** conferences like RANZCOG's Annual Scientific Meeting are a great space to share your findings with your peers and make sure that your research informs practice. They are also a great space to hold discussions and get feedback from others in your field and provide fantastic networking opportunities.

- **Submit a press release:** RANZCOG has an affiliation with the Australia Science Media Centre, an online news portal for journalists with more than 1500 reporters subscribed. Journalists often visit this site to find stories, so if your research is featured here, your chances that it will get picked up by the media increase. RANZCOG is more than happy to help you write and publish press releases in Scimex. If your academic article has recently been accepted for publication in *ANZJOG*, contact the communications team: media@ranzcog.edu.au.
- **Write a media article:** You don't have to wait until a news outlet decides to pick up and publish your research. Outlets like The Conversation accept submissions from academics, which gives you the freedom to write your article with your own voice and ensure precision and accuracy. News outlets often republish The Conversation articles, which means your research's reach will be significant.
- **Provide media commentary:** If writing for the media is not your thing, you can still provide media commentary. Journalists are always looking to fact-check their stories and, as an expert in your research field, who better to do this than you? List your contact details in the Australia Science Media Centre to make yourself available. Feeling unsure about how to talk to media? Come to the next RANZCOG's media training session at the ASM.
- **Share your research on social media:** Social media is a great way to start conversations and share your findings with the broader community. Tag and follow *ANZJOG* and RANZCOG on Twitter. We will retweet your research when possible to make sure it reaches a wider audience.

Research informs practice and moves our specialty forward, but the only way it can do this is if it is communicated with others. While publishing in an academic journal is a great step that provides you with credibility and prestige, publishing in media and social media will make sure your work reaches a broader audience that includes not only academics, but fellow clinicians and women and their families, informing practice and health education on a wider scale.

– Lourdes Zamanillo

Open Research

Research publishing is undergoing a transformation and among the biggest drivers of this are Open Research practices. These practices are having a significant impact on the way that researchers conduct research, write papers and publish their results, and are often grouped into the following 'pillars' of open research practices:

Open Access

Driven by the need for research to be widely available to drive adoption, innovation and invention, we are currently seeing a significant push towards Open Access publishing and away from more traditional journal subscription models. There are two main ways research can be made available under Open Access terms, which encompass both an access element, as well as a copyright element:

Green: Published under a regular copyright agreement in a subscription journal and made freely available on an institutional/subject repository after an embargo period.

Gold: Published under a Creative Commons license and made freely available immediately upon publication in either a fully Open Access journal or within an otherwise subscription-based journal.

Open data

Research data is as important as the published article. When data is FAIR (findable, accessible, interoperable and reusable), the research process becomes more efficient and robust. Data can be used to analyse and reproduce findings, or can be reused and built upon to inform new studies.

Open practices

Open practices encourage transparency throughout the publishing process and include initiatives such as open peer review and the increased use of preprint servers. Sharing how and why we make decisions holds us accountable for our actions and builds trust within our communities, producing results that others can build on. Examples include:

Registered reports: Enabling peer review prior to data collection, emphasising the importance of the research question and the methods. High-quality studies are provisionally accepted, eliminating questionable research practices and publication bias. Preprint servers: Researchers use preprints to accelerate science. Researchers can 'preprint' their work on a preprint server before they submit it to a journal for peer review.

Transparent peer review: The identity of the author and the reviewers are known by all participants. A growing minority of journals do this.

Open collaboration

Online tools to help researchers collaborate with co-authors during the writing process, online annotation and personal article libraries, article sharing guidelines and support. These tools will be essential as collaboration continues to increase. When collaboration is easy, researchers can focus on the impact of their research, instead of the process, strengthening their networks and creating the best possible outcome for their findings.

Open recognition and reward

Researchers and academics are constantly under pressure to demonstrate and celebrate the impact of research, and tools are emerging to manage, report on and increase this impact. Academics can get credit for peer review work through Publons, use Kudos and Altmetric to help measure impact and validate identities with ORCiD, while Open Research Badges help gain recognition for taking advantage of the open practices outlined here, such as data sharing and Registered Reports.

– Simon Goudie

Case reports

Massive haemorrhage with rare Kidd antibody

Dr Anuradha Mahadik
MD, MRCOG, FRANZCOG

Dr Renee Eslick
FRACP, FRCPA, B Med

Dr Lisa Clarke
MBBS, FRACP, FRCPA, MEPi
Haematologist, Australian Red Cross Blood Service

A 39-year-old, G4P2 (two natural vaginal births), patient with placenta praevia, unbooked, was brought in by an ambulance to a hospital with level 4 nursery, with major antepartum haemorrhage at 32+2/40, which was provoked by coitus. The estimated blood loss prior to arrival in hospital was 1.5 L. This was her second bleed following a small sentinel bleed prior to 30 weeks. She was fluid resuscitated and vaginal bleeding settled on arrival to hospital. On assessment, she had mild tightenings but had no active bleeding on speculum exam. She was hemodynamically stable, with a blood pressure of 108/72 and heart rate of 100, and the CTG showed a reassuring fetal trace.

Intravenous access was secured and fluid resuscitation with 3 L of crystalloid was commenced. A group and screen was requested on arrival, which detected the presence of red cell antibodies. The blood bank issued a warning that delays in obtaining crossmatched blood may occur. She was administered 11.4 mg betamethasone and commenced on a $MgSO_4$ infusion. A plan was made for immediate transfer to a tertiary hospital prior to delivery; however, she developed recurrent moderate PV bleeding accompanied by mild tachycardia and borderline hypotension of 90/50. A plan was therefore made to undergo an emergency caesarean section (CS), with neonatal resuscitation and tertiary transfer following delivery. The Newborn Emergency Transport Service (NETS) was contacted preoperatively in anticipation of the neonate needing possible resuscitation and tertiary transfer.

The emergency CS was conducted under general anaesthesia, with a floppy neonate delivered after seven minutes. Intraoperatively, the placenta was found to be focally adherent with ongoing brisk bleeding after manual removal. There was significant uterine atony. The intra-operative blood loss was estimated to be 2.5 L, with a total estimated blood loss of 4 L. The postpartum haemorrhage did not respond to conservative measures including use of oxytocin, ergometrine, Dienoprost, placental bed sutures and use of Bakri balloon. The patient ultimately required a hysterectomy due to hemodynamic instability and ongoing uncontrolled blood loss.

A massive transfusion protocol was activated, and the patient was given 10 units of cryoprecipitate, two units of fresh frozen plasma and 1 g intravenous tranexamic acid. However, she was found to have a panagglutinin alloantibody, which rendered her incompatible to all red cells in the blood bank, causing a lengthy crossmatch delay of over 60 minutes. Her haemoglobin fell to 37 g/L with metabolic acidosis, and she required metaraminol and intravenous crystalloids to maintain her systolic blood pressure. She was eventually transfused four units of incompatible blood, with no immediate adverse reaction. Subsequent testing found she had a very rare blood group, Jk null, with anti-Jk3 antibodies. She had a mild delayed haemolytic transfusion reaction postoperatively, but did not develop life-threatening intravascular haemolysis.

A floppy male infant weighing 2116 grams was delivered with outlet forceps with Apgars of 2, 8 and 10. He initially required intermittent positive pressure ventilation and chest compressions for resuscitation and was transitioned to continuous positive airways pressure. Further desaturations prompted intubation and NETS transfer to tertiary hospital. The baby was transferred back to base hospital on day 9 of life and discharged home on day 27 of life. He did not have any features suggestive of haemolytic disease of the newborn and has had no significant complications since.

