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REPRODUCTIVE HEALTH

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The College

Reproductive health

Women's health

The College

From the President

Dr Vijay Roach
President

Welcome to the Autumn issue of *O&G Magazine*. The theme for this issue is Reproductive Health, focusing on fertility. During the 2020 pandemic there was a lot of discussion as to whether birth rates would increase or decrease. Human fertility is affected by intrinsic and extrinsic factors. For most (admittedly not all), the desire to have children manifests at some point in their lives but control of fertility is limited. The authors explore male and female fertility factors, assisted reproductive technologies, access to fertility investigations and care, and the topic that I believe will dominate reproductive medicine in the future, carrier screening and prenatal genetic diagnosis. Good reading that's relevant to practice for anyone involved in women's healthcare.

We closed the door on 2020 in the hope that summer would bring rest and relaxation and the new year would be different. Alas, the pandemic continues to worsen and we look ahead with uncertainty and trepidation. The vaccine is promising, and the human spirit is ever hopeful but it's also appropriate to acknowledge the crushing effect of COVID-19 on our personal and professional lives. The lack of in-person contact, the restrictions on movement and the inability to share life experiences with family and friends creates anxiety, sadness, anger and resentment. There are different ways that I could write this message. I could fill it with cheerful thoughts, rationalisations, expressions like 'it's not that bad in Australia and New Zealand' but I think that would be unfair. It would fail to acknowledge that our emotional response doesn't require a justification and that happiness and sadness are relative and subjective. It wasn't a good year!

In my life, 2020 meant no travel, not meeting people, endless Zoom meetings and no break. One just fell into a pattern of working every day. It's only now dawned on me how reliant we are on the distractions of life. Going to a movie, eating at a restaurant, planning a holiday or going out with friends. These things give us our rhythm, interspersing work with play, adding variation to our lives. One thing about 2020 was that it was monotonous. With the exception of moments of political upheaval (and even that became predictable!), each day seemed to blend into the next, all of us on COVID numbers watch.

Each of us has been impacted. To all of you who have experienced hardship, anxiety, illness, separation from friends and family, and impacts on your personal and professional lives, I take this opportunity to express my genuine sympathy and send you my best wishes for a better year ahead.

The College has much to look forward to this year. The plans have been finalised for the refurbishment of 1 Bowen Crescent, our new College home, and we hope to move in during June. The new training year has begun, and I've enjoyed 'meeting' the first-year trainees over Zoom. If you need inspiration, talk to a trainee! Their zest and enthusiasm is infectious. RANZCOG will continue our work in areas of mentorship, wellbeing and engagement with consumers. Exams will continue online, reflecting the extraordinary adaption to that format in 2020. The pandemic may have impacted us, but we're determined to maintain business as usual and strive to deliver the best guidance and support to our members and the community. What we will build on is the commitment of our members and staff. 2020 saw an unprecedented level of engagement with the College. Please get in touch. It's your College and we value you and your contribution.

From the CEO

Vase Jovanoska
Chief Executive Officer

Hello and welcome to the first issue of *O&G Magazine* for 2021. I am sure I speak for most of us when I say that for the most part, I am glad that 2020 is behind us, and we can look forward to a new year full of renewed opportunity and growth.

As we move into what has been dubbed our 'COVID-normal', we face new challenges where uncertainty remains an undertone, where the future seems better but, we remain cautiously aware that things might change very quickly.

The College achieved so much in 2020 despite the limitations we faced, and we flourished, found community and engagement in unconventional ways and continued to support our members through many workshops, events, webinars and through the consistent delivery of a high standard of education and training.

I would firstly like to welcome our new trainees to the College and wish you all the best for your journey through the O&G specialty. RANZCOG is committed to providing you the best learning and assessment experience we can. I hope you have enjoyed the orientation sessions facilitated by College staff, we have enjoyed seeing you all and welcoming you to RANZCOG. I am sure that you feel that it is both an exciting and challenging time to commence your training, but we are elated that you have chosen us as your College.

In March 2021, the College will see the appointment of a new President-elect; the formation of a new College Board will take place in July and in November, the 12th College Council will officially commence their term. This activity brings with it many opportunities for engagement and diversity within the College's governance and we look forward to sharing news of these changes as they happen.

In 2021, the College will also relocate to 1 Bowen Crescent, Melbourne, where the construction and fit-out phase of the project is well and truly underway. Our new head office, located in a fantastic part of Melbourne, will provide just the environment for College staff and for our members to work and gather. It will allow for more collaboration and creativity whilst still paying homage to the heritage, history and traditions of Albert Street.

We have several important projects and initiatives that will gain momentum in 2021, including our work on wellbeing initiatives, leadership and mentoring. It is important now, more than ever, that we provide the much-needed support and services to our trainees and Fellows as they dedicate their time to advancing healthcare for women and babies across Australia and New Zealand through the various stages of their career lifecycle.

Following the release of the College's Gender Equity and Diversity Report, a formal Gender Equity and Diversity Policy will be finalised early this year which will provide the guiding principles for RANZCOG to promote, advance, enable and support gender equity and diversity practices at the College, through education and training, governance, and advocacy efforts. Consultation for the College's new Reconciliation Action Plan is already underway, and we are also starting work with He Hono Wāhine on the development of a Māori Strategy.

2020 was an extraordinary year, especially with regards to the coordination and delivery of assessments and workshops. In 2021 we will continue with online assessments and workshops and some face-to-face workshops where feasible. We also plan to facilitate some face-to-face meetings where possible, compliant with state and territory requirements for COVID-19.

I would lastly, but not least, like to acknowledge the tireless efforts of the RANZCOG Board led by President Dr Vijay Roach. The past 12 months have been trying for everyone, not the least our Board, who all reside in different states of Australia and New Zealand and met over 20 times (via Zoom) last year, during the pandemic. Their commitment to College governance and prudent decision making, through an arduous and often disheartening time, has been commendable, and I thank them for their support of all members and staff.

LEADERS IN FOCUS

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

This feature sees Dr Nisha Khot in conversation with women's health leaders 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

Prof Cindy Margaret Farquhar FRANZCOG

Welcome to 2021! A very happy new year to all our readers. As we approach the end of summer, we are all hoping for a more 'normal' 2021. In keeping with the theme of this issue, Leaders in Focus features Prof Cindy Margaret Farquhar. Prof Farquhar trained in medicine at the University of Auckland and went on to complete her speciality training in obstetrics and gynaecology in the UK. She has over 300 peer-reviewed publications and has led a number of clinical trials in subfertility and gynaecology. She has led the Cochrane Gynaecology and Fertility Group since its inception in 1996. She is the past Chair of the board of the NZ Guidelines Group and the past Chair of the Perinatal and Maternal Mortality Review Committee. In 2014, Prof Farquhar was awarded Companion of the New Zealand Order of Merit for her contribution to women's health. In 2019, she was made a Fellow of the Royal Society of New Zealand.

Could you please describe your current leadership roles?

I am the newly appointed Dean of Research and Policy at RANZCOG. I am responsible in part for the development of evidence-based processes and documents within the college. This is a new role established by the College and I am excited by the possibilities for improving outcomes for our patients.

I also lead the Cochrane Gynaecology and Fertility group, a co-director for Cochrane NZ and also a senior editor for Cochrane. I am the Deputy Chair for the WHO Fertility Guidelines currently under development. In my academic role, I am the Postgraduate Professor of O&G at Auckland University and in my clinical role, the Clinical Director of Gynaecology and Medical Director of Fertility Plus for National Women's.

Were you always interested in O&G? What made you choose it as your career path?

I only became interested in O&G as a junior doctor while I was doing the diploma, thinking that this would be good training for general practice. It was a refreshing change from the patients with chronic diseases in the medical and surgical wards at the time. In particular, I found I really enjoyed helping people become parents and also found women with menstrual problems was something that we could really help with.

What advice would you give to junior doctors who are unsure if a career in O&G is for them?

The after-hours work in O&G is a significant burden and this cannot be ignored for the majority of O&G specialists. There were many, many days after I had done a night on-call when I thought we made a real difference – whether it was reading an abnormal CTG and delivering a baby before any harm occurred or diagnosing an ectopic before major haemorrhage or correctly managing an ovarian torsion. Although the hours can be long and onerous, our role makes a real difference to women with these problems. Anyone contemplating a career in O&G should weigh up the out-of-hours time commitment with the satisfaction of having a fulfilling career.

What does a typical day look like for you?

I like to get up early and get on with things. During COVID, I started doing some yoga stretches at home. I have tried to continue a 20–30-minute routine (although not always successfully). Often there is an early teleconference to attend. I am generally in the office or clinic by 8am. My day is usually a combination of clinical leadership and research meetings, teaching and clinical patient care. I stepped away from the after-hours on-call roster five years ago and I have stopped doing major procedures. I continue to do some day cover for acute call as well as some minor surgery.

How do you balance your personal and professional life? What are your interests outside of work?

We always have great holidays! We have a beach house and love all the usual beach activities. I enjoy hiking and cycling (thank goodness for e-bikes!) going to plays and concerts. We walked the Inca Trail (the four-day one) in 2017, which was a real highlight.

I do some gardening and I love cooking. We have two children and one grandson.

What are the major/significant changes that you have noticed in your time as an O&G specialist?

For a gynaecologist, the reduction in the use of hysterectomy has been phenomenal. When I first started as a consultant, I used to do at least two hysterectomies on each half-day operating list as well as a few minors. The hysterectomies were either vaginal or abdominal. Now they are far less common and mostly laparoscopic. The length of stay has reduced from 3–6 days to 1–2 days, but the surgical time has gone up. On the one hand, it is great that women have many non-surgical options for treatment of heavy periods such as Mirena, but on the other hand, the reduction in the number of major surgical procedures has a detrimental effect on junior doctors looking to hone their surgical skills. I am not sure that I have the solution to the reduction in surgical experience, but I am pleased to see the advances in the management of a range of menstrual disorders.

For people with fertility problems, we have many more options than we used to have. I was working as a SHO at National Women's when the first IVF baby was born in 1983. We didn't know who the patient was and the confidentially was maintained. When IVF was first introduced, it was offered only to those with tubal infertility. Gradually, couples with unexplained infertility were included and then, with the advent of ICSI, we could treat male factor infertility. With egg donation, this expanded further to include women who did not have many options prior to this. The world of fertility treatment is very diverse these days and patients have many more choices. At the same time, we have more responsibility to provide patients with evidence for (and against) all the different options. Mostly it is expensive and much of my research activity has focused on looking for cost effective and safe options for infertility. And for the past few years our group has focused on the role of add-ons and their effectiveness. It may surprise some of you that most add-ons have not been proven to be effective and are probably overused. This will continue to be a major area of research as fertility services seek to find ways of improving the success rates of IVF.

How did you come to be an academic?

I was fortunate enough to be appointed as a lecturer in London in 1986, where I was able to lead a randomised controlled trial (RCT) that was eventually published in *BJOG* in 1989. That started my interest in teaching and research. I returned to NZ and was appointed as a job share with a colleague to National Women's Hospital.

In 1993, I attended the RCOG's Annual Scientific Meeting in Hong Kong where I listened to a presentation by Dr Richard Johansen about an RCT of vacuum extraction followed by a systematic review of trials of forceps and vacuum extraction. After his presentation, he explained that Dr Iain Chalmers of the UK National Perinatal Epidemiological Unit was starting an interesting project and planned to publish systematic reviews of all healthcare. I was intrigued and wrote to Iain (with an old-fashioned airmail letter in a stamped envelope!) asking if anyone was interested in systematic reviews on treatments of endometriosis. Dr Chalmers replied promptly to say that no one had shown any interest in any of the gynaecology topics. We met in 1994 and, somewhat surprisingly, he asked if I would like to lead the gynaecology topics for this new venture, which

Prof Cindy Margaret Farquhar

was to be known as the Cochrane Collaboration. In order to prepare, I arranged to do a sabbatical in Oxford in 1995. I prepared an application to register the Cochrane Menstrual Disorders Group. This was officially opened in 1996 and in 1998 we added subfertility topics to our remit. In 2016, we celebrated 20 years of what is now the Cochrane Gynaecology and Fertility Group. However, it all started at a conference...and a cheeky letter...

Do you have some 'secrets of adulthood' to share with our readers?

To quote Steve Jobs, 'The only way to do great work is to love what you do.' My secret, if it can be called that, is that I have loved every aspect and every bit of work that I have done, both clinical and non-clinical (well almost every bit of it....)

What have been the greatest challenges and vulnerabilities during your career and how did you manage to conquer them?

When I first started my research career, I struggled to get funding. This went on for years, but I kept making applications. I think changing tack to focusing on prioritised research topics and undertaking studies with a high-quality study design and working as part of larger network was the key to being successful. Last year our group was successful with a large Health Research Council grant that will fund a clinical trial of IUI and IVF for three years. It was the largest grant I have ever received but it comes after three decades of being a researcher.

What does the future look like? What plans do you have for the next stage of your career?

At this point in time, the future looks a bit busy. I am excited about my new role at RANZCOG. The College membership is justified in expecting the College to take the lead in providing evidence-based advice to guide clinical practice in O&G. The College is well placed to advocate for women's healthcare and to combat misinformation. In short, there is much to do in 2021 and beyond.

Editorial

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Welcome to the Autumn issue of *O&G Magazine*. With maternal age being the best indicator of success for both spontaneous and assisted reproduction, it is fitting that a magazine dedicated to fertility and assisted reproduction is being published following Spring and Summer – a period of widespread new life, birth and growth. It is in the 'Autumn' of many patients' reproductive lives that they will likely need assisted reproductive technologies; and with this analogy I look forward to revisiting Menopause in Winter!

As a FRANZCOG working in a private fertility clinic where the vast majority of my patients are well educated, intelligent people, I am always saddened by the lack of understanding and knowledge patients have regarding declining fertility rates and age. The upshot of a society where women are encouraged to break through the glass ceiling and climb the corporate ladder to achieve career success (that their mothers and grandmothers could only dream about) is a rapid increase in maternal age, a declining fertility rate and a booming IVF market.

On average, by the time a woman is 40 years of age, just over 20% of her eggs will be capable of making it to a blastocyst stage embryo and less than 40% of these embryos will be chromosomally normal.[1,2] This gives each egg a less than 10% chance of producing a chromosomally normal embryo. A woman starting a single IVF cycle at 40 years of age has less than a 10% chance of a successful pregnancy.[3] These rates are confronting to patients and there remains limited awareness within the general public regarding the significant decline in fertility rates with age.

The shock and disappointment when presented with these startling realities reflects the lack of general education to the public. The patients who are aware they should be seeking fertility assistance sooner rather than later due to their age are then often shocked that fertility treatment will not be the magic wand for which they'd hoped. The counter arguments that so many patients offer – the fact they exercise daily, take probiotics and eat organic – demonstrate the limited understanding many patients have about declining fertility rates and their cause. Unfortunately, no matter how well you have treated your body, the fact that your eggs have been around longer than you means that after the age of 35 a woman faces a very steep decline in fertility – whether she is trying for natural conception or undergoing fertility treatment.

A year ago, in response to my growing concerns at this lack of general understanding, I contacted my old high-school, a prestigious girls' school in the leafy suburbs. I offered to speak with the students in the upper years as part of their health education program about fertility rates. I was hoping that, in conjunction with a talk about body image, contraception and sexually transmitted infections, I could impart some knowledge about declining fertility rates with age. My hope was that as these young women conquered the world, they would take the time to consider that if they wished to have a family, exploring this before their 35th birthday was probably a prudent idea. I did not hear back.

The increasing success and interest in oocyte cryopreservation over recent years has helped increase the public awareness of declining fertility rates with age. The concern with oocyte freezing though is that it is best performed before women reach their mid to late 30s, which is the time most patients actually present to explore their options. The chance of success with oocyte freezing is determined by the number of eggs that can be harvested and the quality of the eggs, both of which steadily decline with age. By the time a woman is in her late 30s, a single cycle of oocyte cryopreservation is unlikely to result in a successful pregnancy.

There is no Medicare rebate for 'social egg freezing' – a terrible term, but that is another article completely! At many thousands of dollars for each cycle, with the

knowledge most women over 35 years old would be recommended to have more than two cycles to have a good chance of producing enough eggs to result in a single successful pregnancy, this process is financially out of reach for many women. When oocyte freezing is most likely at its sweet point – around 30 years old, a time when a woman's egg reserve and egg quality is still high and she is most likely to be assessing her options as to what her reproductive plans are – the costs are extremely prohibitive. From a purely economic argument, the government subsidising oocyte cryopreservation could be seen as a wise decision. It would logically result in a significant reduction in the number of (largely unsuccessful) IVF cycles in women over the age of 40, cycles that are currently subsidised.

I would love to see government subsidised non-medically indicated oocyte cryopreservation be introduced to Australia and New Zealand. This would accompany a campaign to encourage people to not only consider their options if they are delaying trying for conception but also educate the public about declining fertility rates with age. This education program needs to start in high school. It is only with knowledge that we empower women to truly have control over their reproduction. Although I feel we have had great success with women in Australia and New Zealand having access to contraception and we are getting closer to gaining easy access to termination services for all women, I believe the new women's movement needs to look at empowering women to have knowledge about their fertility chances as well as access to options that allow them the best chance of having the family they want, when they want.

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Investigation of the infertile couple

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Infertility affects over 10% of couples of reproductive age and is ranked the 5th highest serious global disability.[1] Based on the World Health Organisation (WHO) definition of infertility, couples who have not conceived after 12 months of regular unprotected intercourse should be referred for clinical assessment and investigation.[1] Given the growing trend for women to delay childbearing, the average age for women seeking fertility treatment is increasing with time.[2] Therefore, an earlier specialist clinical assessment may be warranted if the woman is aged over 35 years old or if known causes of infertility are present. The initial assessment of the infertile couple involves assessment of duration of infertility, comprehensive history and clinical examination, before requesting appropriate fertility investigations. The causes of infertility can be divided into female factor infertility (35%), male factor infertility (35%), or unexplained infertility (25%).[3] Infertility can result from these factors affecting any one or more of these processes: ovulation, fertilisation or implantation.

Ovulation test

Ovulatory dysfunction is one of the leading causes of female factor infertility. Women who are undergoing investigations for infertility should be offered a blood test to measure progesterone during the mid-luteal phase, which is seven days before the expected next period (e.g. day 21 in a 28 day cycle) to confirm ovulation, even if they have a regular menstrual cycle.[3] Women with prolonged irregular menstrual cycles should have a progesterone test at day 21 of the cycle and repeated weekly thereafter.[3] The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended.[3] Urinary luteinising hormone (LH) tests kits are less accurate but are simple, inexpensive and can be performed by patients in their own home. Serum hormone tracking with or without transvaginal ultrasound follicle monitoring is a more reliable option for women with irregular cycles to detect ovulation for timed coitus.[2]

Endocrine tests

Women with menstrual irregularities should be assessed for thyroid problems, hyperprolactinaemia, pituitary and hypothalamic disorders as part of initial fertility investigations.[3] A history of clinical hyperandrogenism may suggest polycystic ovarian syndrome (PCOS) and requires further investigation. This includes free androgen index, free and total testosterone, androstenedione, serum hormone binding globulin, dehydroepiandrosterone sulphate (DHEAS), fasting glucose, insulin, HbA1C, and cholesterol studies. Timely diagnosis and management of PCOS is important as it may result in other antenatal complications aside from infertility. Given that PCOS is a diagnosis of exclusion it is essential to investigate for other conditions such as Cushing's disease, non-classical adrenal hyperplasia, or an adrenal tumour.[4]

Baseline hormonal profile

Women should have a baseline hormonal profile at day 2–3 of the menstrual cycle, which includes LH, follicle stimulating hormone (FSH), oestradiol (E2), and progesterone (P4).

A basal gonadotropin level is an indirect maker of ovarian reserve based on feedback inhibition from ovarian steroidogenesis.[4] Hypogonadotropic hypogonadism can be caused by weight changes, excessive dieting, exercise or psychosocial stressors, resulting in dysfunction of the hypothalamic-pituitary axis and anovulatory cycles. On the contrary, hypergonadotropic hypogonadism with high FSH and LH and low E2 levels will likely indicate a diminished ovarian reserve or primary ovarian insufficiency. Women with suspected primary ovarian insufficiency should be advised to undertake Fragile–X mutation and karyotype testing to evaluate for Turner's syndrome.

Uterine abnormalities

A good quality pelvic ultrasound is recommended to evaluate the female pelvic uterine anatomy. Pelvic pathology such as uterine septa, submucosal fibroids or polyps may distort the endometrium, affecting implantation. The presence of an enlarged and fixed uterus, venetian blind shadowing or endometriomas are suggestive of endometriosis or adenomyosis.[4] Abnormal ultrasound findings can also facilitate surgical planning and pre-operative counselling, such as features of severe endometriosis such as 'kissing ovaries', obliterated pouch of Douglas, bowel tethering or deep infiltrating nodules.[4] Given that pelvic abnormalities are more prevalent in the infertile population, there may be a role for utilising 3D imaging, saline sonohysterography or pelvic MRI in this group of women.[5]

Tubal factors

Damaged or blocked tubes are a known cause of infertility and can result from pelvic inflammatory disease, pelvic adhesions, previous surgery or endometriosis. Couples presenting with infertility should be routinely offered a sexually transmitted infection (STI) screen.[3] The uterine cavity and tubal patency can be evaluated using a hysterosalpingo-contrast-sonography (HyCoSy), hysterosalpingogram or hydrotubation during laparoscopy.[3] A HyCoSy visualises the spill of contrast out the end of the tubes under ultrasound, where as a hysterosalpingogram takes an X–ray image after contrast medium is passed into the uterus and down the tubes. Women who are thought to have gynaecological pathology should be offered a laparoscopy and tubal dye test so that pelvic pathology and tubal assessment can be performed concurrently.[3] These tests should ideally be performed during the follicular phase of the menstrual cycle to prevent disruption to a possible pregnancy.[2] There are different advantages and disadvantages of using either of these tests, which can be discussed with a fertility specialist.

Ovarian reserve testing

Ovarian reserve testing is an important component of fertility testing and can be undertaken as a blood test for anti–müllerian hormone (AMH) or measurement of an antral fo)llicle count (AFC) on pelvic ultrasound. The AFC is the total number of follicles in both ovaries between 2–10mm on ultrasound during the early follicular phase. AMH is a peptide growth factor produced in both granulosa and Sertoli cells. In women of reproductive age, AMH declines over time as the ovarian follicular pool decreases with age, reflecting the gradual decline in reproductive capacity until menopause. Given its correlation with small antral follicle count (AFC), it is currently the best available means of assessment of ovarian reserve and prediction of reproductive window or potential. AMH secretion remains fairly stable across the menstrual cycle, with little intra-and inter–cycle variation and therefore can be measured on any day of the cycle.[6] It is worth mentioning that AMH is not a marker or oocyte quality or fecundity, but a prognostic marker for an expected outcome in assisted reproductive technology (ART). Both serum AMH and AFC can provide good predictive accuracy of ovarian response to controlled ovarian stimulation and can be used to individualise ovarian stimulation protocols for women undergoing ART.[7]

Semen analysis

A semen analysis should be conducted as part of the initial assessment of an infertile couple and compared to the WHO reference values, even in the presence of known female factor infertility.[2] The man should observe the 2–5 day period of abstinence prior to producing a sperm sample. A normal semen analysis will normally exclude male factor infertility.[2] In the event of an abnormal semen analysis, a repeat confirmatory test should be undertaken three months after modifying lifestyle factors to allow completion of the spermatozoa cycle.[3] Grossly abnormal tests (severe oligospermia or azoospermia) will warrant a repeat test as soon as possible and further investigations to exclude genetic, anatomical, structural, congenital, hormonal, endocrine or infective causes. These may include hormonal profile (LH, FSH, oestradiol, testosterone), inhibin, prostate sensitive antigen (PSA), STI screening, thyroid function, prolactin, karyotype, Y-chromosome microdeletion, cystic fibrosis gene mutation testing, sperm DNA integrity testing (sperm chromatin structure assay–SCSA), ++anti–sperm antibodies, post ejaculatory urine analysis, and/or a scrotal ultrasound.[8] A referral to a urologist may also be required to optimise sperm production for assisted reproduction.

Karyotype

Routine karyotype testing in a couple presenting with infertility is not recommended.[5] A couple presenting with infertility may be advised to perform karyotype testing as a second line test. Where there is a severe deficit in semen quality or a history if recurrent miscarriages, karyotype should be offered.[3] 13.7% of men with azoospermia and 4.6% of men with oligospermia are found to have an abnormal karyotype.[3] Couples who are undergoing karyotype testing should be offered genetic counselling regarding the possible genetic abnormalities that may be detected.[3]

Preconception and genetic carrier screening
It is good practice to perform serological testing for women trying for a pregnancy, including varicella, rubella, syphilis, Hepatitis B, Hepatitis C, and HIV serology.[9] This allows women to undertake appropriate vaccination prior to embarking on a pregnancy or referral to infectious diseases, as appropriate. Women should also have blood group and antibody testing to exclude the presence of undetected blood group antibodies which may implicate the unborn fetus. Genetic carrier screening should also be offered to all couples trying to conceive, especially in high-risk ethnic populations who have a higher likelihood being carriers of genetic disorders such as cystic fibrosis, Tay-Sachs disease, spinal muscular atrophy and thalassemia.[4]

Conclusion

A complete fertility assessment includes evaluation of ovulation, ovarian reserve, pelvic anatomy, tubal patency, basal hormones, endocrine function, semen analysis and pre-conceptual screening. A comprehensive fertility assessment is key to determining the underlying causes of infertility and provide a basis for personalised counselling, management and fertility care for the couple presenting with infertility.

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Reporting success in ART: what is the best measure?

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Melbourne IVF

How best can we define success in assisted reproductive treatment (ART)? This seemingly simple question has many answers, depending on the type of measurement used.

Outcomes of interest include clinical pregnancy rate (CPR), defined as ultrasound evidence of an intrauterine sac with or without a fetal heart, and live birth rate (LBR), defined as gestation more than 20 weeks or birth weight more than 400 grams, irrespective of multiple births.[1] Furthermore, some studies call for more specific ART outcomes, such as birth emphasising a successful singleton at term.[2]

If we consider these outcomes as numerators, then there are various denominators that relate to different parts of the ART cycle.[3] These include, per treatment cycle initiated (fresh or thaw), per oocyte pick-up (OPU), per embryo transfer (ET), and these can change the statistic reported, given that not all stimulation cycles result in either OPU or ET. Thus, changing the denominator can change the percentage.

The need for rigor in reporting is important for patient education, scientific analysis and regulatory processes. There have been international efforts to standardise reporting;[4] however, data reported by the society for assisted reproductive technology (SART) in the US and the human fertilisation and embryology authority (HFEA) in the UK differ slightly. SART report on 'live births per intended egg retrieval (all embryos transferred) yet, HFEA report 'cumulative live birth event per egg collection', subtly excluding those who do not reach OPU stage.[4] As such, some authors argue that it is not possible to have one single best outcome measure, but that a 'set of clear, relevant, outcome indicators' may be more meaningful in empowering patients to make informed choices about fertility treatment.[4]

Measures of outcome in ART

The majority of reported outcomes may be called 'surrogate outcomes' and may be difficult for patients to interpret. This is due to many outcomes being reported and a variation in clinical practice between centres. Until recently, it was possible to select the most favourable outcomes and to use them for marketing purposes. This often results in misleading outcomes promoted on clinical websites, where it becomes difficult to estimate an individual patient's chance of success. The very definition of success in IVF may differ between patients and service providers.

Overall, it is probable that a chance of live birth of a healthy baby at term per treatment cycle initiated (stimulated cycle) is the most meaningful and easily understood measure of IVF success.

Unfortunately, this seemingly straightforward statistic is not widely available and is difficult to estimate. Due to a diversity of variations inherent in IVF treatment, including different age profiles of patients, use of pre-implantation genetic screening (PGS), utilisation of a 'freeze-all' strategy, treatments from one stimulated cycle being separated in time and increasing prevalence of IVF cycles that do not result in pregnancy outcomes (elective and medical oocyte freezing), coming up with an easily understood measure of IVF success that patients can relate to and make informed decisions about their treatment has proven elusive. Also, more than one baby can be born from one stimulated cycle and these births can be separated in time, often by years, which adds another layer of complexity.

ANZARD ART database

Every ART and donor insemination cycle performed in our two countries is recorded in the Australian and New Zealand assisted reproduction database (ANZARD).[1] This data is publicly accessible and recorded through the following partnership's, the National Perinatal Epidemiology and Statistics Unit of the University of New South Wales and the Fertility Society of Australia and New Zealand.

The most recent ANZARD report published in 2020 reported 2018 data.[1] In 2018, the number of initiated

ART cycles was 84,064. These initiated ART cycles were further differentiated into autologous (own eggs) cycles, either fresh or thaw, oocyte recipient, embryo recipient, oocyte donation, gamete intra-fallopian tube transfer, surrogacy arrangement cycles, commissioning or gestational carrier cycles.

The number of clinical pregnancies was 19,514, giving a CPR of 23.2%. The number of live births was 15,475, thus calculating a LBR of 18.4% per initiated ART cycle. The number of live born babies was 15,980, with a multiple birth rate of 3.2%. The number of live born singletons at term (gestational age of 37–41 weeks) with a normal birth weight (more than 2,500 grams) was 13,018, which was 80.2% of live born babies. Furthermore, ANZARD records multiple patient characteristics (Table 1).[1]

In 2018, of all initiated autologous fresh cycles (48,048), there were 92.8% cycles with an OPU (44,569), 49.3% cycles with a fresh ET (23,704), and after excluding 28.1% freeze-all cycles (13,520), there were 7399 clinical pregnancies and 5799 live births (16.8%).[1] Furthermore, of 31,024 initiated autologous thaw cycles, 96.7% had a frozen ET (30,015) with 11,041 clinical pregnancies and 8,827 live births (28.5%).[1]

Cycle-specific success rates

Cycle-specific rates report the chance of a first live birth from one course of ovarian stimulation, followed by all fresh and frozen/thaw embryo transfers.[5]

ANZARD has now included cycle-specific success rates, with data following a recent cohort of women through consecutive ART treatment cycles.[1] In 2016, 15,404 women were followed from their first fresh cycle through subsequent fresh and thaw cycles until 2018, or until they achieved a live birth. The cycle-specific live birth rate per initiated cycle for all women was 23.1% in their first cycle, and 11.6% in their eighth cycle.[1]

Cumulative live birth rates

Proponents of the cumulative live birth rate (CLBR) state that due to multiple reasons for freezing embryos (such as single embryo transfers or to enable PGS), the CLBR could provide a more meaningful measure than single fresh or frozen cycles, where CLBR informs the chance of at least one live birth after a given number of repeated complete ovarian stimulation cycles.[5]

In their study of ANZARD data from 2009–2012, Chambers et al defined conservative CLBR where women who discontinued ART treatment had no chance achieving LBR if they had continued treatment, and 'optimal' CLBR as the same chance as women who had continued treatment.[5]

Of the 56,652 women who underwent 120,930 complete treatment cycles, overall for all ages the CLBR was 32.7% (95% CI, 32.2–33.1%) for the first complete cycle, rising to conservative 54.3% (95% CI, 53.9–54.7%) and optimal 77.2% (95% CI, 76.5–77.9%) for the eighth cycle. CLBR increased with increasing number of cycles.[5]

The major limitations of CLBR, as noted by the authors, was that population estimates do not account for individual prognostic factors that affect a woman's chance of ART success, including duration of infertility, body mass index, previous childbearing, and ovarian reserve.[5]

Table 1. ART patient and cycle characteristics reported by ANZARD.

ART patient and cycle characteristics reported by ANZARD	
Female age	By year range of <30, 30–34, 35–39, 40–44 or ≥ 45 years.
Male age	Also reported by the same range, or listed as not stated or no partner involved.
Parity	Nulliparous, parous or not stated.
Cause of infertility	Male factor only, female factor only, combined male and female factors, unexplained, no cause, not stated or unknown.
Mode of fertilisation	Conventional in vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI).
Number of embryos transferred	One, two, three or more embryos transferred.
Stage of embryo transfer	Day 2–4 cleavage stage embryos, or day 5–6 blastocyst.
Type of cryopreservation	Slow-freeze or vitrification.

Guidelines for reporting ART results

In 2017, the reproductive technology accreditation committee (RTAC) of the FSA released a technical bulletin providing best practice guidelines in acceptable success rate advertising and information provision (Table 2).[6]

There have been recent studies assessing adherence to the guidelines, suggesting room exists for further improvement in reporting.[8] Of note, the RTAC guideline 2017 states that standardised patient groups for the publication of ART success rates are currently in development.[6]

The future

IVF is a dynamic field and significant changes have taken place over the past 10 years. These include transition to blastocyst transfer, improvements in the lab, vitrification, universal ultrasound guided ETs, wider utilisation of PGS, introduction of new medications and adoption of embryoscope incubators with the possibility of artificial intelligence use for embryo selection. These changes, which are ongoing, may produce significantly different results to the ones reported by ANZARD for 2018.

Given the increased focus on accurate reporting, a direction for the future would be for ANZARD data to be used to create an Australian and New Zealand app where women could input their specific parameters and it would calculate the chance of live birth per stimulation cycle initiated, with a range of possibilities. This may also estimate the anticipated number of eggs collected, number of useful embryos and chance of live birth per fresh

or frozen ET. The SART in the USA already provide such an online calculator, the SART Patient Predictor, based on modelling of nearly 500,000 cycles from 320,000 women in the USA from 2006.[10] Of note, the Australian 'YourIVFSuccess' website was recently launched on 15 February 2021, as a collaboration between the NPESU and the federal government, to provide independent information on all fertility units in Australia.[11]

Table 2. Public information, communication and advertising Australian clinics.

Public information, communication and advertising Australian clinics

(Adapted from FSA RTAC Technical Bulletin 2017)

Success rates should include:

1. Age group used in ANZARD data (ie. <30; 30–34; 35–39; 40–44 and ≥ 45 years at the start of treatment), and not other ranges.
2. Live birth rate (LBR) for fresh and frozen embryo transfers separately.
3. Clarifying information: the time period data collected, and details of population group – IVF, ICSI, PGS/PGD or frozen FET, and age group.
4. Cumulative success rates, provided their mode of calculation is explained in clear language.
5. Qualifying statement of broad factors that affect success rates eg. age, weight, cause of infertility.
6. Statement that not every treatment will result in an egg collection, an embryo transfer or embryos to freeze.
7. Link to FSA Interpreting pregnancy rates: A consumer guide.[7]
8. Clarify the meaning of 'clinical pregnancy' and 'live birth rate.'
9. Peer-reviewed scientific data.
10. Clinical governance and compliance to Australian laws and regulations.

Conclusions

Multiple measurements on the success and statistics of ART exist. Our aims should be to clarify reporting of these results, in a manner that is accessible and understandable for patients, whist also noting that an individual is not the average, and ensuring that sound medical advice is provided and clinical acumen applied to their particular circumstance.

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Australian fertility trends: a sociodemographic perspective

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In the demographic sense, a woman's fertility is the number of live births that she has across her reproductive life cycle. Lifetime fertility is measured by demographers using the completed cohort fertility rate (CCFR). This is the average number of births that a group of women all born in the same year (a cohort) have over their lifetime. Thus, CCFR is based on the experience of a group of women across 35 calendar years as they age together from 15 to 50 years. In Australia, CCFR reached a peak of 3.14 births per woman for women born around 1933 but has fallen continuously for every subsequent birth cohort reaching 2.05 births per woman for women born in 1969. At this level, women born in 1969 replaced themselves exactly. Data for women born from 1970 onwards indicate that CCFR will continue its long-term historical decline.

For most policy purposes, however, the interest is not the number of births that women have over 35 calendar years but the total number of births that occur in each successive calendar year. In each calendar year, births occur to women of different ages. To measure the annual trend in fertility, demographers define a second measure, the total fertility rate (TFR), which is the sum from age 15 to age 49 of the fertility rates at each age in a particular year. This measure is analogous to CCFR except that it is based on the experience of women at different ages in the same calendar year.