Discussion

The Kidd blood group system was discovered in 1951 and is composed of two antithetical antigens, Jka and Jkb, along with a third high-incidence antigen, Jk3.[1] Jk null, also known as Jk(a-b-), is a very rare blood group where patients lack all Kidd antigens. Jk is a urea transporter found within the renal medulla, and Jk null individuals are unable to maximally concentrate urine.[4] If these individuals are exposed to the Jk antigen through transfusion or pregnancy, they are capable of producing antibodies directed against the high-incidence Jk3 antigen. This has serious clinical implications and renders transfusion extremely difficult, as Jk3 is expressed in over 99% of the Australian blood donor pool.

The Jk null phenotype is extremely rare in most ethnic groups, although is reported to be slightly more

frequent in Polynesians, with an estimated incidence of 0.1–1.4%.[4] In Tonga, where our patient was born, the prevalence of the Jk null phenotype is 1.2% .[2]

Kidd antibodies, including those directed against Jk3, are considered to be clinically significant. They may cause acute and delayed haemolytic reactions as well as haemolytic disease of the fetus and newborn (HDFN).[2] To further complicate matters, these antibodies are often present at very low levels and may be difficult to detect. Antibody identification can be delayed due to the need for specialised testing at a Red Cell Reference Service Laboratory.

Jk antigens have been detected on fetal red cells from 7–11 weeks gestation.[4] Given the rarity of anti-Jk3 antibodies in pregnancy, there is limited published experience with HDFN. The largest case series of four maternity patients with anti-Jk3 antibodies described two neonates affected by mild to moderate HDFN, and two unaffected pregnancies.[2] There are other case reports of mild HDFN reported in the literature due to maternal anti-Jk3 antibodies.[6] All affected neonates were successfully managed with phototherapy, with no transfusion required.

In contrast, although rare, several life-threatening cases of intravascular haemolysis have occurred in patients with anti-Jk3 antibodies following transfusion with incompatible blood,[5] and fatal cases have been described. Successful treatment of intravascular haemolysis with therapeutic plasma exchange has been reported.[3] Mild delayed haemolytic transfusion reactions have also been reported. As there is no way of predicting the severity of the haemolytic transfusion reaction, giving compatible blood is strongly preferred. In our case, incompatible blood was administered as an immediate lifesaving measure due to the imminent risk of exsanguination.

Without prior knowledge of this antibody, finding compatible blood in an emergency transfusion setting is almost impossible. If the antibody is detected on antenatal screening, Australian Red Cross Lifeblood is able to source compatible units by contacting known Jk null donors, arranging directed donations or thawing frozen units. Close liaison between the blood bank, haematology and obstetrics is vital in order to ensure compatible blood products are available in the event of a life-threatening haemorrhage.

Lessons learned

Jk null is a rare blood group, although its prevalence is increased in Polynesians. Anti Jk-3 antibodies can cause substantial delay in obtaining compatible blood, have the potential to cause life-threatening transfusion reactions, and have also been linked to HDFN. This case highlights the critical importance of obtaining an antenatal antibody screen, particularly in women with risk factors for obstetric haemorrhage. Early detection of antibodies and close liaison with the blood bank are paramount to prevent potentially catastrophic situations.

Dr Lisa Clarke's commentary on transfusing in the context of a rare red cell alloantibody in the obstetric setting

Red cell alloantibodies can cause haemolytic transfusion reactions and, in the obstetric setting, haemolytic disease of the fetus and newborn. These form in response to exposure to red cell antigens, through pregnancies or transfusion, which are not found on the woman's red cells. The presence of alloantibodies is uncommon, occurring in less than 2%[7] of the population, and are not always clinically significant; identification is therefore imperative to facilitate 'safe' transfusion should it be required. This process can be time consuming, particularly in the presence of a rare red cell alloantibody and challenging outside of a reference laboratory. So, while the provision of antigen negative blood is desirable for all patients with antibodies, the Australian New Zealand Society of Blood Transfusion recommends abandoning this at times of 'massive blood loss if it will result in a delay in the provision of blood products'.[8]

As the majority of postpartum haemorrhages occur in the absence of identifiable risk factors, women who have alloantibodies identified prenatally should be optimised as per the principals of patient blood management. Those with rare alloantibodies require a transfusion strategy established by the obstetric and haematology teams in collaboration with The Australian Red Cross Lifeblood (Lifeblood).

In most instances when rare blood is required, Lifeblood can source a limited supply of fresh or frozen rare red cells from directed donations or national and/or international donors. There are several limitations to these options. Firstly, these units cannot be supplied in a time critical manner or an unlimited quantity and are therefore inadequate in the event of a massive haemorrhage. Should this occur, the rare red cells should be saved until bleeding has begun to slow.[8] Secondly, thawing of frozen red cells is associated with red cell loss of more than 20%, resulting in a smaller haemoglobin increment at the time of transfusion.[9] Finally, directed donations increase the risk of transfusion-associated graft-versus-host disease and must be irradiated prior to transfusion, which reduces their remaining lifespan to 14 days.[10]

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Bilateral OVT associated with severe PID

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Ovarian vein thrombosis (OVT) incidence ranges from 1/2000 to 1/3000 births and is even rarer in non-pregnant women.[1] It is classically characterised by a triad of pelvic pain, fever and a right-sided abdominal mass. Idiopathic OVT excludes puerperium, pelvic inflammatory disease (PID), malignancy, recent pelvic surgery and hypercoagulable conditions.[2] Hypercoagulability, venous stasis and endothelial injury are all part of Virchow's triad and can result in the formation of thrombi.

Clinical features of OVT include fever, tachycardia, abdominal pain and leucocytosis. They can be asymptomatic in puerperium or presenting with severe complications, such as extension of thrombus into the renal veins or inferior vena cava, sepsis and pulmonary embolism (PE).

Venous thromboembolism (VTE) risk factors include obesity, recent caesarean section or gynaecological surgery. Differential diagnoses for idiopathic OVT included appendicitis, pyelonephritis and ureterolithiasis.

Case report

A 39-year-old, non-pregnant, woman presented to the emergency department with fever, left-sided flank pain and dysuria. Examination and investigations revealed tachypnoea, tachycardia, hypotension, leucocytosis and left-sided renal angle tenderness.

A clinical diagnosis of pyelonephritis was made. Within a day, she had been admitted to the critical care unit and started on a noradrenaline infusion for blood pressure maintenance. Broad-spectrum intravenous antibiotics for treating pyelonephritis were also commenced.

Her abdominal pain worsened, requiring strong opioids for pain control. She also complained of foul-smelling, copious vaginal discharge. These symptoms prompted her being reviewed by the gynaecology consultant. A speculum exam was performed and a pus-covered intrauterine device (IUD) of 8 years was removed. A computed tomography (CT) scan of her abdomen and pelvis ruled out appendicitis. Her antibiotics were changed to meropenem to cover suspected severe pelvic sepsis secondary to PID.

She remained septic, with a high analgesia requirement. A repeat CT of her abdomen and pelvis ruled out pelvic abscess; however, it showed bilateral OVT with the left ovarian vein thrombus just extending into the renal vein (Figures 1–3).