Australia's TFR (Figure 1) fell slowly throughout the 1990s to a low point in 2001–02 of 1.75 births per woman. Partly in response to the falling fertility rate, in the 2004–05 budget year, the Howard Government simultaneously introduced the Baby Bonus, the Child Care Rebate (CCR) and substantially increased the payments made to families for each of their children (formerly Family Allowance, now Family Tax Benefit Part A (FTB Part A). After the introduction of this policy package, fertility rates rose sharply at every age. In summary form, this is shown in Figure 1 with the TFR rising from 1.81 in 2004–05 to 2.00 in 2007–08. At 2.00 births per woman in 2007–08, TFR was at its highest level for 30 years.

Given the speed and size of this rise and that it applied to women of all ages, it is hard to argue that the policy package did not have an effect. While it is very likely that TFR would have risen at this time without the policy package because educated women in their 30s began to have the births that they had previously delayed at younger ages, this does not explain the rise in fertility at younger ages. And it may well be that the policy package, particularly the CCR, encouraged older educated women to have the babies that they had delayed or at least to have them earlier than otherwise would have been the case.

The TFR remained historically high to 2012–13 in which year it was 1.92 births per woman, but a sharp downward movement has occurred since then to a rate of 1.66 in 2018–19, the last year for which statistics are available. The Commonwealth Treasury expects that COVID-19 will lead to even lower fertility in the short term as births are delayed due to increased economic uncertainty. At 1.66 births per woman, TFR is at its lowest level in Australian history. So, in just a decade, Australian fertility fell from its highest level for 30 years to its lowest level ever. What happened?

Based on long historical experience, when TFR moves by a large amount in a short period of time, either up or down, the movement is associated with changes in the timing of births, particularly the age at which

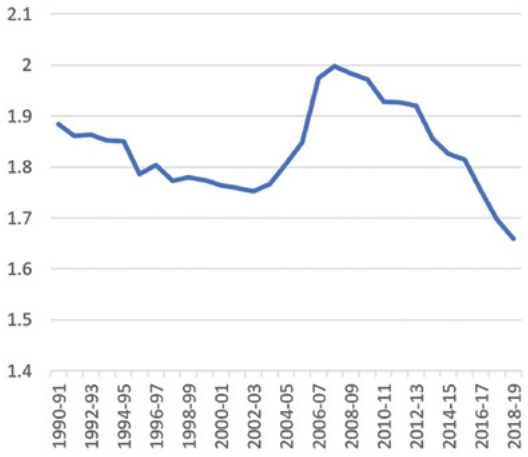

Figure 1. Total Fertility Rate, Australia, 1990–91 to 2018–19.

women have their first birth. When women shift to having their births at younger ages, as they did during the post-war baby-boom years, TFR rises because births are brought forward in time. Likewise, the 2004–05 policy package induced women across a wide range of ages to have their next birth somewhat earlier than otherwise would have been the case, and TFR rose to its highest level for 30 years.

Once a shift of births to younger ages ceases, the TFR can be expected to fall because many women have already had their births at a younger age. This partly explains the fall in TFR from 2012–13 onwards. However, it is also evident that there is a strong, new trend for younger women to delay their first births more than they have ever done in the past. As evidence of this new trend, 86% of the fall in TFR from 2006–07 to 2018–19 occurred at ages 15–30, the younger ages. The sharpest decline was for teenagers (aged 15–19) for whom the fertility rate halved over these years.

There are several possible explanations for younger women increasingly delaying their births. First, women are remaining longer in education. In 2010, 72% of girls aged 15–19 were in full-time education. This had increased to 82% by 2020. A longer period in education then leads to delay of job commencement and career advancement, slower income growth, delay of couple formation and delay of home purchase, all of which contribute to delay of the first birth. Of course, their potential partners experience the same delays. Second, in the past, some teenage girls who had little prospect of advancement in their lives had a baby to give their life greater meaning. Potentially, this attitude has waned in recent years with teenage childbearing now being considered an unwise approach to life. Third, and associated with the previous two possibilities, younger women may have become more effective users of contraception. Fourth, the 2009 Global Financial Crisis (GFC) may have induced a greater sense of caution among both young men and young women and it is possible that young men are also actively avoiding the prospect of early fatherhood. The GFC may also have changed hiring practices so that jobs for young people became less secure in their tenure.

Since the 1970s, except for the five years following the 2004–05 policy package, births have been occurring at older and older ages every year. Conventionally, births were delayed by women up to about age 30 on average but made up (recuperated) from age 31 onwards. This pattern of behaviour led to continuing increases in fertility rates among women aged over 30 (see Figure 2). However, following the peaks related to the 2004–05 policy package, fertility rates above age 30 flattened out initially because, as explained above, many women had had their births at earlier ages immediately following the introduction of the package. However, in the past five years, a very new trend has emerged for women in their 30s. Birth rates between ages 31 and 40 have been falling for the first time in 50 years (Figure 2).

Thus, in the past five years, fertility rates have been falling at all ages from 15 to 40, explaining the very low values for TFR in these years. Rates above age 40 have not fallen but the previous, long-term rising trend at these ages has ended. And, only 3% of total fertility occurs from age 41 onwards. It is interesting that these trends for Australian women are mirrored by similar trends in other English-speaking countries and in the Nordic countries. In New Zealand, TFR fell from 2.10 in 2012 to 1.72 in 2019; in Finland, from 1.80 in 2012 to 1.35 in 2019.

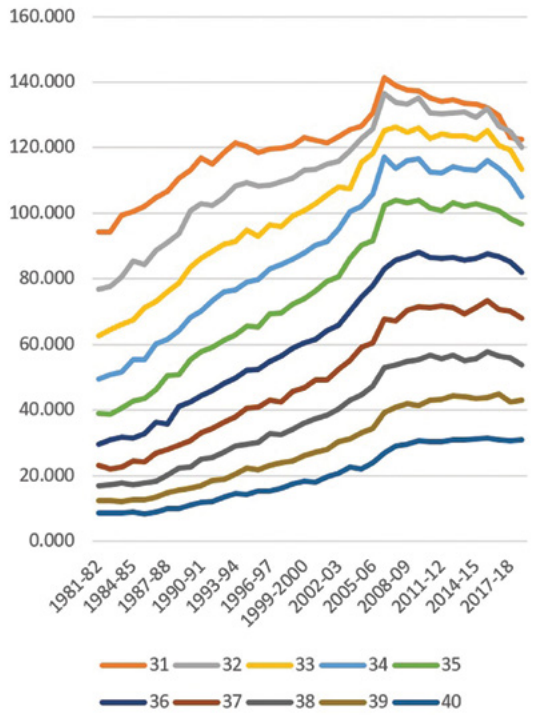

Figure 2. Fertility rates, ages 30–40, 1981–82 to 2017–18.

While it can be expected that the fall in fertility among women in their thirties will slow down or even reverse in the future as the cohorts in their twenties (who have been delaying births) move into their thirties, the declines that have occurred in the past few years for women in their thirties are a very strong indication that TFR will remain low. We are observing a new social trend.

What explains the new and recent behaviour of women in their thirties? This is not an easy question to answer. An obvious point to be made is that, when births are delayed to older and older ages, many of the delayed births never occur. This is because the physiological capacity to reproduce falls away with increasing age but, even more, this occurs because women and their partners reach a stage where they consider that a child or an additional child will be too much of a disruption to their evolving, more settled lives (careers, incomes, lifestyles, relationships). In this situation, the family of three children or more starts to fall away in its frequency, and, in the past 40 years, third or subsequent births have maintained the Australian TFR at a relatively high level of around 1.8 to 2.0 births per woman. Furthermore, one and no child families become more common as first births are delayed by some women to very late ages.

The use of artificial reproductive technologies (ART) can assist those who are eager to have a child but face physiological challenges but ART births constitute only about 5% of births in Australia and, as births are delayed to older and older ages, the technologies become less effective.

For the 70–80%of women who have good or reasonable employment prospects, fertility is enhanced through policies that support the combination of work and family, particularly access to affordable childcare. While Australia introduced a government-funded paid parental leave system

in 2011, international evidence suggests that such leave does not have much effect on the number of births that women have, although, in some situations like Sweden for example, changes in the parental leave system affected the timing of births. The employment participation of mothers does not remain static across time but there is a strong tendency for government support for the combination of work and family to remain static and thereby fall behind changing social behaviour. In Australia, for example, 59 percent of couple families with a child aged 0–4 years in 2019 had both parents employed compared with 48% in 2009. There are benefits, both social and political, in providing enhanced access to childcare.

For the 20–30% of women who do not have post-school qualifications and therefore poor employment prospects, the benefits received from government have fallen considerably since paid parental leave was introduced. From the perspective of the child, the Australian family benefits system is now extremely regressive with poorer children being in families that qualify for little support compared with two-income families that draw large benefits from the childcare and parental leave systems. This is because the larger government benefits related to children (paid parental leave and childcare subsidies) are now highly contingent upon workforce participation. There is still a baby bonus payment for non-working parents, but its value is very small now compared with the time that paid parental leave was introduced. And those not working are only entitled to a maximum of 20 hours per week of childcare support compared with 40 hours for a working parent. The FTB Part A Supplement designed for poorer families is now just $15 per week per child and is only obtainable after the end of the financial year. In the interests of equity for the children in these families, attention needs to be given to increases in FTB Part A and to longer hours of childcare for children in poorer families.

Fertility services in rural and remote Australia

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Why i now grocery shop online and other challenges of providing fertility services in rural and remote australia

One Sunday afternoon, I decided to pop into the local supermarket to pick up a few groceries for the week. I stood in the aisle trying to decide which coffee to buy when I noticed, out of the corner of my eye a pregnant lady and who I presumed was her husband, coming down the aisle. Being a small town, I wondered if she was one of my patients, but soon went back to trying to decide between coffee bags or pods. As they got closer, I went to move out of their trolley's way when, with a smirk and at the top of his voice, her husband announced, 'Oh look honey, there's the man who got you pregnant!' The surrounding other shoppers and staff looked towards me with horror. I quickly went bright red, realising I would have to shop online from now on. I had also discovered another challenge of providing fertility services in rural and remote Australia!

Rural women and their families face significant multifactorial challenges in accessing and undertaking fertility treatments. There can also be challenges for rural specialists in trying to balance access and risk in providing such services locally. A literature review failed to find any significant research into this area, but there have been a number of recent media articles detailing personal stories of remote women and the challenges they faced in accessing fertility services. For some rural women and their families, these additional challenges have been so great that they have been unable to proceed with fertility treatment. These challenges can be even more prohibitive for Aboriginal women living in remote communities who don't have easy access to the most basic of fertility services. In this article, we discuss the challenges of accessing and providing fertility treatments for rural and remote women and develop some recommendations to try and reduce this access inequality.

Access to testing

Fertility tests often seen as routine in metropolitan areas can be difficult to access and time in rural areas. In many remote regions, even taking blood tests can be challenging with phlebotomy services only available weekly or fortnightly when a doctor or nurse is visiting. Any time-sensitive tests can also be difficult as often bloods will need to travel for over 24 hours until they arrive at the laboratory.

Sometimes, other advanced testing is not available locally and would require the patient to travel or consider more invasive options. An example of this are tests for tubal patency such as hysteron-salpingo contrast sonography (HyCoSy) or hysterosalpingogram (HSG). Rather than travelling, some patients elect to have a 'lap and dye', which has the added risks of general anaesthesia and laparoscopy. With the need to be in the first part of the cycle, trying to time flights and ultrasounds adds another challenge.

For the male, a routine semen analysis can also be difficult to access. In Western Australia, this service is not available north of Perth and travel associated with having the test is not covered by the patient travel assistance scheme. Therefore, to undertake an analysis will require at least two to three days of travel, added flight costs often in excess of $1000, and time off work and away from family. Testing is frequently opportunistic such as when if the patient is travelling to a metropolitan area for work.

Access to monitoring

Many fertility treatments require intensive monitoring that can be difficult to predict and plan. This can be challenging in rural areas with services such as ultrasound only visiting intermittently and with a long waitlist. Some blood tests may also need to travel to larger laboratories, leading to a delay in receiving and acting on results. Many towns are serviced only by visiting specialists who are therefore unable to provide day-to-day hands-on monitoring

Access to advanced treatments

Most advanced fertility services are confined to larger regional towns and cities, due to the required laboratories and other support services. To access these facilities, rural women and their partners often have to spend extended periods away from home, which adds further costs and stressors. While there are patient travel assistance schemes to help offset these travel costs, they seldom cover all costs, especially if needing to stay in a hotel or other accommodation. For the male, only their travel to the first and second appointment is covered, meaning they will need to self-fund costs if they want to accompany their partner on further appointments and procedures. There are also added costs of taking leave from work or businesses and organising care

for other family members and dependants left at home. With these added costs, more and more rural patients are applying to access their superannuation to pay for fertility services, a practice that has financial implications later in life.

Added medical risks

For rural doctors providing fertility services, it can be challenging to balance risks with trying to provide treatment close to home for these rural women. An example of this can include whether you should start ovulation induction or perform a diagnostic laparoscopy prior to accessing a semen analysis for the partner. Often the ability to monitor patients through blood tests and ultrasounds are limited and this may increase the risk of higher order pregnancies.

Patients may elect to have treatments that are not evidence based, as they are unable to afford or access more of the considered standard care. Examples from my personal practice include carrying out more ovarian drilling in rural areas compared to my practice in the city, or persisting with ovulation induction for much longer periods in rural areas rather than progressing to IVF. Doctors may also advise rural patients to proceed straight to IVF in many circumstances rather than IUI or ovulation induction as this is overall easier to provide.

Added challenges for Aboriginal women

I visit a number of very remote Aboriginal communities and the infertility rates are higher than expected. The main causes appear to be anovulatory cycles with high rates of polycystic ovary syndrome and tubal factors from pelvic inflammatory disease. The women present very young after trying to fall pregnant for a number of years and describe 'big shame' regarding their infertility. Providing fertility treatment can be very challenging. Blood tests may only be able to be taken once a week when the 'mail plane comes' and patients then need to travel for all other tests. It can be very challenging to involve the male partner as the infertility is seen only as a 'women's problem.' With high rates of smoking and excess alcohol use, it could be argued that there often may be a male factor as well. With limited health education, ovulation induction can also be extremely high risk in these communities, compounded by the limited opportunities for monitoring its progress. With the high rates of tubal disease many women also require IVF to treat their infertility. The majority however do not proceed due to the direct and indirect costs, as well as lack of partner cooperation or involvement in the process. These women present year after year, but there is ultimately little we can offer them in these situations, which can be very distressing for both the patient and doctor.

Reducing access inequalities

Many IVF services are very accommodating and supportive of rural patients and the added challenges they face. Ways in which these access challenges can be further addressed include:

- Expanded use of telehealth for initial appointments
- Fertility units developing relationships with rural ultrasound and pathology providers to allow patients to stay locally as long as possible with cycle tracking and other treatments
- Use of rural general O&G specialists with support and advice to carry out as much treatment as possible in rural areas
- Advocacy for further funding for rural patients to help offset indirect costs of travelling for fertility services
- Culturally appropriate fertility services that encompass education and support for Aboriginal patients, including accommodation and travel support.

Hopefully with ongoing technological advances, we will be able to see more and more fertility treatments available in small to medium size towns, which will further allow more rural women and their families access to investigations and treatment closer to home.

Recurrent pregnancy loss: the way forward

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Pregnancy loss is a significant life event for many couples, and accounts for a large number of presentations to an emergency department, with considerable resources being allocated to these devastated couples. While a single miscarriage may be an isolated event, most likely due to a genetic abnormality, recurrent pregnancy loss (RPL) is a separate entity. One of the most difficult aspects of dealing with these couples is the lack of consensus on whom to test, what tests to offer, and how to treat. This dilemma is compounded by the fact that every country has a different approach, with RANZCOG guidelines following the RCOG Green-top Guidelines dated 2011.[1] Europe follows the ESHRE guidelines,[2] dated 2018, and the USA follows the ASRM guidelines,[3] dated 2012.

Background

Pregnancy loss is divided into embryonic or fetal. Embryonic is defined as a loss at ten weeks post the last menstrual period or less. Fetal losses are losses after ten weeks and up to 24 weeks. A RPL/miscarriage clinic has been held at the Women's and Children's Hospital (WCH) in Adelaide since 2007. Approximately 2000 patients have attended, referred from a number of different areas. Over the years, investigations have been added or discarded, depending on the available evidence. This article will discuss risk factors for recurrent miscarriage, upon which the investigations currently offered at the WCH are based, and the proposed way forward, based on the latest evidence from recurrent miscarriage groups internationally.

We offer a workup to couples with pregnancy losses after two embryonic losses, one ultrasonically confirmed fetal loss, or one embryonic and one fetal loss. We do include non-visualised losses if the histopathology was positive for pregnancy, as Kolte et al[4] demonstrated that these losses decreased the relative risk for a live birth by 10%, which is the same impact conferred by a clinical miscarriage.

Risk factors

Epidemiological factors have been identified as risk factors for further miscarriages, including maternal and paternal age, and the number of previous miscarriages. After three consecutive pregnancy losses, the risk of a further miscarriage is estimated to be approximately 40%, and this risk increases with maternal age.[1] Environmental risk factors, such as smoking and alcohol consumption, have been linked with sporadic miscarriages, and the recent ESHRE guidelines have made the suggestion that smoking and alcohol cessation should be recommended.[2]

Antiphospholipid syndrome is an important, treatable cause of recurrent miscarriages with antiphospholipid antibodies present in 5–20% of women with recurrent miscarriages.[2,5]

Chromosomal abnormalities of the embryo account for a significant proportion of miscarriages (between 30–57%) with an increase seen with advancing maternal age.[1] Parents who are carriers of a balanced translocation are at increased risk of miscarriage and these are found in 3–5% of recurrent miscarriage couples;[6] therefore parental karyotyping is recommended by ASRM,[3] but not by ESHRE,[2] who suggest only testing if there is an increased risk after individual assessment.

Anatomical factors, mostly uterine malformations, have been linked with recurrent miscarriage; however, the exact role they play is unclear. Both congenital and acquired uterine defects are seen in women who experience recurrent miscarriages and therefore imaging to look for septate, bicornuate, didelphys and arcuate defects, as well as fibroids and polyps, is recommended.[6]

Endocrine factors play a role in recurrent miscarriage. Overt hypothyroidism clearly increases the risk of miscarriage; however, the impact of subclinical hypothyroidism is less clear. The role that positive thyroid antibodies have is also unclear, although positive thyroid antibodies with subclinical hypothyroidism may increase miscarriage risk.[5] Insulin resistance or hyperinsulinism has been thought to be associated with pregnancy loss, particularly in patients with polycystic ovarian syndrome.[1]

The male partner is investiaged as it is believed that sperm DNA damage may contribute to adverse pregnancy outcomes, and when sperm from couples experiencing RPL was compared with sperm from couples without pregnancy loss, a lower percentage of normal sperm morphology, concentration and progressive motility was found in the pregnancy loss group compared to those without loss. Obviously, sperm quality may affect embryonic development by genetic, as well as epigenetic, mechanisms.[7,8] These sperm-borne epigenetic marks are, in turn, affected by a variety of paternal factors, including genotype, age, obesity, smoking and exposure to environmental contaminants.[9]

Investigations

When patients are seen at the WCH RPL clinic, a thorough history is obtained from both partners, including medical history, medications, allergies, lifestyle factors and family history. The body mass index (BMI) of the patient is recorded.

We offer the following investigations to couples seen in the RPL clinic.

Females:

- Thyroid function tests ('subclinical hypothyroidism' is treated if the TSH is greater than 2.5 mIU/L)
- Thyroid antibodies (noted but not independently treated)
- Antiphospholipid antibodies (2 positive tests required, minimum 6 weeks apart, for positive diagnosis)
- Anti-nuclear antibodies (for information regarding other autoimmunity)
- 75g oral glucose tolerance test with insulin studies
- Fasting homocysteine levels
- Folate and B12 levels and vitamin D levels
- +/- Karyotype, if genetics of last loss unknown
- 3D pelvic ultrasound in the luteal phase of the cycle

Males:

- +/- Karyotype
- Glucose and insulin
- Homocysteine
- Folate and B12 levels and vitamin D levels

Discussion: the way forward

Khalife et al[6] and Popescu et al[10] have suggested strategies for the optimal evaluation of pregnancy losses, which include the incorporation of a 24-chromosome microarray on the products of conception (POC), as microarrays increase the chance of identifying an aneuploidy compared to conventional karyotyping, and potentially avoid maternal cell contamination. They suggest that the products from the second pregnancy loss should be tested, and if abnormal, then the expensive evaluation could be avoided in these patients. Using this method, Khalife et al detected aneuploidy in 63% of those tested, thus negating the need for the costly evaluation that could result in unnecessary treatment for presumed causes.[6] These arrays also identified an unbalanced translocation in 4% of the POC which could have originated in the parents, hence parental karyotyping was then offered. The remaining 33% of 'normal' chromosome microarray analyses (CMAs) were offered a full RPL work up, as there was no other explanation for the losses. There is, however, a considerable cost involved in performing CMAs, and they may not be available in all centres.

A trial is currently underway in our centre, comparing the evaluation of the products of conception via the conventional Karyotype method or via microarrays.

Conclusion

While recurrent miscarriages are common, and regarded as minor medical issues by many emergency departments, there is increasing evidence that these patients may be a high-risk population for adverse obstetrical outcomes when they do finally become pregnant, necessitating increased antenatal surveillance. Rasmark Roepke et al, in a retrospective cohort study, showed that women suffering RPL when compared to women who had not had losses, had an increased risk of pre-eclampsia, preterm birth, small for gestational age babies, abruption and stillbirth less than 37 weeks, suggesting that these issues are associated with placental dysfunction.[11]

Research has also shown that women who suffer recurrent miscarriages are at an increased risk of future cardiovascular disease of total coronary heart disease after adjusting for traditional cardiovascular risk factors.[12] The risk appears to be independent of BMI, hypertension, waist-to-hip ratio and white cell count.[13]

Thus, miscarriages may reflect a bigger picture of overall cardiovascular health, and as such, could be a primary healthcare issue with possible preventative interventions for this group.

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The endometrium and implantation

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Subfertility is a global problem and,as such, many couples seek assisted reproduction. This has led to over 2.5 million IVF and intracytoplasmic sperm injection (ICSI) cycles being performed annually. Over the last 40 years, techniques have improved but the pregnancy rates following an embryo transfer still remain at 35%.

Endometrial receptivity and selectivity are two complementary concepts introduced by Macklon and Brosens[1] to describe how the endometrium interacts with the embryo presented to it for implantation. Selectivity is the endometrium's intrinsic ability to recognise and reject abnormal embryos. In contrast, receptivity is when the endometrium is an optimal environment for embryo implantation and development.

Implantation failure occurs as a result of either impaired embryo development potential or impaired endometrial selectivity/receptivity. Embryos account for one third of implantation failures, while the endometrium is at fault in the remaining two-thirds of these cycles.

The endometrium and the characteristics of the window of implantation (WOI) have been studied for more than 80 years. Endometrial receptivity is characterised by a 4–5 day WOI, coordinated by an incompletely defined complex of endocrine, paracrine and autocrine factors. This limited period can be found from LH surge +6 days to LH surge +9 days in a natural cycle or from progesterone +4 days to progesterone +7 days in hormone replacement therapy (HRT) cycle. Despite increased understanding of the processes associated with embryo-endometrial cross-talk and implantation, little progress has been achieved in development of diagnostic tests and treatments for suboptimal endometrial receptivity.

Two areas that have received attention and translation to clinical usage over the last few years are the endometrial scratch, and tests assessing the molecular receptivity of the endometrium; but have they improved outcomes?

Endometrial scratch

Endometrial scratch in assisted reproduction has been advocated for over 20 years, to improve the chance of embryo implantation.

In 2000, endometrial biopsies were taken as part of a study to assess the endometrial characteristics of women, where IVF had failed to assist them in falling pregnant. The biopsies were taken during the luteal phase of the cycle preceding an IVF cycle. A chance finding was that 11 out of 12 of these subfertile women conceived after that IVF cycle.[2]

This led to a cascade of randomised control trials (RCTs) and subsequent reviews on endometrial scratch research. Conclusions have been everything from increased clinical pregnancy and live birth rates to no difference. Mostly the reviews suggest moderate quality studies performed on a diverse population of patients using a variety of different mechanisms to scratch with different protocols and timing. In addition to this, the biological plausibility of how a scratch is beneficial is yet to be determined. The thought is that it induces an array of pro-implantation cytokines to flood the endometrium during the window of implantation in the subsequent cycle to improve this process. Whether it is useful for implantation failure patients or for general IVF/ICSI patients, it has gained wide clinical usage with up to 83% of clinicians in some countries advising patients of this treatment option.[3]

The most recent review was published in 2019,[4] which included 14 RCTs on 2537 participants. The effect of scratching was assessed for three distinct patient groups; IVF naive patients (Group 0), patients with one full failed IVF/ICSI cycle plus frozen transfers of cryopreserved embryos (Group 1) and patients with 2+ failed IVF/ICSI cycles plus transfer of cryopreserved embryos (Group 2).

In Group 1, no difference in clinical pregnancy rate (CPR) (RR=1.01) (95% CI 0.68–1.51) or live birth rate (LBR) (RR 1.04) (95% CI 0.74–1.45) was found. For Groups 0 and 2 pooled analysis couldn't be done, due to heterogeneity, and the results of the individual RCTs ranged from negative to neutral to positive in support of endometrial scratch. Multiple pregnancy and miscarriage rates were assessed in each of the 3 groups; no difference was found for multiple pregnancy (RR=1.06) (95% CI 0.84–1.35) or miscarriage (RR=0.82) (95% CI 0.57–1.17).

Researchers tried to improve the heterogeneity by removing trials where control group patients had unintentional endometrial injury, such as a hysteroscopy. This did allow pooled analysis of

Groups 0 and 2. Only CPR was improved in Group 0 (RR 1.28 (95% CI 1.02–1.62) and Group 2 (RR 2.03) (95% CI 1.20–3.43) but there was no difference in LBR, miscarriage or multiple pregnancy rate.[4]

The ultimate conclusion drawn from this review is that studies to determine if endometrial scratch is beneficial in improving implantation failure are both clinically and statistically heterogeneous due to variations in the timing, frequency and even method of intervention, patient population being treated and also definitions of the outcomes. There was also a high risk of bias in the study methodologies throughout many of the studies.[4]

The clinical utility of endometrial scratching is further questioned after a more recent, large RCT involving 1364 women undergoing IVF reported that scratching did not result in a higher rate of live birth than no intervention.[5]

It may seem that endometrial scratch is easy, but it is not without possible harm (infection, treatment burden, false hope). At best, scratching may have a positive effect on CPR in patients with recurrent implantation failure after two IVF/ICSI cycles, but the data is heterogeneous and of moderate quality only. For all other patients and outcome measures, it is likely unhelpful.

Endometrial receptivity assay

We use a number of tools, including ultrasonography and blood hormone levels, to monitor the WOI to allow for the optimum time for embryo transfer. These lack precision and objectivity because there is both inter patient and inter observer variability in these tools, plus the WOI is hard to define.

The endometrial receptivity assay (ERA) was developed as an objective tool to accurately and reproducibly determine the receptivity status of the endometrium. Using 'omics', ERA profiles, the transcriptome of 238 genes that are expressed at different times in the endometrial cycle which then, coupled with a computational predictor, enables personalised timing of the embryo transfer (pET).

The ERA has been demonstrated to be reproducible in patients across multiple menstrual cycles and more accurate than histological sampling.[6] Its application in the clinical setting is gaining traction and research interest.

Ruiz-Alonso and others[7] assessed the endometrial receptivity in 85 women scheduled to undergo frozen-thawed embryo transfer in natural or HRT cycles. ERA test identified a higher rate of non-receptive endometrium in women with recurrent implantation failure (22/85, 25.9%) compared to women without recurrent implantation failure (3/25, 12%). Women diagnosed with non-receptive endometrium on the initial ERA test achieved a pregnancy rate of 50% (4 out 8 women with follow-up data) after pET.[7]

More recently, researchers completed a large multicentre RCT on 458 good prognosis patients undergoing IVF with blastocyst transfer to determine if pET increased pregnancy rates over frozen embryo transfer (FET) and fresh embryo transfer in IVF.[8] This was not limited to recurrent implantation failure patients. The study was hampered by a 50% drop out rate and so was underpowered to detect a statistically significant difference by intention-to-treat analysis; however they did find that cumulative pregnancy rates were higher in pET (93.6%) compared with FET (79.7%) (p=0.0005) or fresh embryo transfer (80.7%) (p=0.0013). Per protocol analysis demonstrated statistically significant improvement in pregnancy, implantation and cumulative LBR in pET compared with FET and fresh ET. Subgroup analysis considered the number of previous failed IVF cycles and suggested consistently higher percentage points in pregnancy and LBR across all groups. Of interest, they also looked at the impact of the 'endometrial scratch' to obtain the tissue sample for ERA and ruled out any beneficial or detrimental effect of the injury on outcomes.[8]

Personalised medicine is still quite new to reproductive medicine, but most specialists will agree that one size does not fit all and that modification of the timing of embryo transfer to optimal endometrial receptivity warrants ongoing focus and the ERA is likely to help improve this.

Emerging science: the endometrial microbiome

It was thought that the endometrium was a sterile environment however studies suggest a unique population of micro-organisms are present in the uterine cavity, different to that found in the cervico-vaginal environment. Given that changes in the human microbiota have been linked to several disease states, (we also know that changes in the vaginal microbiome, such as with bacterial vaginosis, has been associated with miscarriage and preterm birth) then the potential for the uterine microbiome to be linked to reproductive health outcomes warrants consideration.

New research has determined that the presence of a non-Lactobacillus-dominated microbiota in a receptive endometrium (as determined by the ERA test) is associated with a significant decrease in pregnancy and live birth rates.[9]. The endometrial microbiome should be considered as an emerging influence of implantation failure and pregnancy loss and is gaining traction as an area of interest for the development of diagnostic tests and treatment.

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The process of IVF: a consumer perspective

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Author

I was never good at science. In high school I memorised the table of elements because it sounded like a poem to me – hydrogen, helium, lithium, beryllium – but I never understood how the elements fitted together. Letters in words made perfect sense, but letters that stood for chemical compounds did not. Even biology was hard. How cells behaved, how anatomical parts interacted, how genes transmitted information, none of this information would stick to my brain.

Embarking on an IVF program felt like a return to this state of anxious ignorance. The gynaecologist explained to me what would happen, drawing little pictures on a notepad to give me visual images of the process. But an hour after the appointment I'd forgotten the details. There would be lots of appointments and procedures, that much I gathered. I kept a detailed diary, turned up for things on time. Appointments I could do. But remembering exactly what I'd be turning up for would be harder.

One broken relationship, three miscarriages, and five years of trying to have a child; I finally opted for IVF treatment. My early miscarriages had been interspersed with long periods of apparent infertility. If there was something wrong with me, no doctor had yet been able to establish what it was. Grief had ruptured my relationship, and I was no longer with someone who wanted to have a child. My best option was to choose a sperm donor and go it alone. It was early in 2003, I was 38 years old and running out of time.

Before the IVF specialists could start match-making my eggs with the donor sperm, they needed to make sure I had a good supply of healthy ones. My egg production would be boosted with hormone injections, and it would be up to me to self-inject the magic fluids. I was given a miniature suitcase containing phials of pharmaceuticals and plastic-wrapped syringes and told to make sure the drugs were refrigerated.

The first time I injected myself in my belly, my hands were shaking. Will it hurt? Have I got the right spot? What if there's an air bubble in the tip of the syringe? Air bubbles were dangerous, I knew that much, and spent a long time studying the syringe to make sure it didn't look like a spirit level. Then, pinching my belly skin, I pushed the needle into my white flesh. When the pain came, it was surprisingly mild. Nothing like my memories of childhood vaccination needles. And then later, nothing like the pain of an embryo dislodging itself from the lining of my uterus and making its way to the nearest exit. That pain made no sense to me. Such a tiny thing travelling a short distance. How could it possibly leave me bent double? This was one of the revelations; needles were the easy part.

The side effects of the hormones were harder to endure. My belly was bloated, my head ached, and I felt tired all the time. I'd always suffered from PMT, becoming teary and anxious each month before I bled. The hormones I was now taking doubled the dread. Sometimes I wished I had a partner who could drive me to and from medical appointments, someone who'd listen to me recounting the indignities of lying splayed on a gurney while masked people inserted instruments inside me.

In the absence of a partner, my mother stepped into the breach. Month after month she picked me up from appointments, took me to a cafe and handed me tissues as I rode the waves of hope and fear accompanying each egg harvesting procedure, each embryo implant. The news from the gynaecologist wasn't good. I wasn't producing many eggs, and those I did produce were not in great shape. A couple of times the fertilised embryo hung in there for a few days after my period was due, and I held my breath and crossed my fingers. But then I'd begin bleeding heavily, and the whole complicated round of interventions would have been in vain.

The IVF process ground on. In November the gynaecologist told me I had one stored embryo left. The Christmas holidays were approaching, so if the next implant didn't stick, we'd have to put things on hold for a few months. They were clearly baffled by my failure to produce good eggs. Could I have a mysterious condition that hadn't yet been diagnosed? Was this why my eggs were so shabby, and why I'd had three miscarriages? No one could give me a clear answer. There was still so much they didn't know.

It had now been six years since I first started trying to have a child. Could I keep going with this for another year? Keep duelling with hope, month after month, licking my wounds every time I failed.

I looked up the statistics on childbirth. The previous year, in 2002, there were 250,000 babies born

in Australia, and in the same year, four million babies born around the globe. There were babies everywhere, pushed in prams along the streets of my suburb, spoon fed in high chairs in my local cafe, smiling at me from banner ads on the sides of buses, bouncing up and down on television ads for toilet paper, being dandled above the shallows at my local beach. So many births, so many babies, and none of them mine.

The last embryo didn't stick. I called my mother and we met at a cafe near her work. Sitting in an alcove, I wept into a paper napkin. 'I'm so tired,' I told her. 'I want to get away.' But when I tried to work out what I wanted to get away from, I realised – it was me. My mother was silent, at a loss. There was nothing she could do to fix this.

'I need to stop now.' As I heard myself speaking these words, I realised the decision had been made. The part of me I wanted to get away from had had enough. Time to give up. Time to become someone else.

A few years later my GP orders some blood tests. I'm tired all the time, have been for ages. The tests reveal that I have something called 'hypothyroidism'. I'm not even sure what my thyroid does. I do an internet search.

The thyroid gland secretes the hormones thyroxine and triiodothyronine. Hypothyroidism occurs when the thyroid gland does not produce enough thyroid hormones. If hypothyroidism is not treated, the symptoms slowly get worse and it becomes more and more difficult to function normally. Symptoms include tiredness, sore muscles, constipation and sensitivity to the cold. Bingo! I've been dealing with all these symptoms for years. Then this:

Also fertility problems and increased risk of miscarriage. Wait. What?

Had I wasted six long years because of a dicky thyroid? All the doctors I'd seen, all the money I'd spent doing IVF, all those blood tests, and no one had discovered this problem? Should I try again? Sort out my thyroid and climb back on the IVF merry-go-round?

The thought only lasts a few seconds. I'm 43 years old. It's too late.

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Male infertility: a clinical approach

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Lower reference limits of sperm parameters (5th centile with 95% CI)

Semen volume: 1.5 mL (1.4–1.7)
Total sperm numbers: 39M per ejaculate (33–46)
Sperm concentration: 15M per mL (12–16)
Total motility: 40% (38–42)
Progressive motility: 32% (31–34)
Sperm morphology: 4% normal forms (3.0–4.0)

Obstetrics and Gynaecology, may have had little or no exposure to addressing male disorders. It is estimated that men contribute around 50% to overall infertility.[1] Therefore a thorough evaluation of the male partner is important. In particular asking questions regarding symptoms and conducting an examination which may prove confronting.

Nevertheless, an in-depth evaluation of the male partner is important. In many cases it is possible to obtain a diagnosis and commence appropriate treatment in order to improve a couple's chances of conceiving. It is also important to include the male partner in all discussions and decision making in order to keep him engaged and supported in the couple's infertility journey.