She was diagnosed with OVT related to severe PID, despite negative microbiology cultures. The fever is attributable to OVT complicated by sepsis secondary to PID due to an infected intrauterine device. She was initially commenced on a low-molecular-weight heparin (LMWH) for seven days, which was transitioned to oral dabigatran therapy for six months. Antibiotics were also switched to oral administration. Her abdominal pain improved immediately after commencing anticoagulation. Her discharge instructions were GP follow-up in one week, gynaecology clinic follow-up in six weeks and a repeat CT in three months to review the need to continue anticoagulation therapy.

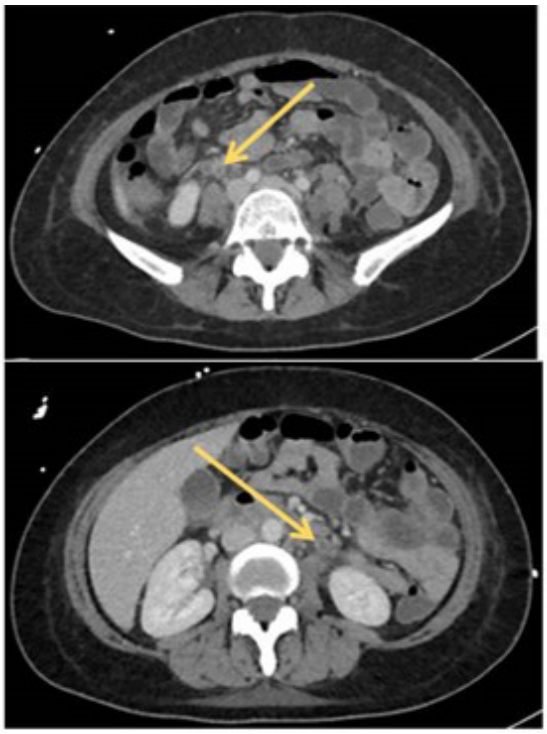

Figure 1. Axial CT with contrast, demonstrating enlarged left and right ovarian veins with decreased intraluminal attenuation and mural enhancement, consistent with bilateral OVT.

Discussion

In non-pregnant women, 45% of OVT cases are right-sided; compared to being left-sided in 41% of cases and bilateral in 14% of cases. The raised incidence on the right side is due to the right ovarian vein being longer compared to the left, as well as lacking competent valves on that side.[3]

The diagnosis of OVT is nowadays determined by CT with a sensitivity of 78–100% and a specificity of 63–99%.[2] Due to its lowered cost and faster access, it is the 'gold-standard' of OVT imaging. CT may show an enlarged ovarian vein that is hypodense centrally. Alternatively, magnetic resonance imaging (MRI) has a sensitivity of 92% and specificity of 100%.[3] Complications such as inferior vena cava or renal vein extension can be detected on MRI or CT. Diagnosis of PE is via ventilation-perfusion scan or CT pulmonary angiogram.

Most cases resolve spontaneously; however, due to the high risk of complications, treatment is recommended. Most experts recommend that treating rare thrombi can be equivalent to treating VTE of the lower extremities. The rational choice is utilising VTE guidelines given that the outcomes are similar.[4] Due to more frequent use of CT scans for diagnosing the surgical abdomen in recent years, most cases of OVT are now treated early. Some studies documented resolution after 7–14 days, whereas others show that anticoagulant therapy of 3–6 months is recommended until imaging confirms thrombus resolution.[2]

The approach to management of OVT is either medical or surgical therapy, with both reporting similar success rates. The literature states that in non-complicated OVT cases, broad-spectrum antibiotics are used with anticoagulation. A reasonable treatment regime for anticoagulation may include a LMWH, warfarin or a novel oral anticoagulant (NOAC) for three to six months.[4] NOACs to consider include rivaroxaban, apixaban or dabigatran. In the most recent guidelines from the American College of Chest Physicians, dabigatran was recommended over warfarin and LMWH for long-term anticoagulant treatment of VTE with no malignancy.[5]

Antibiotic treatment of OVT is indicated if complications like sepsis are suspected. The recommendations are broad-spectrum antibiotics for 7–10 days, based on response to treatment.

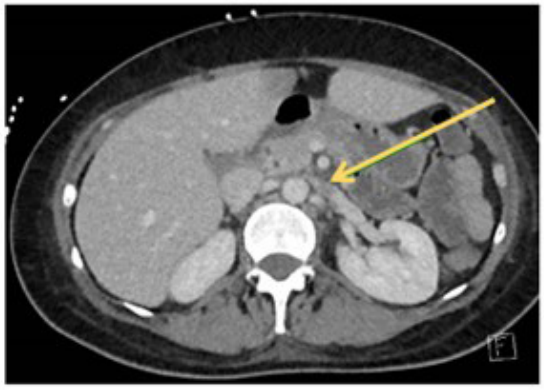

Figure 2. Axial CT with contrast, demonstrating extension of thrombus into left renal vein.

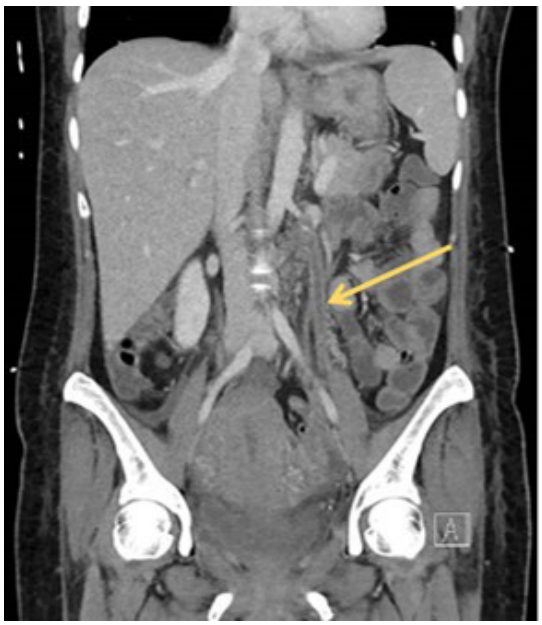

Figure 3. Coronal CT with contrast, demonstrating an enlarged left ovarian vein with decreased intraluminal attenuation and mural enhancement, consistent with left ovarian vein thrombosis.

While initial management of OVT with surgery is controversial, the indications for surgical treatment are complications associated with recurrent VTE despite medical treatment, free floating thrombus and contraindication to anticoagulants.[2]

The prognosis for untreated OVT includes a PE incidence of about 25% and mortality rate of about 52%.[2,4] With anticoagulant therapy, mortality dropped from about 25% to 5%.[2] Partial or complete recanalisation of ovarian veins with anticoagulation occurs in approximately 76% of patients.[6] If anticoagulation is interrupted, 17% of patients will experience recurrent lower extremity deep vein thrombosis.[7] The rate of significant bleeding is the same as typical VTE treated with anticoagulation.

Up until now, only 10 cases of idiopathic OVT were reported in clinical literature.[2] The cause of this patient's OVT is not absolutely certain, but is likely related to the pelvic sepsis she had associated with the IUD. Clinical suspicion of this condition is crucial to institute timely treatment and prevention of further extension causing renal vein thrombosis or, rarely, PE.

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An AOFOG adventure in Manila

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It's another early start today. The traffic is so heavy that we need to be on the bus and on our way before 7am. We're in Manila, one of the most densely populated cities in the world, and there is no shortage of commuters!

On board the bus are 28 O&Gs from 18 countries across Asia and the Pacific. Despite the early hour, it's not long before we are chatting with one another. The traffic congestion in no way dampens our enthusiasm.

We're in Manila as recipients of the Young Gynaecologist Award (YGA), an initiative of the Asian Oceania Federation of Obstetricians and Gynaecologists (AOFOG). As YGAs, we have been given the opportunity to participate in a Community Fellowship Program (CFP), an intense week of visits and activities organised by the Philippine Obstetrical and Gynecological Society (POGS). The first task was learning all the acronyms!

The aim of the CFP is to expose YGAs to different healthcare systems and foster closer relationships among future leaders of AOFOG. The CFP was first introduced at the AOFOG Congress in Kuching in 2015, and the second was held in 2017 in Hong Kong. Both proved successful.

The Manila 2019 CFP was facilitated seamlessly by Dr Ryan Capitulo, an enthusiastic Filipino O&G consultant. Under his guidance, we visited many hospitals and universities and learned a lot about obstetric care in the Philippines. With such a diverse range of participants (from countries such as Myanmar, Bangladesh, Malaysia, Mongolia, Papua New Guinea and Fiji), the discussions were dynamic and enlightening.

Stories and experiences were exchanged, and we realised that although we come from vastly different settings, we share similar challenges. Our hospitals are all subject to resource limitations (admittedly to varying extents) and there are competing interests for health system investment.

At the famous Dr Jose Fabella Memorial Hospital, we heard that approximately 14,000 babies are born per year in the unit. You can understand why it is colloquially known as the 'baby factory'! This volume of patients causes major issues with overcrowding; for instance, we saw 3–4 women sharing two beds pushed together. Despite these challenges, the staff are proud of the facility and work hard to optimise outcomes. We were shown the busy Kangaroo Care ward, which has been proven to reduce newborn morbidity and mortality, and decrease the NICU admission rate. It is an example of a cost-effective intervention that is highly applicable to many developing settings.

The ever-topical issue of caesarean section rates was discussed in detail. On the day we visited Fabella Hospital, there had been 44 deliveries, with 45% of them caesarean sections. Although the national average is approximately 19%,[1] larger referral facilities perform a relatively high number of operative deliveries. Local consultants explained that they often need to manage complex intrapartum issues, particularly in women referred from other centres. We were also fascinated to learn that most women in the Philippines receive a midline incision, something that is not standard in other Asian or Pacific countries. This reflects that Filipino O&Gs are heavily influenced by local teaching and practices, and that norms differ greatly between countries.

Figure 1. YGAs at the Ministry of Health main office.

Figure 2. YGAs at the World Health Organization headquarters.

It was saddening to hear that in 2018 there were, on average, eight maternal deaths every day in the Philippines. Depressingly, this number has not changed since 1990. The causes are similar to many other countries (haemorrhage and hypertension, and associated issues, cause a large proportion of deaths), but unsafe abortion is also a leading contributor to maternal mortality.

Many Filipino women cannot access contraceptives and unintended pregnancy is common. The influence of Catholicism is such that discussion of family planning is prohibited in many hospitals, forcing women to travel elsewhere for birth control advice and solutions. Further, termination is illegal, and approximately 1000 women die each year from unsafe abortion practices and associated complications.[2] It is a major public health problem, but a challenging one to address due to the prevailing political and religious beliefs.[3,4]

As with many countries, there are significant disparities in healthcare access and quality across the Philippines. This was evident when we visited a private hospital and toured the birth suites, noting CTG telemetry, birthing baths and elaborate private rooms. The associated reproductive fertility services were impressive, but not accessible to the majority of Filipinos.

At the Department of Health (DoH) and the World Health Organization (WHO) Western Pacific Regional Office (WPRO), we learned about national and regional efforts to improve maternal and child health outcomes. DoH staff explained that ongoing training and support for midwives is a major challenge and a key barrier to women receiving high quality care. We also heard from Dr Howard Sobel (WHO Regional Coordinator for Reproductive, Maternal, Newborn, Child and Adolescent Health) about the 'First Embrace' campaign, which is a focus of WHO efforts to improve neonatal outcomes. The program focuses on educating patients and clinicians about the benefits of skin-to-skin care for newborns. It is showing positive signs.

During the AOFOG Congress itself, there were several inspirational presentations from world leaders in maternal healthcare. Dr Lesley Regan (President of the Royal College of Obstetrician and Gynaecologists) sensitively and eloquently discussed the 'elephant in the room' of access to safe, legal terminations. Dr Christine Tippett, a FRANZCOG from Melbourne, gave a thoughtful and insightful presentation on careers in O&G. Other outstanding lectures included a gynae-oncology update from Australia's Prof Neville Hacker, and a talk on appropriate caesarean rates from Ireland's Dr Michael Robson.

We were also inspired to learn that the President of the Royal College of Obstetrician and Gynaecologists and the Presidents Elect of the American College of Obstetrician and Gynecologists and the International Federation of Obstetricians and Gynecologists (FIGO) are all women. This is a very positive sign for female leadership in our profession.

Over the two weeks of the YGA CFP and AOFOG Congress, we made friendships with other young, passionate consultants around the Asia and Pacific. Although we work in very different settings, we face similar challenges, and it has been refreshing to chat to international colleagues about solutions and success stories.

Our experience in Manila was very positive and we want to thank RANZCOG and AOFOG for the tremendous opportunity. We were sad to say goodbye at the end of the program, but we certainly won't miss Manila's traffic!

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Honouring Jack Courier's Legacy

Maha Sidaoui

There is an innate ambition in some people to leave the world a better place than they found it and so it is instinctive that science and philanthropy should often meet and become natural partners.

On 11 December 2019, guests, via invitation of RANZCOG and Gibson's Gallery in Armadale, arrived on a warm night at 6pm to attend the opening of The Jack & Mary Courier Selling Exhibition. A large crowd, dressed for an 'occasion', gathered upstairs in a large warehouse gallery to witness the generosity of an artist, the late Auguste John (Jack) Courier, who served science through his art.

Jack Courier was born in 1915 and died in 2007. The RANZCOG Women's Health Foundation was the beneficiary of a generous bequest from Jack, which included a range of his own works, as well as pieces by other accomplished artists including his late wife, Mary Courier McLeish, Peter Jacobs and Kenneth Jack. There were hundreds of etchings, drawings, prints and major works on canvas that had been in storage, and which Jack had trusted to the RANZCOG Women's Health Foundation.

It was a responsibility that could not be taken lightly; a duty to preserve the work and promote the legacy of Jack, so that his work, his bequest, could be appreciated for generations to come.

For more than 70 years, RANZCOG has shown a commitment to improving the health of women and their families. RANZCOG Women's Health Foundation, the philanthropic arm of RANZCOG, is dedicated to fostering clinical and scientific research in women's health, supporting global health projects and promoting Aboriginal and Torres Strait Islander and Māori women's health initiatives.

It was also Jack's intention that the RANZCOG Women's Health Foundation support a perpetual scholarship, dedicated to the memory of Mary, who died from cervical cancer. In 2008, the Mary Elizabeth Courier Research Scholarship was established. It was with great care, hard work and consideration that the RANZCOG Women's Health Foundation was able to honour Jack's bequest through a selling exhibition.

Guests enjoyed the wine and champagne as they were invited to tour the gallery and buy artworks. There where hundreds of pieces lining the walls. Jack's work, a mix of standing figures, landscapes and still lifes, adorned a feature wall. European in influence, romantic in appearance, they were simply stunning.

The intention of the evening was, of course, to sell the work, with proceeds going back into the Foundation. It wasn't long before red dots began to appear below the paintings (indicating the sale of an artwork), making it apparent that the night was already a success. There were 19 works sold on the night and several more are expected to go at auction early this year.