It is also important to look beyond the semen analysis report as there is increasing awareness that male fertility is an indicator of overall health. Evidence points to increased incidence of co-morbidities such as cardiovascular disease, type 2 diabetes, increased incidence of testicular cancer, and increased mortality in men with semen abnormalities.[2] There is increasing evidence that both genetic and non-genetic factors in sperm, for example microRNA's, have an influence on the health of children.[3]

Evaluation of the male

The first encounter with the male patient is often the semen report. The accepted reference for semen testing along with laboratory techniques are found in the World Health Organisation (WHO) laboratory manual.[4] This manual includes a reference range based on sampling a large population of men with a healthy sperm count.[5]

It is important to remember that one abnormal parameter on its own is not a predictor of infertility. The presence of multiple abnormalities has more clinical relevance.[6] And there is considerable variability in sperm quality between samples in healthy men.[7] Therefore it is recommended that at least 2 samples are examined.[8] More advanced testing of samples, such as DNA fragmentation has reported effects on conception and miscarriage risk.[6]

In addition to semen testing, it is important to thoroughly evaluate the male by taking a medical history, conducting an examination, and where appropriate, conducting further investigations. Also many men may volunteer information and confide in having suffered from low libido, and tiredness which may relate to low testosterone.

A surprising number of previously undiagnosed conditions such as undescended testes are detected by the physical examination. It may be helpful to use orchidometer beads to assess testicular volumes. Particularly important is palpation of the vasa deferentia, because congenital absence of the vas deferens (CBAVD) is relatively common. Examination of the scrotum is best performed in the standing position, as this will make detection of varicoceles easier.

Evaluation of azoospermia

The initial encounter with a patient presenting with azoospermia can seem challenging. However, having a systematic approach and referring to the classification system of causes, will make this task easier.

Classification of azoospermia
- Pre-testicular (hypogonadotropic)
- Testicular
- Obstruction
- Retrograde and anejaculation

Clinical clues which help with diagnosis include examination of testicular volumes (typically low in testicular disorders and in early onset hypogonadism) which are very small in Klinefelter syndrome (KS). Around 90% of the ejaculate volume derives from the prostate and seminal vesicles. Semen volume is low in CBAVD, ejaculatory duct obstruction, retrograde ejaculation and chronic hypogonadism. Failure to palpate the vasa deferentia will diagnose CBAVD. Also check for unilateral renal agenesis (URA) and cystic fibrosis gene mutations in these patients. Examination of post ejaculate urine and transrectal prostate

Classification	Testicular	Obstruction	Pre-testicular	Retrograde ejaculation
Semen volume	Normal	Normal or low (depending on the site of obstruction)	Normal or reduced	Reduced
Testis volume	Small	Normal	Normal or reduced	Normal
Vasa	Palpable	Absent in CBAVD	Palpable	Palpable
Gonadotrophins	Elevated FSH	Normal	Reduced FSH and LH	Normal
Testosterone	Normal or low	Normal	Reduced	Normal
Treatment	Micro TESE	Needle extraction (testis or epididymis)	Treatment of cause and gonadotrophin supplements	Sperm from urine or needle extraction

ultrasound will help where ejaculatory volume is very low. Elevated follicle–stimulating hormone (FSH) (over 7.5mU/mL) points to testicular causes.[6] Low Luteinizing hormone (LH) and low morning testosterone are noted in hypogonadotropic patients. Obstructive causes account for around 40% of patients with azoospermia.[9]

Causes of obstruction / ejaculatory azoospermia
- Post vasectomy
- CBAVD
- Ejaculatory duct obstruction
- Retrograde ejaculation
- Anejaculation e.g. spinal injury

Management of these patients is relatively straightforward. Needle collection of either sperm or tubule tissue can be used for intracytoplasmic sperm injection (ICSI). In cases of retrograde ejaculation, an alternative is to use sperm from post ejaculation urine. Vasectomy reversal is an option in those men who underwent the vasectomy under 10 years previously.

Testicular sperm extraction (TESE) is a brief outpatient procedure on the awake patient. Local anaesthetic is infiltrated directly into the scrotal skin and testis whilst grasping the testis. A 19 gauge needle is used to extract seminiferous tubule tissue which is examined immediately by the scientist. Occasionally more than one needle pass is needed in order to collect an adequate sample. TESE tissue is usually cryo-stored in straws which may be thawed individually as needed. The technique for percutaneous epididymal sperm aspiration (PESA) is similar, but instead of extracting tubules, free sperm is aspirated, and this is used on the same day as the egg retrieval. Surgically extracted sperm is only suitable in the context of ICSI.

Testicular disorders are sometimes referred to as non-obstructive azoospermia (NOA) and account for around 60% of azoospermia cases.[9]

Causes of testicular (NOA) azoospermia
- Undescended testis
- Torsion
- Injury
- Orchitis
- Post chemotherapy
- Klinefelter syndrome
- Micro Y deletions
- Other genetic causes
- Unknown

Included in this group is the relatively common KS. In addition it is important to check for micro–Y deletions.

There is increasing awareness of other genetic causes.[9] Unfortunately, in many cases the cause is unknown.[6] In patients where spermatogenesis has been stored in isolated tubules, it may be possible to surgically extract sperm. Traditionally, random testicular biopsy, and more recently micro–TESE have been used.

Micro–TESE is an advanced technique used to improve surgical sperm retrieval rates in men with testicular cause azoospermia. A powerful operating microscope is used in order to better identify potential tubules. This procedure is conducted in the operating theatre under general anaesthesia, and may take up to four hours. Typically, two scientists are present in the theatre in order to immediately examine the samples for sperm. This technique has largely replaced random testicular biopsies and is more likely to lead to successful retrieval.[10] Sperm retrieval rates are reported in the 40–60% range.[10]

Pre-testicular (hypogonadotropic) is the least common cause of azoospermia.

Pre-testicular causes of azoospermia
- Androgen intake
- Pituitary tumours (craniopharyngioma)
- Head trauma, surgery, irradiation
- Kallmann syndrome
- Thyroid dysfunction

Management of these cases includes correction of underlying conditions where possible and may include treatment with human chorionic gonadotropin (hCG) and FSH injections. It may take 12 to 18 months for a sufficient quantity of sperm to appear in the ejaculate to allow cryo-storage. The sperm is used for ICSI treatment.

Reduced semen quality

Sperm quality influences time to pregnancy.[11] Since recordings began in the 1930s there have been indications of a decline in sperm quality.[12] This decline is also influenced with the increase in male age which in turn increases the risk to pregnancy and offspring.[11,12,14] A broad range of influences affect

Adverse environmental conditions affecting male fertility

- Aging male
- Obesity
- Poor diet
- Unhealthy lifestyle, including smoking, excessive alcohol and recreational drugs
- Medical disorders such as diabetes and hypertension
- Varicocele
- Infections
- Exposure to environmental chemicals and toxins
- Excessive heat

male fertility including a number of rare disorders such as Immotile Cilia Syndrome.

This is the time to discuss measures to improve the man's health. Checking for co-morbidities which are known to be more common in subfertile men.[2] Discussing lifestyle choices, including healthy diet, regular physical activity, and managing obesity.[2] Addressing the use of alcohol, smoking and recreational drugs. This is also an opportunity to encourage testicular self-examination particularly in view of an increased testicular cancer risk.[15] There is evidence for benefit in correction of a clinically palpable varicocele.[16] Antioxidant supplements have received considerable attention.[17]

Management of erectile difficulties will increase opportunities for intercourse and reduce the need for IVF. Consideration can be given to prescribing adjunctive medications such as, hCG, in order to improve libido and semen quality.

Summary

Evaluation of the male partner is an important part of the infertility work up. It is possible in many cases to improve sperm quality in order to facilitate natural conception and to improve health outcomes for the children. It is an excellent opportunity to engage the male partner with health disorders. And it is possible in many cases to induce production and collection of sperm from men with azoospermia for use in assisted reproduction.

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Fertility treatments other than IVF

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Infertility is a common condition with approximately one in six couples experiencing difficulties while trying to conceive. In Vitro Fertilisation (IVF) is a highly successful treatment option for infertility with an overall live birth rate (LBR) per embryo transfer of 27.3%.[1] Increasingly, with low cost IVF clinics becoming more prevalent, IVF is commonly used as primary treatment option; however, this is not without risk. While IVF is an appropriate first line option for patients affected by tubal, unexplained and male factor infertility, there are numerous alternative treatment options available. These include lifestyle modification, ovulation tracking (OT), luteal phase support, intrauterine insemination (IUI) and ovulation induction (OI), all of which are less invasive, less expensive and offer good rates of success.

IVF indications

IVF is indicated as a first-line option for unexplained infertility, tubal factor infertility, severe male factor infertility and for those making use of preimplantation genetic diagnosis (PGD) It is also useful as a second-line treatment for patients who have failed less invasive options. IVF is used in surrogacy (uterine factor) or with donor oocytes or embryos for patients with premature ovarian insufficiency. It is also reasonable to consider IVF as a first-line treatment for patients of advanced maternal age where fertility preservation is desired.[2]

Indications for fertility treatments other than IVF

For patients without absolute indications for IVF, it is best practice to offer less invasive treatment options first. Causes of subfertility that can be considered for treatment other than IVF include:

- Unexplained infertility
- Ovulatory disorders
- Social infertility
  - Geographical separation (eg. Fly-in-fly-out workers)
  - Single individuals (donor sperm)
  - Same sex female couples (donor sperm)
- Mechanical infertility
  - Vaginismus
  - Erection or ejaculatory disorders
- Luteal phase deficiency

Normal fertility

A couple of reproductive age has a fecundity of 20–25% per cycle. Approximately 85% of these couples will conceive within 12 months and this increases to 93% after 24 months.[3] Fecundity decreases with time and increasing maternal age.[4] Success rates for non-IVF treatments are limited by the expected fecundity of a fertile couple. Care should therefore be individualised taking into account maternal age, duration of infertility and previous treatments. An individual's indications for progression to IVF needs to be discussed prior to the commencement of non-IVF treatment, in the event of non-IVF treatment failure.

Treatment options

Lifestyle modifications

Lifestyle factors can negatively affect fertility, and modifying these factors can improve a couple's chance of conception. Couples should avoid smoking, alcohol consumption and recreational drug use. Not only are these substances harmful to general health and health in pregnancy, but they also negatively affect fertility rates.[5] Being underweight or obese is associated with an increased rate of infertility.[6] This can be addressed with a healthy diet, regular moderate exercise and targeting a BMI of 18.5–25. Weight loss of just 10kg in an anovulatory obese patient can restore ovulation in up to 90% of patients.[7] Female patients are recommended to take folic acid and iodine supplementation and to limit caffeine intake to a maximum of 200mg per day (approximately 1–2 cups of coffee per day.[5]

Ovulation tracking

Each month, a couple has an approximately six-day fertile window during which conception is possible. Intercourse is most likely to result in pregnancy when

it occurs on the day of ovulation or up to three-days prior to ovulation.[6] Cycle awareness is an important aspect of achieving a pregnancy and OT is useful for couples where the cycle length varies significantly. OT is performed as part of initial fertility workup and offers both diagnostic and therapeutic benefit. As a treatment modality, its primary aim is to detect lutenising hormone (LH) and to optimally time intercourse. For the patient, it involves serial serum hormonal monitoring beginning on day- two of the menstrual cycle. A Cochrane review demonstrated that appropriately timed intercourse improves pregnancy rates up to 14–23% per cycle.[8] As OT involves only blood tests and timed intercourse, it is a low-risk first-line option for the couple presenting with infertility.

Luteal phase support

Progesterone production is critical to natural reproduction and a lack of progesterone impacts the secretory endometrium and normal embryo implantation. It can be a challenging condition to diagnose but should be suspected in a patient with a luteal phase of less than nine days or if there is a history of premenstrual spotting.[9] A progesterone less than 30pmol/ml seven days following LH surge supports this diagnosis. Luteal phase support is most commonly provided with micronised vaginal progesterone commenced three to four days post LH surge at a dose of 200mg/day and continued until placental progesterone production is established at approximately 10 weeks gestation. Progesterone is generally well tolerated but can be associated with side effects such as breast tenderness, acne and mood changes.

Ovulation induction

Ovulatory disorders affect 20% of couples presenting with infertility and can be broken up into three categories:

- WHO Group 1: Hypogonadotrophic hypogonadal anovulation. Common examples include physical or emotional stress, excessive exercise or weight loss.
- WHO Group 2: Normogonadotrophic normoestrogenic anovulation, of which the most common example is Polycytic ovarian syndrome (PCOS).
- WHO Group 3: Hypergonadotrophic anovulation, which includes premature ovarian insufficiency.

OI is an effective treatment for women in both WHO group 1 and 2 and involves treatment with either oral medications (clomiphene citrate and letrozole) or injectable gonadotrophins. The treatment cycle is monitored with serial serum hormonal monitoring and transvaginal ultrasound. This is combined with recombinant HCG to trigger ovulation and is followed by timed intercourse or intrauterine insemination (IUI). Luteal phase support is offered, if required, and a pregnancy test is carried out 16 days following ovulation.

Clomiphene citrate

Clomiphene is an oral non-selective oestrogen receptor antagonist administered in the follicular phase. It is indicated for use in anovulation secondary to PCOS with a response rate of 70–80%.[10] Risks of clomiphene treatment include multiple pregnancy and ovarian hyperstimulation syndrome (OHSS).[10] If clomiphene is successful in inducing ovulation, it is reasonable to continue treatment for three to six cycles before moving onto alternative treatment options. Clomiphene has largely been replaced by letrozole due to antagonistic effects on both cervical mucous and endometrial receptivity secondary to its non-selective effect. Letrozole has also been demonstrated to have a higher LBR (27.5% versus 19.1%) and a reduced rate of multiple pregnancies (twin rate 3–7% versus 7–10%) when compared with clomiphene treatment. [10 11]

Letrozole

Letrozole is an oral aromatase inhibitor administered in the follicular phase of the menstrual cycle at a dose between 2.5–7.5mg per day. Letrozole works by inhibiting the conversion of circulating androgens to oestrogens. This reduces negative oestrogenic feedback to the pituitary gland resulting in the release of gonadotrophins and thereby inducing ovulation. Aromatase inhibitors are widely used for the treatment of postmenopausal breast cancer but have more recently been used off-label in the treatment of WHO Group 2 anovulation. They were initially used as a second-line treatment option for clomiphene resistant disease but are more commonly being prescribed first line for OI in patients with PCOS. If letrozole is successful in inducing ovulation, it is reasonable to continue treatment for three to six cycles before considering alternative treatment options.

Gonadotrophin therapy

GT is used in women with hypogonadotrophic hypogonadism and for those who demonstrate resistance to oral therapy. GT involves daily subcutaneous injection of recombinant follicle stimulating hormone (FSH) alone or in combination with recombinant LH (hypogonadotrophic hypogonadism). GT will induce ovulation in 90% of patients and will achieve a fecundity of 25% in WHO Group 1 patients and 5–15% in WHO Group 2 patients.[10] Treatment with GT carries an increased risk of both multiple pregnancy and OHSS. The risk of multiple pregnancy is 15% however, this risk can be reduced with close monitoring, ultrasound to confirm unifollicular development and cycle cancellation when appropriate.[10]

Intrauterine insemination

IUI is an outpatient procedure which involves placing laboratory-prepared sperm directly into the uterus at the time of ovulation. It delivers significantly larger quantities of high-quality sperm to the uterus than would otherwise be achieved via intercourse. IUI is commonly utilised in donor cycles or when mechanical or social issues preclude intercourse. IUI can be used as a stand-alone procedure or combined with ovarian stimulation. Approximately 60% of couples will conceive after six cycles of IUI and the success rates are highest for the first three cycles and decline thereafter.[12] The risks of the procedure itself are low, with upper genital tract infection being an uncommon potential complication. When IUI is combined with ovulation stimulation there is an increased risk of both multiple pregnancy and OHSS.

Conclusion

The non-IVF treatment options available to patients with infertility are many and while some patients will have an absolute indication for IVF, many will not. Alternative treatment options to IVF are often less invasive, less expensive and are associated with reduced risks. When suitably selected patients are offered treatment with lifestyle modification, OT, luteal phase support, IUI or OI, they have a reasonable chance of achieving a live birth while avoiding the increased risk and financial costs of IVF treatment both to the consumer and the healthcare system.

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The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Excellence in Women's Health

Western Australian State Committee Casual Vacancy Election

Term: Remainder of the Eleventh RANZCOG Council to November 2021

Following the conduct of an election for one Casual Vacancy and upon ratification by the RANZCOG Board, the following member has been elected onto the RANZCOG Western Australian State Committee for the remainder of the term of the Eleventh RANZCOG Council to November 2021.

Elected Member of the Western Australian State Committee Casual Vacancy

One Fellow Representative position

- Dr Hong Lim Lee

The RANZCOG Board and Council congratulates the abovenamed individual on their election.

IVF 'add-ons': what's the evidence?

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Since the birth of the first IVF baby in 1978, the process of IVF has advanced in scope, sophistication and success rates. Australia and New Zealand undertake approximately 85,000 treatment cycles each year, representing one of the highest utilisation rates in the world.[1] Even with the many significant advances in IVF technology and innovations, live birth rates for IVF have plateaued at approximately 17% per cycle started.[1] Despite our best efforts, most of the time IVF fails. IVF add-ons have emerged as optional extras which usually aim to increase the chance of IVF success.

IVF add-ons

There is no consensus definition of an IVF 'add-on'. They are a heterogeneous group of treatment options, including procedures, medicines and techniques that are generally considered additional to standard IVF. Examples include 'injury' of the endometrium in the cycle prior to an embryo transfer (endometrial scratching), selection of sperm for injection under ultra-high magnification (intracytoplasmic morphologically selected sperm injection, [IMSI]) or treatments to suppress immune cell activity in the endometrium (e.g. intralipid infusion). The use of IVF add-ons is widespread. Recent research reports that as many as 21 different IVF add-ons are advertised on IVF clinic websites in Australasia, and in an Australian survey IVF add-ons were used by 82% of IVF patients.[2,3]

The evidence base for IVF add-ons

Although there are notable exceptions, the majority of randomised controlled trials (RCTs) evaluating IVF add-ons are small and underpowered. They often lack methodological rigour, such as adequate randomisation methods (to ensure allocation concealment) and prospective trial registration in a recognised database.[4] As a consequence, most IVF add-ons are not supported by robust evidence to demonstrate that they improve the probability of pregnancy and live birth, or are safe to use.