An evening where artists were honoured and tributes were paid, it was also a night of reunion. Old friends from Caulfield Tech, now Monash University, found each other and exchanged stories. Family of Jack and Mary reunited and reminisced, friends of the artists identified painted settings, scenes and sketches. Pictured below, we also see the daughter of Mary Courier McLeish brought to tears as she marvelled over a forgotten portrait, painted more than 80 years ago. Now 92, she was 12 at the time. The night was a reunion for many of Jack's friends and for those who were taught lithography by him in 1969

Figure 1. Mary Courier's daughter admires a portrait of herself as a young girl, painted by her mother.

There were three speakers at the gallery, with Dr Rebecca Mitchell welcoming guests on behalf of the RANZCOG Women's Health Foundation. She reminded us of the importance of philanthropy and how it plays a significant role in our society by providing opportunities and championing projects and endeavours. Dr Mitchell spoke about the Pacific Island Cervical Cancer Screening Initiative (PICCSI), for which she volunteers her time and expertise. This particular project has been supported by Jack's generous bequest.

Women are one of the greatest assets in the Pacific. Losing mothers, daughters, sisters and aunts to cervical cancer impacts the sustainable development of these communities and countries. The aim of PICCSI is to screen women in the Pacific for the virus that causes cervical cancer – Human papillomavirus (HPV); this is very similar to how women are screened in Australia and many parts of the world. Most cervical cancer is preventable, yet available data for Pacific Island countries shows alarming incidence rates. When women test positive for the virus, they are offered a small procedure as treatment. The PICCSI Project screens and treats women on the same day at a health service close to their home. This helps to decrease the number of women who are lost between getting results and receiving treatment, and subsequently, the number of women who go on to develop cervical cancer.

Peter Jacobs, fellow artist, old friend, colleague and confidant, spoke after Dr Mitchell. He recalled the technical and often arduous process involved in bringing Jack's work to life, illustrating the mastery behind lithography. He told us that when Jack was satisfied with an image, he would lock himself away for weeks to print an edition. Each colour in the print was drawn separately, proofed and then printed. There were times when it was a one-colour print, where he would complete the image on just one stone, against a white paper surface. This process evident in one of his famous prints, The Black Standing Figure.

Peter recently oversaw a collection of Jack's works at the National Gallery of Australia, where a portrait of Jack hangs. He reiterated a conversation he had with Roger Butler, a senior curator at the national gallery, who said that 'Jack is arguably Australia's finest stone lithographer whose place in Australian printmaking history is now fully recognised.'

Dr Juliette Peers, a postgraduate supervisor, senior researcher at RMIT and author of *More Than Just Gumtrees*, talked about Jack's soulmate and fellow artist, Mary Courier McLeish, whom he met later in life and married. Mary was an accomplished artist in her own right. Dr Peers spoke to the crowd about the period in which Mary painted, and the Melbourne Society of Women Painters and Sculptors founded in the late 1800s. They were the seldom-heard voices of women artists and craftworkers, amateur and professional, radical and conservative and provided us with personal, social and artistic history. Mary Courier McLeish was indeed a trailblazer for her time, with many of her works finalists of the prestigious Archibald Prize.

Philanthropy itself means the love of humanity and is thus exclusively carried out with the greater good in mind. The latest fire devastations have helped us to understand the importance of charity. It is immediate, often short-term, and focused primarily on rescue and relief. The Women's Health Foundation centres

Figure 2. Posing with one of Jack's lithography stones. From left to right: Dr Juliette Peers, Peter Jacobs, Cathie Stocky, Dr Rebecca Mitchell and Jenny Gibson.

on philanthropy. It is much more long-term, more strategic and focused on rebuilding. Philanthropic donations play an indispensable role in supporting early-stage basic research, often being a catalyst for the establishment of major research centres and initiatives. The contribution of philanthropy is unique, complementary to other funding sources, and incredibly valuable for scientific research.

We, as friends and supporters of the community at RANZCOG, came together to pay homage to both Jack and Mary's work in a way that will not be forgotten. It was also an evening where guests came to pay tribute to Jack's philanthropic bequest, where audiences were informed, asked questions and shared stories. An evening for us all to cherish.

If you wish to purchase a piece of Courier artwork, please contact Jennifer Gibson at Gibson's Gallery.
e: jennifer.gibson@gibsonsauctions.com.au
t: 0413 202 520

You can view the Jack and Mary Courier Collection on their website: www.gibsonsauctions.com.au/jack-and-mary-courier-collection

To find out more about the PICCSI project you can go to any of these sites:

- www.youtube.com/channel/UCzxJ05bNPTWN1F9taQURa4w
- https://piccsi.org/who-we-are/
- www.healthserve.org.au/projects-of-health-serve-australia/142-articles/101-women-s-health-project-fiji.html

For more information regarding The Mary Elizabeth Courier Research Scholarship, or if you wish to donate or discuss leaving a bequest to RANZCOG, please contact:
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Enhancing good governance

Andre Khoury
Head of Communications and Public Affairs

Late in 2019, RANZCOG's Constitution was amended to introduce a number of changes, one being the inclusion of two new directors to the Board. *O&G Magazine* speaks to Julie Hamblin and Dr Judith Gardiner.

When a Special Resolution was passed by Fellows at last year's Annual General Meeting, RANZCOG President, Dr Vijay Roach, welcomed the news. That's because its passage meant the College's Constitution would be amended to introduce a number of changes, one being the inclusion of two new directors to the Board – a Diplomate Board Director (the Chair of the Diplomates Committee sitting on Council) and an Independent Board Director.

Those two new Directors are Dr Judith Gardiner (Diplomate Board Director) and Julie Hamblin (Independent Board Director).

'This is a positive and progressive outcome for our College,' Dr Roach said at the time. 'These positions will ensure good governance and a mix of skills and expertise on the Board.'

For Ms Hamblin, joining the Board continues a career spanning more than 25 years as a lawyer and policy consultant in health law, clinical risk, disability and international development. 'I was drawn to a position in the health sector, and I am pleased to be able to build on the work I have done over many years on law and policy relating to obstetrics and sexual and reproductive health generally. I am also very interested in the international connections that RANZCOG is building,' Ms Hamblin says.

Ms Julie Hamblin.

A former partner of law firm HWL Ebsworth, Ms Hamblin has served on numerous government and other advisory bodies in the health sector, including the Australian Research Integrity Committee, the NSW Clinical Ethics Advisory Panel, the MBS Review Clinical Committees for Obstetrics and Gynaecology and the Attorney-General's International Pro Bono Advisory Group.

She has a particular interest in global health, having worked with the United Nations Development Programme and other organisations on projects relating to public health and HIV/AIDS in more than 20 countries in Asia, the Pacific, Africa and Eastern Europe.

In addition to her RANZCOG role, she chairs the Board of Autism Spectrum Australia and is Deputy Chair of charity Plan International Australia.

'I have been involved with professional associations throughout my career and I think the governance of them is really important,' Ms Hamblin says. 'Having diversity of views and experience on any board is central to good governance. I hope I can bring a non-clinical perspective to the RANZCOG Board as well as a different voice. The beauty of a good board is that the total is greater than the sum of its parts. Having that mix of voices can be quite energising – you can get a real dynamic going that generates good decisions that are often better than the decisions any individual board member could make.'

Continuing to engage Fellows and trainees in the work of the College – given much of this work is pro bono and is time intensive – and ongoing challenges for health funding in Australia, including finding the right balance between public and private funding, are just two issues Ms Hamblin identifies as challenges for the O&G speciality.

For Dr Gardiner, who has been a GP Obstetrician since 1980 working in regional, rural and remote locations, being on the Board presents an opportunity to represent Diplomates. 'By and large the Board is engaged and attuned to the needs of GP obstetricians, so this appointment creates an opportunity to provide relevant information and guidance to the Board, increasing awareness of what we do.' Dr Gardiner says.

Dr Gardiner is an advanced RANZCOG Diplomate and the current Chair of the RANZCOG Diplomates Committee and Vice Chair of the Conjoint Committee for the Diploma of Obstetrics & Gynaecology. She is also a DRANZCOG examiner and the Diplomate representative on the NSW State Committee.

Dr Judith Gardiner.

Rural GP obstetricians must be involved in the development of maternity service policies, protocols and guidelines to ensure an appropriate level of care for women in their local area, and the College has a crucial role in advocating this to governments, according to Dr Gardiner. 'Rural and remote women don't want to go to the city,' Dr Gardiner says, 'it's a major imposition and disturbance for their family life, particularly for Indigenous women.'

With a considerable shortage of GP obstetricians in more isolated locations throughout Australia, Dr Gardiner says there is a need to think of ways to guide Diplomates to establish skills to provide intrapartum care and give them the confidence to move to places where these skills are best utilised.

Both Dr Gardiner and Ms Hamblin say with the expansion of the Board to nine Directors, the College will continue to address its governance, fiduciary duties, education and training delivery, policy development and advocacy with vigour, bringing along its members and trainees.

'A central role of the Board is to strengthen the engagement with members,' Ms Hamblin says. 'We want them to believe that what the College does is important, and we want members to be involved. The Board is actively seeking ways to encourage that involvement, which includes addressing structural issues and other disincentives that may exist currently. I believe that needs to be a priority for the Board.'

Dr Gardiner says: 'Members have to feel they belong to the College to start with and Dr Roach has made great advances in reaching out to all members of the College. As a Diplomate, I have never felt a stronger connection with the College as I have more recently.'

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Excellence in Women's Health

RANZCOG congratulates our 35-Year Fellows

The below Fellows are being recognised for achieving 35-year Fellowship prior to retirement from practice.

Dr Luan Ang
Dr Peter Ashton
Dr John Bates
Dr Mark Beale
Dr Christine Bessell
Dr Warwick Birrell
Dr Lawrence Brunello
Dr Edwin Caldwell
Dr Gordon Campbell
Dr John Campbell
Dr Donald Cave
Dr Andrew Child
Dr Geoffrey Clarke
Dr Phillip Clarke
Dr Phillip Cocks
Dr Timothy Cropley
Mr Nicholas Diamond
Dr Peter Dobson
Dr Peter Fisher
Prof John Fliegner
Dr Gregory Fox
Dr David Francis
Prof Ian Fraser
Dr Anthony Frumar
Dr Leslie Gan
Dr Bruce Gilbert
Prof Wayne Gillett
Dr Peter Goldman
A/Prof Eric Green
Dr Graham Hamdorf
Dr Kevin Hill
Dr Ian Hocking
Dr Ian Hoffman
Dr Keith Hollebone
Prof John Hutton
Dr Maurice Hynes
Dr David Itzkowic
Dr Daya Jayasinghe
Dr Douglas Johnson
Dr George Kaladelfos
Dr Pravin Kasan
Dr Peter Kraus
Dr Kim-Boo Kuah
Dr Raphael Kuhn
Dr Yean Lim
Dr Ruary MacKenzie
Dr Raymond Marin
Dr Christopher Maxwell
Dr Peter Mayall
A/Prof Charles McCusker
Dr Francis McMahon
Dr Robin Monro
Dr Biswanath Mukerjee
Dr Victor O'Toole
Dr John Overton
Dr Surinder Parhar
Dr William Patton
Dr Geoffrey Paul
Dr Michael Price
Dr Peter Renou
Dr Yehia Saleh
Dr David Salter
Dr John Sangster
Dr Mukhtiar Sidhu
Dr David Smith
Dr Richard Speed
Dr Graham Standen
Dr Simon Stewart-Rattray
Dr Ian Symington
Dr Alex Szirt
Dr William Tai
Dr Thomas Tait
Dr Eric Tarr
Dr Adrian Thomas
Dr Grahame Vaughan
Dr Christopher Verco
Dr Edward Vesey
Dr John Walton
Dr Mary Watt
Dr Reuben Wein
Dr Rolf Weissenberger
Dr David Wilde

Obituary

Dr Michael David Kaye
1941–2019

Michael Kaye was born on 14 May 1941 at the Royal Hospital for Women in Sydney. He attended Sydney Boys High School and, in 1956, started studying medicine at the University of Sydney. He graduated in 1964 and became a resident medical officer at Sydney Hospital. He was interested in paediatrics and he did a residency at the Royal Alexander Hospital for Children in 1965. He was appointed the medical officer at Mount Hagen Hospital in Papua New Guinea, where he did paediatrics and looked after leprosy patients. He went to London and obtained his DCH, after which he worked at the National Women's Hospital in Auckland, New Zealand, and completed a diploma in obstetrics.

In the 1970s, he worked at the Department of Gynaecology and Obstetrics at the University of Sydney as a research fellow. He was an O&G registrar at the Wollongong Hospital, St Margaret's Hospital and King George V Hospital in Sydney. In 1973, he completed his PhD at the University of Sydney and his thesis was called 'Immunological Studies in Mammalian Placentation'.

In 1975, he sat for the MRCOG in London. Between 1977 and 1978 he worked in the Department of Clinical and Basic Immunology and Microbiology in Charleston, South Carolina, and the Laboratory of Human Reproduction and Reproductive Biology at Harvard Medical School Boston on a World Health Organization Grant and Fulbright-Hays Scholarship.

On returning to Australia, he worked as a senior registrar at the Flinders University Hospital in Adelaide. After this, in 1980, he was a staff specialist in O&G on Thursday Island. He wrote more than 20 papers and much of his work was focused on infertility. In 1982, he was made a Fellow of RANZCOG. He married Ingrid in 1983 and they had twin sons in 1984 at Mona Vale Hospital. He was appointed a VMO at Mona Vale Hospital in 1980 and later was Chairman of the Medical Staff Council 1999–2001.

He enjoyed surfing, sailing and nature. In 2019, he had an accident at home and died on 19 September 2019. A memorial service for Michael was held at the Avalon Lifesaving Club. He is survived by his wife, Ingrid Carlstrom, and two sons, Cody and Nicholas.

Dr Jim Roche OAM CLJ
FRANZCOG

Remembering Our Fellows

Our College acknowledges the life and career of Fellows that have passed away:

- **Dr Michael Guy Laney**, NZ, 11 December 2019
- **Dr Graham Knox Williams**, NSW, 12 January 2020

RANZCOG members awarded Honours on Australia Day

The College congratulates the following RANZCOG members on recently receiving an Australia Day Honours award:

Senior Australian of the Year

Prof John Newnham AM is recognised as one of the world's leading authorities in the prevention of preterm birth and has been described by the world's leading scientific journal as 'an intellectual leader of modern obstetrics who has changed the practice of medicine and the lives of women and infants'.