Of 21 add-ons offered by Australasian IVF clinics, none were found to be supported by high-quality evidence and most were not supported by any level of evidence.[2] However, three add-ons were supported by moderate-quality evidence of benefit. These were assisted hatching, EmbryoGlue and androgen supplementation. An additional two add-ons had low-quality evidence of benefit: physiological intracytoplasmic sperm injection (PICSI) and use of growth hormone.

The Human Fertilisation and Embryology Authority (HFEA) in the UK has released a patient-facing website which regularly reviews the evidence of IVF treatment add-ons using a traffic light system. The HFEA classifies add-ons based on whether there is high-quality evidence from RCTs demonstrating that the add-on safely improves live birth rate.[5] None of the 11 add-ons that have been reviewed to date have been given a green light. Five were considered amber (conflicting evidence for effectiveness and safety, not recommended for routine use), and six were considered red (no evidence of improvement in live birth rate or add-on is unsafe).

Two examples of common IVF add-ons, their evidence base and associated costs are described below.

EmbryoGlue

Hyaluronic acid is an adherence compound that can be added to embryo transfer media, such as the commonly used EmbryoGlue. Hyaluronic acid is a naturally produced compound that functions as a binding and protective agent in human tissue. It has therefore been suggested that its addition to embryo transfer media may facilitate successful implantation and improve live birth rates. EmbryoGlue is a common add-on, being offered by many IVF clinics in Australasia at a median cost of $200 AUD and is used routinely in some clinics for all IVF patients.[2]

A recent Cochrane review analysed the results from 26 RCTs with a total of 6704 participants.[6] The review reported moderate-quality evidence of an improvement in pregnancy and live birth rates with the addition of hyaluronic acid in high concentrations to transfer media. The pooled results from meta-analysis suggested that, among women reaching embryo transfer, EmbryoGlue increases the live birth rate from 33% to somewhere between 37% and 44%. Further, there was no difference in the rate of adverse events with or without EmbryoGlue.

The Endometrial Receptivity Array (ERA)

The ERA is a novel diagnostic test which aims to determine the window of receptivity for implantation for an individual woman. The ERA test requires a carefully timed endometrial biopsy which is then processed to measure the expression of 238 genes, thereafter a sophisticated computer algorithm returns a result of either receptive, pre-receptive, or post-receptive. The IVF clinic then tailors the timing of embryo transfer to best align with each woman's unique window of receptivity.

There is only one published RCT available for ERA, with the primary analysis demonstrating no improvement in live birth rates with its use.[7] This test also has several drawbacks: it requires at least one endometrial biopsy procedure (which can be painful), and necessitates the use of a freeze-all cycle with associated costs and delays for the patient. The test is provided by a commercial company at a cost of approximately $3000 AUD. Despite lack of evidence to support use of this add-on, it has been used by over 150,000 patients globally and is offered by several IVF clinics in Australasia.[2,8]

Decision making in a vacuum

The lack of clear evidence about whether many add-ons are effective or safe presents a difficult situation for patients and clinicians. Decision making about unproven add-ons should consider the possibility that the add-on may reduce the probability of success. It is common to assume that these extra procedures may offer some benefit while the potential for harm or a reduced probability of conception is overlooked. It is worth noting that when existing evidence is uncertain (with wide confidence intervals around the reported treatment effects), this usually indicates the add-on could cause either substantial improvement or reduction in live birth rates, or anything in between.

It is against this uncertainty that fertility specialists and patients are left to make decisions about IVF add-ons. Anecdotal stories of success with add-on use, from friends, family and those in online forums, can be a persuasive influence for patients. As patients become increasingly disheartened and frustrated with IVF failures, the prospect of trying something new, albeit unproven, may become an increasingly attractive option. However, let's not forget that ony around one in six stimulated IVF cycles will result in a live birth.[1] We should therefore consider whether the best option may be to simply roll the dice again on another standard IVF cycle, rather than opt for IVF add-ons – especially when these attract a high price. Cost is often an additional consideration for patients. Most add-ons incur fees, some of which are substantial. Add-ons such as the ERA and preimplantation genetic testing for aneuploidy usually cost thousands of dollars. Patients should consider whether the addition of add-ons may amount to a cost which might encroach on their budget for subsequent IVF cycles – might their money be better saved for future IVF?

Given the complexity of decision making regarding unproven IVF add-ons, is it ethical to offer (and often charge) patients for an add-on treatment that may or may not work, and at worst could cause harm? Those in support of offering add-ons suggest it is paternalistic to deny patients access to add-ons that may help them, so long as they are informed about the uncertain evidence. They argue rigorous evaluation in RCTs delays access to promising treatments for patients who are up against their biological time clock. However, the applicability of informed consent when evidence is sparse or efficacy is uncertain should be questioned. Fertility specialists should be IVF patient's most trusted resource with a duty to ensure these patients are fully informed when making decisions about IVF add-ons.

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Donor gamete and surrogacy regulations

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Governance of assisted reproductive treatment (ART) and surrogacy in Australia and New Zealand (NZ) includes a complex mix of ethical guidelines and legislation. In Australia, New South Wales (NSW), Victoria, South Australia (SA), and Western Australia (WA) have legislation regulating ART and all states and territories except the Northern Territory (NT), have legislation governing surrogacy. Clinics must also adhere to the National Health and Medical Research Council *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research 2017*,[1] and self-regulatory requirements established by the Fertility Society of Australia (FSA) and its Reproductive Technology Accreditation Committee (RTAC). In NZ, ART and surrogacy are governed via the *Human Assisted Reproductive Technology Act 2004* and guidelines issued by the Advisory Committee on Assisted Reproduction.

ART and surrogacy must be 'conducted in a manner that shows respect, minimises potential harms and supports the ongoing wellbeing of all parties, including persons born as a result of ART'.[1] This recognises that ART involving donor and surrogacy (with or without donor) may lead to complex biological and/or social relations, in which there is a need for exchange of information and possibly, contact between donors, recipients, persons born and surrogates. It also aims to prevent exploitation and commodification of individuals participating in donor or surrogacy arrangements.

Gamete/embryo donation and surrogacy is altruistic only in Australia and NZ, but reimbursement of out-of-pocket expenses enforced, which may include medical, counselling, legal, childcare, travel or accommodation costs, loss of income, or costs associated with health, disability or life insurance that would have otherwise not been obtained. International donation of gametes may occur subject to local regulatory requirements.

The Reproductive Technology Accreditation Committee (RTAC) require donors of gametes and embryos to be screened for infectious diseases, family and personal medical issues and lifestyle issues. Sperm donors need to be between 21 and 50 years old with a normal semen analysis; oocyte donors need to preferably be between 21 and 35 years old and have completed their family.

Donor gamete/embryo

Access to Information

Donors of gametes may be known or unknown to the recipient. When unknown the donor must nevertheless be 'open identity' to enable access to information about biological heritage and relations.

While disclosure of donor-conception status is encouraged, it is not mandated in any jurisdiction. Some donor-conceived people report open disclosure within their families from an early age, while others report finding out accidently via DNA testing, during family breakdown, or as a result of illness (their own or family). Victoria is the only state to include an addendum to the birth certificate which informs the relevant person at age 18 that there is more information held on the birth register about them at their request. This acts as an incentive for recipient parents for early disclosure.

NZ, NSW, Victoria, and WA operate mandatory registries of donors and donor-conceived persons which record and release information about biological heritage and relations. In NZ, Māori donors must include additional detail on tribe and ancestry. Only Victoria enables access to information regardless of when the donation took place (including regarding donors who may once have thought their donation anonymous); while contact is subject to the donor's consent. In the other jurisdictions, the registers act prospectively, access to information permitted for all donations after the law came into effect (NZ: 2005,

Table 1. Surrogacy requirements across jurisdictions.

	Surrogacy type	Requirements: commissioning persons	Requirements: surrogate	Transfer of parentage	Access to Information
ACT	Gestational	2 people with intention to apply for a substitute parenting order; 1 must be genetic parent. Counselling and assessment. At least 18yo. Resident of ACT.	Counselling and assessment	Parentage Order 6 weeks to 6 months post birth. Child living with commissioning persons.	Information about birth parents >18yo (as for adoption).
NSW	Gestational or traditional	Single person or member of couple. ≥25yo or maturity established. Medical or social need. Counselling Legal Advice Resident of NSW Written Arrangement	>25yo Counselling (both prior to agreement and between birth and parentage order). Legal advice	Parentage Order 30 days to 6 months post birth. Child must be living with the applicant(s).	Central Register: birth parents and donors.
NT	No specific laws (may be enacted in the future)			No provision to transfer legal parentage	
Qld	Gestational or traditional	Any person No genetic connection required. Medical or social need Arrangement made prior to conception. Legal advice Counselling	>25yo Legal advice Counselling	Parentage Order 1–6 months post birth. Child must live with applicants >4 weeks.	Disclosure encouraged by commissioning persons but not mandated, no central registry.
SA	Gestational or traditional. Genetic connection with intended parent unless medical certificate.	Intended parent: • female who cannot or should not become pregnant; OR • would risk transmission serious disease/illness; OR • unlikely to fall pregnant due to gender identity/sexuality etc. SA resident >25yo Australian citizen/permanent resident. Criminal Hx report	>25yo Australian citizen/ permanent resident Criminal Hx report Written surrogacy agreement with proof of counselling and legal advice for all parties.	Parentage order 1–12 months post birth	Kept at BDM but access unclear (register to be established).
Tas	Gestational or traditional	Single person or couple >21yo when agreement made. Medical or social need. Commissioning female cannot or should not conceive/carry a pregnancy, at risk of transmitting serious genetic condition/disorder. Legal advice and counselling. Tasmanian Resident	>25yo Given birth to live child. Counselling: prior to both surrogacy agreement and parentage order. Legal advice Tasmanian resident.	Parentage order 1–6 months post birth.	Original birth certificate becomes restricted, historical record. Child born can access with counselling.
Vic	Gestational only (surrogate oocyte must not be used)	Person(s) unlikely to become pregnant. Commissioning female: cannot or should not conceive/carry a pregnancy.	>25yo Given birth to live child. Counselling. Legal advice.	Parentage order. Child living with applicants.	Persons born can apply for information about donors in the central registry (doesn't include birth mother).
		Agreement subject to approval by Patient Review Panel; can grant exemptions from requirements			
WA	Gestational or traditional	Eligible woman or heterosexual married or de facto couple. Eligible: cannot or should not conceive due to medical reasons or at risk of genetic abnormality or disease (not including maternal age). >25 years old. WA resident.	>25yo. Given birth to live child (some exceptions). All parties undergo counselling and sign agreement (including gamete donors). Medically suitable.	Parentage Order 1–6 months surrogacy agreement and written plan regarding contact with birth parents. Child in the care of commissioning persons.	Register holds donor information only (not birth parents); Person born can access original birth registration at BDM; and apply to the Court for record of proceedings re transfer of parentage.
		Agreement subject to approval by Human Reproductive Technology Council.			
NZ	Gestational or traditional	Commissioning female cannot or should not conceive.	Preferably completed family.	Adoption through NZ Family Court open to homosexual/ heterosexual couples married or de facto, single persons.	Disclosure encouraged. Person born can request original birth certificate at 20yo.
		Agreement subject to approval by ECART, requiring appropriate counselling and legal advice.			

NSW: 2010, WA: 2004). Release of information to the donor- conceived person is at the age of 18 (16 in WA) or recipient parents if younger than 18. NSW and WA also have voluntary registries for access prior to these dates. Donors can access limited non-identifying information about persons born from their donation.

In other states and territories, access may occur via requests to clinics, noting the NHMRC Guidelines have stipulated since 2004 that all donations must include consent to information release. SA is in the process of establishing a central donor register.

Increasingly, people born as a result of donor-conception are accessing direct-to-consumer DNA testing to find their biological heritage and relations.

Family limits

The number of families that may result from the use of a donor is limited, including previous/current spouse or families of donor, to:

- NSW: 5 women
- Vic: 10 women
- WA: 5 families worldwide
- SA, NT, Qld, ACT, Tas: (no legislation therefore RTAC guidance): 10 families worldwide

The donor is able to stipulate lower limits than these.

Surrogacy

Altruistic surrogacy is legal in Australia and NZ. A child born to a surrogate mother, with or without a partner, is considered their legal child until a parentage order or adoption is granted following birth, requiring consent from all parties and the court agreeing that this is in the child's best interest.

Surrogacy agreements are not enforceable, meaning commissioning parents or surrogate couple can change their mind during the surrogacy and after the child is born.

Jurisdictions vary regarding whether a surrogate may use her own ova ('traditional') or not ('gestational'), the requirements of commissioning persons and surrogate, and method of transfer of legal parentage (Table 1).

International surrogacy

It is an offence for residents of the ACT, NSW and Queensland to travel to another country to engage in commercial surrogacy. When people do engage in international commercial surrogacy from Australia, a child born as a result may be granted 'Australian citizenship by descent' if one or both intended parents are its genetic parent(s). Thereafter, Family Court granted 'parenting' orders may be sought and obtained on a case-by-case basis; however, State Court 'parentage' orders will not be granted in cases of identified commercial surrogacy. In NZ, in the absence of citizenship by descent, the Minister of Immigration may consider the temporary entry of a child born as the result of an international surrogacy arrangement on a case-by-case basis. A genetic link is required between at least one of the commissioning parents and the child, as well as evidence that adoption proceedings are underway with the New Zealand Family Court.

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Induced lactation

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Typically, lactation follows pregnancy and childbirth. Less well known is that the timing can be more fluid (excuse the pun) and that lactation can be induced without a pregnancy.

Induced lactation allows a woman who has not given birth to breastfeed or provide breastmilk to a child, and may be desired in situations such as adoption, surrogacy or production of milk for an infant born to a women's partner/sister. Women seeking induced lactation may never have been pregnant nor lactated previously (nulliparous women) or may have lactated before but not the birth mother for this baby. Previous birth or lactation experience is not necessarily required. The process of induced lactation is assisted by mimicking the physiology of breast changes that occurs during pregnancy and early postpartum, using a combination of pharmacological and non-pharmacological techniques.[1]

Physiology

During pregnancy, increased levels of oestrogen, progesterone and prolactin support the pregnancy but also prepare the breast for lactation.[2] Oestrogen stimulates proliferation of the glandular tissue, while progesterone is mainly responsible for the proliferation of the ducts and lobules. After childbirth and removal of the placenta, oestrogen and progesterone levels drastically drop, allowing prolactin to initiate milk production. The ongoing production of milk is known as galactopoesis and relies on the regular removal of milk. We refer to this phase as under autocrine (or local) control.

Benefits

Induced lactation may be an option for women starting a family using surrogacy, as it allows them to experience the process of breastfeeding, which facilitates bonding as well as providing nutrition and immunity for the newborn. When families are planning to adopt an infant or young child, timing is usually uncertain, which makes planning the steps for induced lactation more difficult and success may be measured in the emotional attachment rather than milk supply.[3,4] Some families have found that older adopted children benefit from the bonding effects of breastfeeding.[5] Same-sex female couples may also consider the option of the partner inducing lactation or relactating (if they have breastfed in the past) in order to provide more options for feeding and caring for their newborn/s.

Regimen

A typical regime is to commence a combined oral contraceptive (COC) like Microgynon 30 ED™ on a daily basis, three to five months prior to the expected due date (EDD). The aim is to mimic pregnancy, so the usual monthly break is not needed. After a week or so, the galactogogue domperidone can be added (usually 10mg ii tds) and this continues as long as needed. Usually the COC is stopped about six weeks prior to the EDD, mimicking the end of pregnancy, and breast expression is started immediately.[6] The combination of these medications usually causes breast fullness, and demonstration of the technique of hand expression will usually elicit drops of clear or cloudy milk. Once the COC is ceased, breast massage and hand expression are recommended three hourly or so, to simulate the infant feeding and stimulate the onset of milk production. When the milk volume starts to increase, an electric pump can be carefully used.

Considerations

A detailed medical history is needed prior to this regime, and in practice some women will have contraindications to oestrogen or domperidone. If oestrogen is contraindicated, the minipill (progesterone only) could be used as an option. Domperidone is commonly used off-label for lactation stimulation, but is contraindicated in people with a history of cardiac irregularities or if taking another medication that potentially increases the QT interval.[7,8] An ECG could be ordered to check the corrected QT interval prior to commencement, but is not mandatory.[9,10]

Success of induced lactation should be discussed in relation to the mother's feelings about her breastfeeding experience rather than the quantity of milk produced or how long she breastfeeds. There are no guarantees of obtaining a full milk supply with induced or relactation, but any milk production will be considered a huge success for some women. The goal is not exclusive breastfeeding. Additional milk (infant formula or donor milk) can be given using a supplemental feeding tube at the breast. Using a feeding line ensures the infant is receiving adequate nutrition and is stimulating milk supply at the same time.[11]

Here are a couple of examples of induced lactation in practice:
The female partner of a woman expecting monochorionic monozygotic twins was referred to the breastfeeding service at the Royal Women's Hospital, Melbourne, as birth was planned at 32 weeks gestation and both partners were keen to help produce milk for the twins. The healthy non-pregnant partner was seen at 18 weeks and she had no significant medical history. The suggested timeline for lactation induction is shown in Figure 1. She began the COC as her period had just finished and there was no chance of pregnancy. One week later, she commenced domperidone 10mg i tds, and increased to ii tds after another week. Four weeks prior to the planned birth, she stopped the COC and began expressing manually. By the time of birth, the non-birth mother was expressing 20 mL per expression; up to 140 mL per day. Twin boys were born at 32 weeks and the birth mother commenced breastfeeding/expressing with the infants in special care nursery. The non-birth mother was expressing 50 mL per expression. Both infants were exclusively breastmilk fed for five weeks while in hospital. Both mothers breastfed both infants, often alternating infants each feed. The couple provided this quote for our poster presentation: 'Induced lactation allowed us to have a supply of breast milk stored for when the boys arrived. Induced lactation also enabled us both to breastfeed and was a perfect way for both of us to bond with our twins.'[12]

In contrast, a recent referral from the neonatal service for a same-sex couple was a different scenario. The birth mother was struggling with low milk production and staff suggested her partner might be able to help. However, the nonbirth mother was aged 45 years, had never been pregnant, and lived with several physical and mental health conditions requiring medications not compatible with domperidone. Following an explanation of the process of inducing lactation and after discussion, the couple did not proceed with this. The couple were encouraged to focus on supporting the birth mother to increase her supply, rather than add an extra stress at the time.