Officer (AO) in the General Division of the Order of Australia

Prof Shaun Brennecke, for distinguished service to medical education and research in the fields of obstetrics and gynaecology, and to professional societies.

Prof Michael Permezel, for distinguished service to medicine, and to medical education, in the fields of obstetrics and gynaecology, and to professional colleges. Prof Permezel is a Past President of RANZCOG.

Member (AM) in the General Division of the Order of Australia

Dr Desiree Yap, for significant service to women's health, and to medicine.

Medal (OAM) of the Order of Australia in the General Division

Dr Phillip Cocks, for service to medicine, and to medical associations.

Letter to the Editor

A/Prof John Svigos AM
FRANZCOG
Discipline of Obstetrics and Gynaecology
Faculty of Health Sciences
University of Adelaide
Senior Visiting Obstetrician
Lyell McEwin Hospital, SA

Dr Basil Antonas
FRANZCOG
Discipline of Obstetrics and Gynaecology
Faculty of Health Sciences
University of Adelaide
Senior Visiting Obstetrician
Women's and Children's Hospital, SA

Today, real public discussion has become problematic as the negatives that are directed to any individual uttering anything remotely controversial invariably results in that individual no longer bothering to discuss issues for which there may well be solutions.

This can certainly be applied to ageism, where even the spelling, let alone the word, evokes controversy and, nowadays, a certain amount of resignation rather than indignation!

The RANZCOG Board has recently circulated Fellows with a personal letter, 'Operating with Respect', in which there was espoused a wish to eliminate discrimination, bullying and sexual harassment to achieve the goals of inclusion, respectful communication and safety in the workplace; however, the elephant in the room – ageism – received scant attention!

Rupert Sherwood's treatise on the ageing surgeon[1] very eloquently dealt with their technical abilities and possible solutions along with touching on their emotional responses with the often quoted solution of 'early preparation for retirement', which may no longer be applicable to the documented increasing number of Fellows who might wish or need to work longer.

Industry however, due to demographic and fertility trends, have recognised that companies, in order to increase cognitive diversity, must bring back or retain older workers who are well placed with their knowledge and experience to take advantage of this initiative and 'add to the economic edge' of progressive organisations.[2]

There are a number of solutions that have been proposed to seamlessly include older employees, but perhaps the most significant is that organisations must teach younger leaders how to utilise older workers' talents in an inclusive and respectful fashion.

Hence, to make a positive social statement in 'Operating with Respect' then, RANZCOG should encourage the omission of the negative intonation and inference of terms such as 'succession planning', 'technologically inept', 'resistant to change' from the common vernacular and, like our colleagues in industry, be proactive in setting the agenda for older Fellows to 'add to the clinical edge' of our specialty.

References:
1. Sherwood R. The Ageing Surgeon. *O&G Magazine* Vol 21. No 3. Spring 2019.
2. Berzin J, Premuzic T. Age adds to the economic edge. *New York Times*, 2019.

RANZCOG Women's Health Foundation

2020 Research Scholarships, Fellowships and Travel Grants

The RANZCOG Women's Health Foundation aims to foster clinical and scientific research in women's health, support global health projects, and promote Aboriginal and Torres Strait Islander and Māori women's health initiatives.

Under the oversight of the Research Grants Committee, the College supports promising early-career researchers across Australia and New Zealand by annually awarding research fellowships, scholarships and travel grants to those practising in the field of obstetrics and gynaecology. The assessment process was once again very competitive this year, with 32 eligible applications received across Australia and New Zealand.

The RANZCOG Women's Health Foundation is pleased to advise that the following applicants have been offered scholarships and fellowships for research and travel in 2020:

Arthur Wilson Memorial Scholarship, 2020–2021

Recipient: Dr Claire Henry
Institution: University of Otago, Wellington
Project: Molecular profile of Endometrial Cancer in New Zealand women

Dr Claire Henry is a research fellow at the University of Otago, Wellington, with an interest in the molecular biology of gynaecological cancers. Dr Henry's project is a pilot study to investigate the molecular profile of endometrial cancer in NZ women, focusing on the impact on outcomes and feasibility in routine clinical practice.

Fotheringham Research Scholarship, 2020–2021

Recipient: Dr Tristan Hardy
Institution: SA Pathology
Project: Pregnancy Loss to Preimplantation Genetic Testing: improving the pathway for couples affected by stillbirth, congenital abnormality or neonatal death

Dr Tristan Hardy is a RANZCOG Fellow, currently completing a Fellowship in genetic pathology with the Royal College of Pathologists of Australasia. He aims to be the first dual-qualified specialist O&G and genetic pathologist in Australia and New Zealand. Dr Hardy's project aims to help couples transition from pregnancy loss to IVF and embryo genetic testing, using information from tests performed in their first pregnancy.

Norman Beischer Clinical Research Scholarship, 2020–2021

Recipient: Dr Manarangi De Silva
Institution: University of Melbourne
Project: Improving maternal health in the Asia-Pacific region

Dr Manarangi De Silva is a RANZCOG Advanced Trainee and a previous recipient of the RANZCOG Women's Health Foundation Miriam O'Connor Travelling Scholarship. Dr De Silva is a PhD candidate at the University of Melbourne. Her project aims to investigate the main factors that contribute to poor maternal outcomes in the Solomon Islands, as well as the effect of betel nut consumption.

RANZCOG NSW Regional Committee Fellow Research Grant, 2020

Recipient: Dr Monica Zen
Institution: Westmead Hospital/Charles Perkins Centre
Project: Childhood health consequences and cognitive outcomes in children exposed to preeclampsia in utero

Dr Monica Zen is a RANZCOG Fellow and a previous recipient of the RANZCOG Women's Health Foundation Norman Beischer Clinical Research Scholarship. Dr Zen's project aims to analyse data obtained from birth records, hospital admissions and education for all infants born in NSW from 2001 to determine whether preeclampsia has an independent effect on the health and school performance of exposed children.

RANZCOG NSW Regional Committee Trainee Research Grant, 2020 (Three awarded)

Recipient: Dr Kelly McNamara
Institution: University of Sydney
Project: Pregnancy Intention, Contraception and Obstetric Outcomes in Women Who Use Alcohol and Other Drugs in Pregnancy

Dr Kelly McNamara is a RANZCOG Advanced Trainee and a PhD candidate. Dr McNamara's PhD aims to design an evidence-based process to reduce unplanned pregnancy in women who use alcohol and other drugs. This project forms part of her PhD and focuses on women with substance use in pregnancy. It will examine unplanned pregnancy and its association with pregnancy, birth and neonatal outcomes, contraception use and barriers that limit access to contraception.

RANZCOG President, Dr Vijay Roach, at the November 2019 Presentation Ceremony with recipients of RANZCOG Honours and 2020 RANZCOG Women's Health Foundation Scholarships.

Recipient: Dr Madeleine Sheppard
Institution: Kolling Institute, Royal North Shore Hospital
Project: Asymptomatic Bacteriuria in Pregnancy

Dr Madeleine Sheppard is a RANZCOG Core Trainee, working as an O&G Registrar at Royal North Shore Hospital. Dr Sheppard's study aims to determine the prevalence of asymptomatic urinary colonisation in the second and third trimesters, which may be implicated in some cases of stillbirth, preterm labour and premature rupture of membranes.

Recipient: Dr Katherine Whitton
Institution: Royal Hospital for Women
Project: Can markers in serum and follicular fluid be used to predict the outcome of in-vitro oocyte maturation?

Dr Katherine Whitton is a fourth year RANZCOG Trainee, who is also undertaking a Master of Reproductive Medicine at the University of New South Wales. Dr Whitton's project aims to determine if you can predict the outcome of in-vitro maturation by measuring certain factors in a woman's blood and the fluid surrounding the collected follicles.

Robert Wrigley Pain Research Scholarship, 2020–2021

Recipient: Dr Karen Chan
Institution: Women's Health and Research Institute of Australia
Details: Randomised double-blinded crossover trial assessing the efficacy of topical amitriptyline combined with oestriol in the treatment of women with pudendal neuralgia or vulvodynia

Dr Karen Chan is a RANZCOG Advanced Trainee undertaking additional training in pain management through the Faculty of Pain Medicine. Dr Chan's project aims to add to the body of evidence in the management of women with pudendal neuralgia and vulvodynia by determining whether topical amitriptyline 0.5%/oestriol 0.03% in Organogel results in an improvement to quality of life.

Taylor-Hammond Research Scholarship, 2020

Recipient: Dr Charlotte Reddington
Institution: Royal Women's Hospital
Project: The impact of age and parity on the experience of relief and regret in women who have undergone hysterectomy for benign disease

Dr Charlotte Reddington is a RANZCOG Fellow in her second year of the AGES Fellowship training program. Dr Reddington's project aims to describe what factors (such as age, pregnancy history and medical conditions) affect the experience of relief and/or regret after hysterectomy for benign conditions. She is inviting all women who had a hysterectomy for benign disease at the Royal Women's Hospital, aged less than 51 during an eight-year time period, to take part.

RANZCOG NSW Regional Committee Travelling Scholarship, 2020

Recipient: Dr Galabadage Jayasinghe
Institution: Westmead Hospital Network
Details: For her visit to Port Moresby General Hospital, Papua New Guinea

Dr Galabadage Jayasinghe is a RANZCOG Core Trainee from Westmead Hospital. Her placement at Port Moresby Hospital will provide her with exposure to the challenges faced by clinicians working in the Pacific Region. In addition to providing a beneficial service to the community, she will be able to further develop her clinical obstetric, operative and diagnostic skills in a resource-limited environment.

Beresford Buttery Travel Grant, 2020

Recipient: Dr Jennifer Pontré
Institution: King Edward Memorial Hospital
Details: For her visit to the University of Sao Paulo Medical School and Digimagem Diagnosticos Medicos, Sao Paulo

Dr Jennifer Pontré is a RANZCOG Fellow and a Consultant O&G, who has completed her AGES Fellowship in advanced laparoscopic surgery. The

objective of Dr Pontré's visit is to undertake a one-week training program with Profs Mauricio Abrao and Manoel Goncalves at the University of Sao Paolo, undergoing intensive training in transvaginal ultrasound for deeply infiltrating endometriosis.

Brown Craig Travelling Fellowship, 2020

Recipient: Dr Jerome Melon
Institution: McGill University, Montreal, Canada
Details: For his attendance at the International Urogynecological Association / American Urogynecologic Society (IUGA/AUGS) Joint Scientific Meeting in Nashville, USA

Dr Jerome Melon is a RANZCOG Fellow and urogynaecology subspecialty trainee, currently completing a 12-month Fellowship in Montreal, Canada. Dr Melon attended the IUGA/AUGS Joint Scientific Meeting in late-September 2019, where two of his research papers were accepted for oral presentation.

Scholarships/Fellowships continuing in 2020

Ella Macknight Memorial Scholarship, 2019–2020

Recipient: Dr Monika Skubisz
Institution: South Australian Health and Medical Research Institute
Project: A randomised controlled trial to investigate the necessity of prenatal folic acid supplementation beyond 12 weeks gestation

Glyn White Research Fellowship, 2019–2020

Recipient: Dr Roxanne Hastie
Institution: University of Melbourne/Mercy Hospital for Women
Project: Improved Characterisation of Eclampsia (ICE study)

Mary Elizabeth Courier Research Scholarship, 2019–2020

Recipient: Dr Daniella Susic
Institution: Royal Hospital for Women, University of New South Wales, Sydney
Project: The uterine microbiome in obesity-related endometrial cancer: identifying its composition and relationship with clinicopathological features and local and systemic biomarkers

Norman Beischer Clinical Research Scholarship, 2019–2020

Recipient: Dr Carole-Anne Whigham
Institution: University of Melbourne/Mercy Hospital for Women
Project: Detecting Circulating Maternal Biomarkers to Predict Fetal Size: FLAG 2 (Fetal Longitudinal Assessment of Growth)

Support the Foundation

The RANZCOG Women's Health Foundation is very grateful to all those who have so generously supported its philanthropic work in the past year.

RANZCOG members can support the Foundation via the payments section of the my.RANZCOG members portal. To login and donate, please go to my.ranzcog.edu.au/login.

For donation enquiries, please contact Ms Leigh Craig, RANZCOG Women's Health Foundation Coordinator on foundation@ranzcog.edu.au or +61 3 9412 2993.

2021 RANZCOG Women's Health Foundation Scholarship applications open late-April and close 30 June 2020.

College Statements update November 2019

Revised College Statements

The following statements were approved by RANZCOG Council and Board in November 2019:

Intrapartum Fetal Surveillance Guideline

- Updated references
- Refer to summary of changes to recommendations

Routine Antenatal Assessment (C-Obs 3a)

- This statement replicates a lot of the content of the Department of Health National Pregnancy Care Guidelines and therefore proposed its retirement and replacement with a link to these guidelines, which the College had significant input into. However, the decision was made to keep the statement to provide guidance for New Zealand members.
- Additional links to new College Statement on Reproductive Carrier Screening

Vitamin and Mineral Supplementation in Pregnancy (C-Obs 25)

- Rewrite
- Updated references

Vasa Praevia (C-Obs 47)

- Updated references
- A number of recommendations were changed to 'good-practice points'

Management of Hepatitis B in Pregnancy (C-Obs 50)

- Updated reference to the Australian Immunisation Handbook regarding Hepatitis B timing of vaccination for infants, children as and other risk groups.
- Updated evidence surrounding Tenofovir, including reference to a meta-analysis on the efficacy of Tenofovir in preventing mother-to-infant transmission of Hepatitis B virus
- Added information regarding a study about perinatal transmission of Hepatitis B among women undergoing invasive procedures

Emergency Contraception (C-Gyn 11)

- Updated references

Late Abortion (C-Gyn 17a)

- Rewrite
- Updated references and terminology

Statements retired

Standing orders for prescribing narcotic drugs (C-Obs 8)

- Developed in 1995 when little guidance existed on this issue. Regulations around standing orders are now outlined in national guidelines as well as hospital policies and protocols

Collaborative maternity care (C-Obs 33)

- Developed in 2010 following the introduction of eligible midwives in Australia, due to the legislative requirement that they must have signed collaborative arrangements with a GP obstetrician or obstetrician and the uncertainty regarding scope of practice, supervision and responsibility for practice.

RANZCOG Patient Information

There are 41 RANZCOG Patient Information Pamphlets, including the new Pregnancy and Childbirth pack of 18 pamphlets, now available. All of these products can be viewed and ordered from: www.ranzcog.edu.au/Womens-Health/Patient-Information-Guides/Patient-Information-Pamphlets.

The following titles were approved for publication and are now available:

- Genetic Carrier Screening
- Frequently Asked Questions in Pregnancy
- Contraception

Prof Yee Leung
Chair
RANZCOG Women's Health Committee