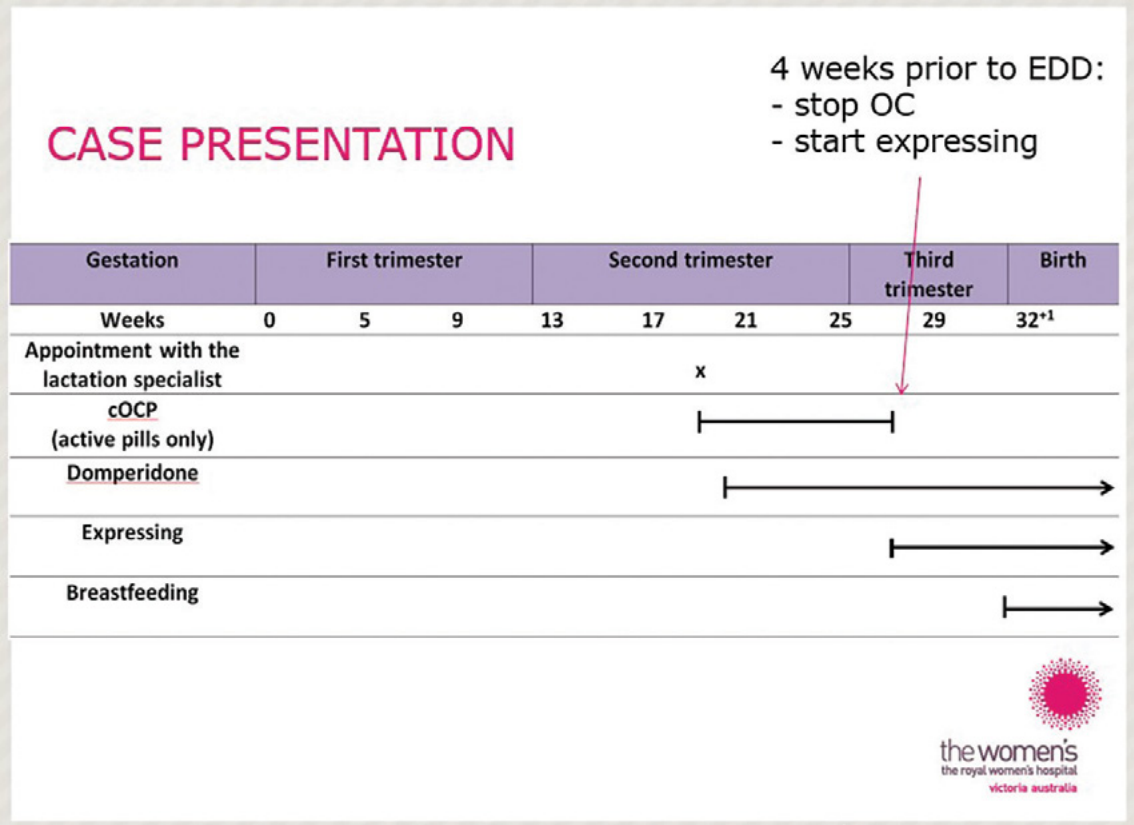

Figure 1. Plan for induced lactation in non-birth mother showing medicines to simulate pregnancy and then expressing prior to expected date of delivery of monochorionic twins.

We have had seen many successful outcomes such as the case of a woman with premature menopause who was able to almost exclusively breastfeed her infant born through surrogacy. Another woman who had a history of thrombosis after hysterectomy and was unable to take oestrogen, successfully induced lactation taking the progesterone only pill in the pregnancy simulation stage.

What next?

Healthcare professionals should be aware of the possibility to induce lactation without a pregnancy. The increase in multi-mother families has led to an increase in awareness within the community of induced lactation as an option. A recent research study found that some couples would have appreciated information on this topic:

> 'I wish we could've known (about induced lactation). Because then we really would've sat down and said, "Is this something we really want to do?" She (non-gestational partner) really would've considered it. It would change the landscape in terms of her work, how much time she got off and all. It definitely would've been nice to know a lot earlier.'[13]

Early referral for specialist assistance is essential; ideally around week 16 of pregnancy. The Academy of Breastfeeding Medicine provides clinical protocols for many breastfeeding issues. A recently published protocol 'Lactation Care for Lesbian, Gay, Bisexual, Transgender, Queer, Questioning, Plus Patients' provides some information on induced lactation.[14] The Australian Breastfeeding Association has information on induced lactation and relactation to share with families.[15]

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Preimplantation genetic testing for aneuploidy

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Most miscarriages result from chromosomal variations in the embryo. The increasing difficulty that older women have in conceiving and their higher risk of miscarriage is also thought to result from the higher rate of non-disjunction in the ageing oocytes leading to aneuploid embryos (Figure 1).[1] It therefore seems intuitive that testing the chromosome number in embryos, prior to replacement in the uterus at the time of IVF, should improve the chance of conception and prevent aneuploidy-related miscarriage. The reality, however, is not so straightforward and the clinical role of preimplantation genetic testing for aneuploidy (PGT-A), formerly known as preimplantation genetic screening, of IVF embryos remains uncertain with only limited evidence of effectiveness.

What is involved?

The technique itself is straightforward and well established. The embryos are grown for five days to the blastocyst stage, where the inner cell mass (from which the fetus is derived) is clearly separate from the outer trophectoderm (from which the membrane and placenta are derived). Following laser-assisted hatching of the outer zona pellucida, a few cells are aspirated from the trophectoderm layer of the blastocyst (Figure 2).

The DNA is extracted from these cells and amplified using polymerase chain reaction (PCR). Following amplification of the DNA, the chromosomal constitution of the cells can be assessed using a number of techniques. In the early days of preimplantation genetic testing (PGT), the original technique used was fluorescence in situ hybridisation (FISH) which produced images of five of the high-risk chromosomes. Sadly, it is now clear that this was a flawed technique and clinical studies of the effectiveness of PGT based on FISH are only of historical value.[2]

The next technique adopted for DNA analysis was array comparative genomic hybridisation (aCGH). This technique, which utilised a hybridisation of the embryonic DNA to an array platform containing various probes, enabled, for the first time, all 24 of the chromosomes to be assessed. However, aCGH, only has a limited capacity to distinguish between complete aneuploidy and embryonic mosaicism, a state where the result is mixed; i.e. some of the cells are euploid while others appear to be aneuploid. This limitation in detecting mosaic embryos may also be a contributing factor to the relatively high rate of miscarriage following aCGH-based PGT.[3] The newer technique of next-generation sequencing (NGS) gives a much clearer distinction between full aneuploidy and a mosaic embryo. In this technique, the total DNA is quantified for each of the chromosomes using parallel sequencing of multiple small DNA fragments, allowing high resolution of chromosomal abnormality detection (Figure 3). Importantly, NGS can more effectively identify mosaicism.[4]

Many mosaic embryos are suitable for transfer and can lead to a healthy child, albeit with a lower success rate.[5] The chromosome involved in the mosaicism, along with the proportion of affected chromosome (segmental versus whole chromosome mosaicism) is critical and these cases are normally handled with expert clinical genetic support. Where a pregnancy results from a mosaic embryo, an amniocentesis should be performed to confirm the fetal karyotype.

For couples with translocations, NGS can identify unbalanced translocations in the embryo but cannot distinguish between a balanced and a fully euploid embryo. For individual genes or small chromosomal rearrangements from a preimplantation embryo biopsy, a more complex molecular technique such as karyomapping is required.[6]

What are the drawbacks?

There are a number of drawbacks. The removal of cells from the outside of the embryo may affect the implantation potential of the embryo.[7] During the biopsy, the embryologist carrying out the procedure has to ensure that only trophectoderm (TE) is biopsied and not the inner cell mass (ICM) of the embryo (Figure 2).

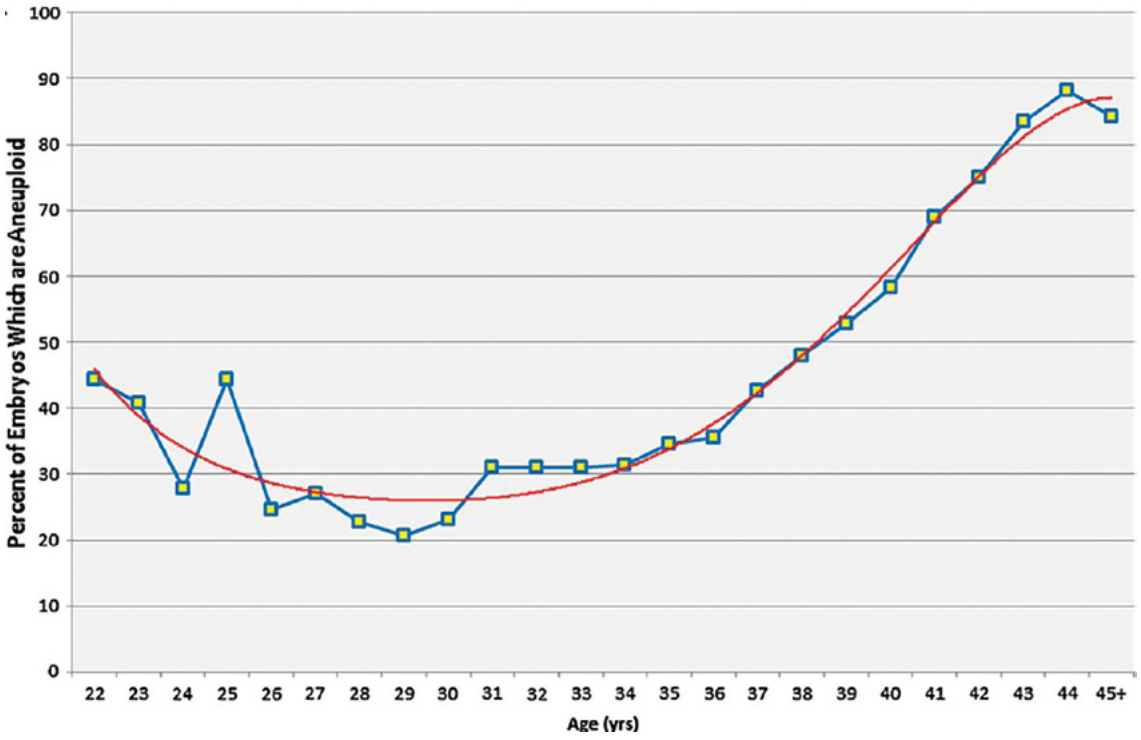

Figure 1. The rate of embryo aneuploidy relative to maternal age.[1]

Non-invasive preimplantation genetic testing, where free embryonic DNA from the culture medium is analysed, has the potential to avoid embryonic biopsy. This technique is highly promising but is not yet reliable enough for clinical use.

There are also growing concerns that PGT-A may over-diagnose aneuploidy in the fetus itself, limiting the number of embryos available for transfer.[8]

While PGT is clearly expensive, the overall health economics, taking into account the avoided unsuccessful transfers, may be quite reasonable.[9]

What is the evidence for its effectiveness?

A number of studies have demonstrated an improved implantation rate per embryo following PGT-A.[10] This is not surprising though, as embryos selected on the basis of having a euploid karyotype are, inevitably, going to be more likely to implant than a population of unselected embryos. The more important endpoint is the cumulative livebirth rate from one egg collection, but here studies are very limited.

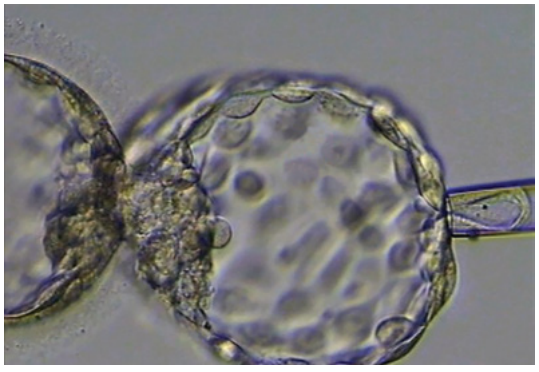

Figure 2. An embryo being biopsied for preimplantation genetic testing.

One randomised controlled trial, the STAR study,[11] compared the success rate per egg collection from transfer of a morphologically selected embryo against a PGT selected embryo but did not find any difference in the livebirth rate. In addition, many patients in the PGT-A group did not have any embryos to transfer, suggesting an overall reduction in the cumulative livebirth rate with PGT-A.

What is its current clinical role?

Some clinics, particularly in the US, routinely perform PGT-A on all embryos prior to transfer. This is not widespread practice in Australia, where PGT-A is normally used more selectively. The sort of patients who may consider PGT-A would include older women who are at higher risk of having aneuploid embryos (Figure 1) or couples who have previously gone through the traumas of a late diagnosis of an aneuploid pregnancy. Miscarriage is more complex, as most are a consequence of a chromosomal variation in the embryo, PGT-A may reduce this risk. However, studies in patients with recurrent miscarriage have not found that PGT-A is effective at reducing miscarriage risk in this population.[12]

What ethical issues are raised?

PGT for aneuploidy has been questioned as a form of 'designer babies'. The technique, however, does not identify individual genes and its value lies in preventing the transfer of non-viable embryos to avoid the trauma of an unsuccessful transfer or a potentially avoidable miscarriage. Nonetheless, the technique has attracted criticism from the intersex community for discriminating against intersex people through the potential for elimination of karyotypes

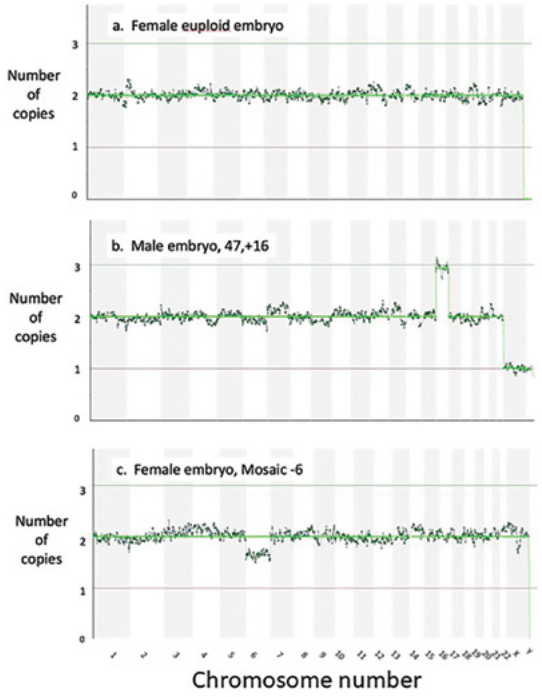

Figure 3. The readouts after next generation sequencing, showing the chromosome count for each chromosome for (a) a female euploid embryo (b) a male aneuploid embryo with an extra Chromosome 16 and (c) a female embryo mosaic for a missing Chromosome [6].

such as 45,XO and 47,XXY, which are consistent with a healthy life.[13] It is therefore critical to avoid the judgemental language of 'normal' and 'abnormal' in this context.

How should a pregnancy be managed after PGT-A?

Regardless of whether PGT-A has been done, the routine process for prenatal screening for aneuploidy should still be followed. It is important to be aware that PGT-A cannot identify individual genes or tiny chromosomal deletions such as microdeletions.

Conclusion

In summary, in Australia, very few IVF clinics will have a policy of routine PGT-A for all embryos as the effectiveness of the intervention is still uncertain. However, most fertility specialists will offer PGT-A to selected patients following careful discussion of the pros and cons of the approach.

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Complications of assisted reproductive technology

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For the woman

Acute complications

Complications of ovarian stimulation are well known. Ovarian cyst accidents include haemorrhage, rupture, ovarian hyperstimulation syndrome (OHSS) and, perhaps most serious, torsion. OHSS is now less common due to preventative measures such as judicious use of follicle-stimulating hormone (FSH), adjuvant metformin, gonadotropin-releasing hormone (GnRH), agonist induction of oocyte maturation, the decision to make the cycle a 'freeze-all cycle'and use of cabergoline after oocyte collection.[1] Infection of the ovary is uncommon, but serious, as it is sometimes unrecognised and is associated with abscess formation.

Pregnancy complications

Pregnancy after assisted reprocuctive technology, (ART) is different to pregnancy after natural conception, even if singleton and even with the use of cryopreserved embryos in natural ovulatory cycles. Gestational diabetes mellitus, polyhydramnios, oligohydramnios, preterm birth, low birth weight and birth weight which is small for gestational age are all increased.[2] The risk of abnormalities of placentation is increased after fresh embryo transfer, placental abruption, placenta praevia and vasa praevia. After cryopreserved embryo gestational hypertension is consistently increased. Postpartum haemorrhage and thromboembolic disease associated with pregnancy is also increased in ART pregnancies.

Long term

The available evidence suggests that the lifelong risk of breast cancer and ovarian cancer are not increased after ART;however a woman is more likely to manifest breast cancer in the 12 months after an IVF cycle, much as she is after a pregnancy or after taking combined oral contraceptives. Having infertility is a risk factor for ovarian and uterine cancers, but these are not increased further by having an IVF cycle. There have been studies suggesting that borderline tumours of the ovary are increased in women having FSH treatment, but it is still controversial.

Aetiology of pregnancy and long-term complications for the female and its implications for practice

Debate about the association of complications of ART and the pathogenetic basis of obstetric and long-term health complications is ongoing. Whether women who access ART are at increased risk of these complications (and therefore may manifest them in natural conceptions) or whether the process of ART has a direct influence is uncertain. Women with reduced ovarian reserve and those with premature ovarian insufficiency (who may access donated oocytes) are at increased risk of a number of cardiovascular morbidities that may manifest as pregnancy-related hypertension and preeclampsia. Pregnancy following use of donated oocytes is associated with increased pregnancy-related hypertension, which may be the first manifestation of underlying cardiovascular risk. The long-term cardiovascular complications associated with early ovarian failure are only partially ameliorated by hormone replacement therapy. Preventative strategies for these long-term complications and risks potentially can be discussed with the woman at the time of fertility treatment, but timing of these discussions is often difficult and problematic as infertility tends to be an all-encompassing health issue for couples with infertility, and future considerations are often seen as less important. Written or spoken information with the patient and her partner and communication with the primary care physician may be useful but public information, education and community awareness will be of importance in the future.

For the man

There is no evidence that long-term health of men is affected by ART per se (excluding surgical sperm retrieval); however having an abnormal seminal fluid analysis, particularly oligospermia, is associated with an increased all-cause mortality.

Semen quality is a biomarker of male somatic health. One of the risks of ART for the man is forgone intervention opportunity if there is inadequate assessment of male reproductive health and general health. As many men are under the care of gynaecologists who have made a career commitment to women's health, the opportunity to intervene to improve long-term health outcomes of men may be missed. Gynaecologists who offer fertility treatment in 2021 are expected to have skills in assessing men's health, or have a close referral relationship within their health team to ensure that every man with an abnormal sperm count is examined and the implications for his long-term health and potential interventions are discussed with him.

Male factor infertility may be the first manifestation of pituitary disease or testosterone deficiency in

the male. Medical assessment is also important if any erectile dysfunction is present. Men with abnormal sperm counts are at increased risk of testicular cancer and this is not influenced by ART. Physical examination with or without testicular ultrasound is a standard of care. Regular testicular self-examination is recommended with prompt presentation to a general practitioner should a lump or abnormality arise.

For the child

Ongoing review of children has established that children conceived by ART are at increased risk of congenital defects and of long-term adult disease (such as diabetes and high blood pressure) compared to naturally conceived children. Children conceived through IVF and intracytoplasmic sperm injection (ICSI) had a 30–40% increase in the risk of major congenital abnormalities compared to the risk in normally conceived children.[3] A significant defect detectable at birth that requires treatment such as surgery occurs in 3 of every 100 naturally conceived children in the general population, but this incidence increases to at least 4 of every 100 children conceived with IVF/ICSI. The risk of birth defects is further increased by use of ICSI, particularly for male factor infertility.[4] Higher estimates of birth defects are seen when children are assessed at a later age. A common birth defect after ART is infantile haemangioma, but many defects (blastogenesis, cardiovascular, musculoskeletal, genitourinary) are increased. Male offspring of men needing ICSI to conceive have lower sperm counts than those conceived naturally.[5] Whether the birth defects result from the process of ART or whether the population accessing ART is at increased risk is uncertain. Evidence is conflicting.[6]

Epigenetic problems in children conceived by ART

ART procedures involve the culture and handling of embryos in the laboratory. It has been suggested that the laboratory environment may affect the way some genes are permanently switched on or off resulting in an increase in rare but serious genetic conditions called Beckwith Weidemann and Angelman syndromes. The risk of these disorders may be increased from about 1:14,000 in naturally conceived pregnancies to 1:4,000 in IVF/ICSI births.

Genetic issues with ICSI

ICSI-conceived offspring are more likely to have chromosomal abnormalities. An increase from 1 in 200–400 births in naturally conceived pregnancies in the general population, to about 1 in 100 ICSI births. The most common of these is Klinefelter's syndrome (47XXY) but other chromosomal abnormalities are also increased.

About 4% of severely infertile men have deletions of the Y chromosome and these Y deletions are inherited by any sons. Similarly, some forms of bilateral congenital absence of the vas deferens relate to mutations in the cystic fibrosis gene which will be inherited by the offspring and are particular significant if the female has a mutation of cystic fibrosis gene.

Risks of multiple pregnancy

The risk of having a multiple pregnancy is substantially reduced by transferring only one embryo and Australia is a world leader in single embryo transfer. However, monozygotic pregnancies can occur (approximately 1 in 40 pregnancies following ART) and concomitant natural conceptions can occur (most commonly in natural cycle frozen embryo transfers). The complications of multiple pregnancies are well known to the Fellowship and are outside the scope of this article.

Outcomes for singleton babies conceived following ART compared to naturally conceived singleton babies

Singleton babies born after ART are 2–3 times more likely to be premature and of low birth weight compared with naturally conceived singleton babies. A singleton ART baby is more likely to be born by caesarean section than a naturally conceived singleton.

Follow-up studies to compare the health and development of children after IVF/ICSI and natural conception have largely shown no significant differences between these groups of children up to the age of five (once the effect of multiple and early births are adjusted).

The risk of cancer in offspring conceived by ART

The meta analyses of observational cohorts of the risk of childhood malignancy following ART are discordant and therefore it is uncertain if ART poses a risk of childhood cancer to the children conceived. A linkage study from Denmark has indicated a small but significant increase in risk of childhood cancer after frozen embryo transfer but no other forms of treatment. No increased risk was reported in a population-based study in Israel.[7,8]

Risk of long-term adult disease in IVF & ICSI babies

It is unclear whether children conceived by ART are at any increased risk of health problems in middle and late adulthood. There is evidence that low birth weight and prematurity in naturally conceived children are associated with an increased risk of diabetes and coronary heart disease. There are reports of increased hypertension and insulin resistance in children conceived by ART.

Summary

While there are some risks associated with ART treatment, well over 90% of children conceived after ART are born, and remain healthy. Some risks of ART can be reduced by avoiding multiple births. Some complications may be unavoidable and be due to the couple's underlying infertility or to, as yet, unidentified factors such as culture conditions in the laboratory. As data becomes available on the long-term health outcomes of children, it is inevitable that laboratory conditions will have changed and the contemporaneous implications will therefore be uncertain.

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Uterine transplantation: a dream, now a possibility

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Uterine transplantation: once a dream, now a reality
The idea of uterine transplantation has been around since the 1960s. Animal studies conducted in Sweden, UK and the USA demonstrated it was possible to transplant the uterus resulting in successful pregnancies in multiple animal models.

The first uterine transplant was performed in Saudi Arabia in 2000[1] and the first live birth following uterine transplantation took place in Sweden in 2014.

Since then, many more transplants have been performed around the world with the details of 45 reported in 2019.[2] By late 2020, more than 70 uterine transplants had taken place with 23 live births, mostly from live donors. There has been evolution of the surgical technique using same arterial input but use of ovarian veins for drainage and reduction in operating time.

Uterine transplantation is for uterine factor infertility, which is defined as the lack of a functional uterus. This can be congenital or acquired. The vast majority of cases performed were for women with Mayer-Rokitanski-Kuster-Hauser syndrome (MRKH). MRKH occurs secondary to the incomplete development of the Müllarian duct. In type 1, the upper vaginal and uterus are under developed and in type 2 other organs such as fallopian tubes, kidneys and spine

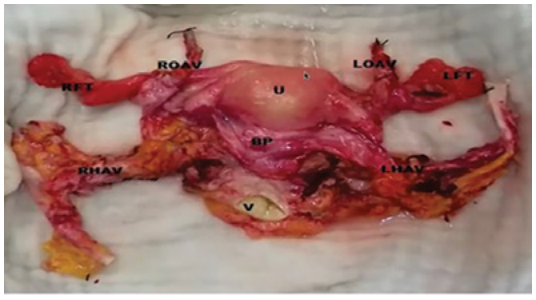

Figure 1. Photograph of surgical specimen prior to transplantation, courtesy of S Saso, Imperial College, London.

are also affected. The only options for women with MRKH to reproduce have been surrogacy or adoption. In many countries throughout the world, surrogacy is illegal and therefore not an option for women. The most common acquired indication in the women undergoing transplantation is hysterectomy for reasons such as cancer and haemorrhage and indications have included Asherman's syndrome.

There are ethical, medical and resource issues to consider with regards to uterine transplantation. Most organ transplants are life preserving procedures and the most experience and information is with renal transplantation. Uterine transplantation is life enhancing rather than life preserving, giving women who otherwise would not be able to have children the option of childbirth. Obstetricians have seen many successful pregnancies following renal transplantation of women taking immunosuppressive medication. Immunosuppressive medication such as tacrolimus and cyclosporine have been used in pregnancy for some time and are also used to prevent rejection of the uterine transplant.

Donation has taken place after brainstem death and the first live birth following this was in Brazil in 2017. There are advantages of live donation in reducing risk of ischaemic injury; however, the risks to donor are an important consideration. Risks to the donor and recipient need to be assessed and minimised. As this is a relatively new procedure, the risks and complications have been outlined in case series and include graft failure due to thrombosis, graft rejection, ureteric injury, vesicovaginal fistula and vaginal cuff dehiscence as well as pulmonary embolism secondary to long operating time. Pregnancy complications include preterm birth and low birth weight. Units performing transplants have established guidelines for assessment of both donors and recipients and have developed exclusion criteria. Delivery is by caesarean section and subsequent hysterectomy is performed so that immunosuppressive therapy can be discontinued.

Support for this procedure is variable amongst practitioners and the wider community. Ethical considerations are important with the need for appropriate counselling and support. The surgery is complex and requires a multidisciplinary team. Women seeking pregnancy are a vulnerable group and may underestimate their risks. Surgical techniques have improved, and operating times halved since the early cases. Women who do not have access to adoption or surrogacy may seek this option if it is available.

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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 What makes a good morbidity and mortality (M&M) meeting?

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A Although I set out to provide clear answers to this question, I found myself down a big fat wombat hole of meeting structures, change management psychology, M&M meetings, quality and safety meetings, audits, root cause analyses, and other confusing terms. It wasn't long before I began to wish I had done a postgraduate qualification with the Australasian College of Medical Administrators.

Is an M&M just obstetric storytelling?

There are many great reasons to tell each other stories, since 'Stories help us smooth out some of the decisions we have made and create something that is meaningful and sensible out of the chaos of our lives.'[1] Telling stories allows us to gather a group of people who can support us; however, an effective M&M meeting is far more than an opportunity to experience collegiate support – it can also encourage uptake of an important guideline and help teach junior staff best practice.

An M&M is a peer review process of cases. This is quite a different process to a safety and quality meeting, which is taken from the perspective of the administration and addresses problems from a systems point of view. Both these types of meetings operate together to address patient factors, human factors, systems factors, as well as acknowledge the information that is not known. They are both meetings designed to make care safer, and psychology research seems to suggest that helping clinicians to change and make care safer is no longer about managing with either a carrot or stick, but about forming stronger relationships and engagement with each other.[2]

Establishing a meeting structure

It will come as no surprise to learn that having a structure for your meetings can be helpful to staff who can then feel more prepared and able to follow a process. Here are a few tips that might help you to think about the aims of your meetings and the structure you may use to help you achieve them:

1. Determine your criteria for data collection: near misses, morbidity, mortality. Then establish a system to collect the data. Riskman and other software is not always the best option: frequently people are exhorted to use it more, and then don't; even more frustratingly, one group might use it more than another and thus bias the data. If there is one thing you can be certain about, making the process more difficult by insisting on cumbersome software is a sure way of making sure no one uses it. A *Choice Architecture* method suggests a simpler approach – a dedicated email sent to the clinician tasked with the responsibility to investigate and populate databases for record and analysis.
2. The case presentation should meet predetermined criteria (does anyone really care about the Rubella status any longer?) and can be about a contemporary case (some bad thing which just happened) or an audit of indicators. These indicators may be determined by your area, or could be adapted from those published by professional bodies such as a colleges (eg. RANZCOG) or state groups (eg. Perinatal services performance indicators or Victorian audit of surgical mortality).[3] Also, keep in mind that not every meeting needs to focus on everything that has gone wrong – perhaps the Christmas period M&M could refocus on all the things your group did well this year.
3. After presenting the case, review the literature to determine if there is a standard to follow –the evidence ranges from Standards with a capital S (eg. the Heavy Menstrual Bleeding Clinical Care Standard from Australia: www.safetyandquality.gov.au/standards/clinical-care-standards/heavy-menstrual-bleeding-clinical-care-standard) or national guidelines, college guidance and statements to more recently developing evidence, such as that presented in systematic reviews, trials, series, case reports, and then see if this tallies with hospital guidance etc.

4. At the conclusion of the discussion, document the factors – patient, human, systems, etc, and discuss to what degree the outcome was preventable (eg. RCS: www.rcseng.ac.uk/standards-and-research/standards-and-guidance/good-practice-guides/morbidity-and-mortality-meetings/). Decide who is responsible for fixing the problem and determine the timeline.

There are a range of other factors you might like to consider. One of the most fundamental of these is who should present? An M&M can be an excellent opportunity for junior staff learning; however, there are strong arguments for having the most senior staff present, as they often do not receive feedback in any other forum. Either way, you should also consider whether it is best for staff to present their own cases or have a colleague present for them. Having a case presented by an uninvolved staff member could help everyone to see the case from a different angle.

As well as thinking about the individual presenters, you should also think carefully about who mediates the meeting. It seems obvious that it should be someone who has the respect of others and speaks respectfully to them – a mediator who is blame focused/prioritising individual responsibility/of the 'try harder' school rather than systems focused, is unlikely to achieve change.

Another point to consider is how many people you want to attend these meetings. Obviously, you should include O&Gs, junior staff, midwives and midwifery students, medical students, paediatric doctors and nurses. However, this won't necessarily provide the full picture, which is why you might need to think about including imaging staff or pathologists. You might also want to consider having meetings that include Admin staff who manage the logistics and people from IT who manage the data. Rather than trying to include everyone in every meeting (and feeling like you're running a circus), you could think about having M&M meetings that focus on particular groups and their perspectives. Also consider frequency: more often to nip things in the bud, less often for higher participation.

Of course, meetings are rarely anyone's favourite part of the workload, so you might want to provide incentives to attend. This could include having people paid for their time, or having the meeting time recorded to count towards a certificate for their CPD points. At the risk of pointing out the obvious: people are far more likely to participate well if they feel their efforts are being noticed and rewarded.

Acknowledgements
Thanks to Bridget Pinnuck, Steve Bolsin and Lauren de Luca.

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Further reading

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Royal College of Surgeons of England. Morbidity and mortality meetings tools and templates. www.rcseng.ac.uk/standards-and-research/gsp/morbidity-and-mortality-meetings-tools-and-templates/

Case reports

Ventouse delivery of a hand presentation

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Compound presentation refers to the presentation of a fetal extremity alongside the presenting part. It is most often the fetal hand or arm presenting with the vertex, although can also occur in breech. Compound presentation has been reported to complicate between 1 in 250 and 1 in 1000 deliveries; however, this is a crude estimate because transient cases are not consistently documented or recognised.[1,2] It is more likely to occur when the pelvis is not completely occupied by the fetal presenting part; risk factors include low birth weight, premature rupture of membranes, polyhydramnios and multiple gestation.[1] External cephalic version can also predispose, wherein the limb is caught underneath the body during rotation, although this will often resolve prior to labour.

Compound presentation may be suspected when the fetal head deviates from the midline and remains persistently unengaged after membrane rupture. It is most often diagnosed after palpation of a fetal extremity during vaginal exam; however, cases have also been identified using intrapartum ultrasound.[2] There is a strong association with cord prolapse, so if a fetal limb or other unusual mass is palpated during examination it is important to assess for pulsatility. In this instance, the compound presentation progressed to limb prolapse during labour.

Clinical Record

A 33-year-old woman presented for induction of labour due to intrauterine growth restriction. She was 38+3 week's gestation (G3P0T2), had gained 4kg since conception and her pre-pregnancy BMI was 21. Her pregnancy was complicated by a benign multi-nodular thyroid goiter that caused fluctuating hypo/hyperthyroidism since 2009. She was clinically euthyroid with normal thyroid function tests throughout pregnancy and all other antenatal blood tests were normal. She smoked 4–5 cigarettes a day up until delivery.

She was diagnosed with gestational diabetes at 30 weeks and maintained good blood sugar control with diet. An ultrasound scan at 34 weeks estimated an abdominal circumference in the 21st centile and a fetal weight of 2070g (13%). By 36 weeks, abdominal circumference had decreased to the 14th centile and estimated fetal weight was 2328g (8%), consistent with an intrauterine growth restriction. Doppler studies at 37+4 weeks were normal; however, amniotic fluid index had increased to the 95th percentile. Throughout her pregnancy, there were significant social stressors and she presented to birthsuite for recurrent decreased fetal movements at 29, 34 and 38 weeks. During each presentation, fetal movements and CTG were reassuring. Her induction of labour and the events that occurred throughout are detailed in Table 1.

After birth, the baby was transferred to the special care nursery in a stable condition, birthweight was 2500g. His respiratory distress improved so he was weaned from CPAP to high-flow oxygen. Oxygen saturations remained above 97% and heart rate was stable at 110–130bpm. A chest X-ray revealed a left pneumothorax that was treated conservatively. By Day 4, he was ventilating on room air and a repeat X-ray on Day 5 confirmed the pneumothorax had resolved. His left arm, which had prolapsed, was significantly bruised and grey, but remained well perfused with capillary refill less than two seconds. Initial X-ray revealed a greenstick fracture of the proximal radius, so the arm was splinted. Orthopaedic review and X-ray at Day 7 confirmed that the arm and hand made a complete recovery and retained full function. There was no clinically significant injury to the head from ventouse delivery. The mother's recovery was uncomplicated and the episiotomy wound healed completely with no residual incontinence one month after discharge.

Figure 1. Occipit-Anterior presentation with hand prolapsed down the left of the vertex.

Table 1. Significant events after induction of labor at 00:00. Time represents hours after induction.

Progression of Labor	
00:00	Cervidil Pessary inserted (10mg Dinoprostone)
17:05	Cervidil removed, 2mg Prostin E2 inserted irregular, mild contractions 1–2:10, lasting 30–45 seconds
19:50	Bishops Score 5, Additional 2mg Prostin, CTG commenced
20:15	Variable deceleration on CTG, transferred to birth suite
27:08	Contracting 2–3:10, mild, lasting 45–60 seconds Vaginal Examination: baby's wrist and fingers presenting flush against head. Ultrasound: baby cephalic, spine to left Attempt by midwife to manually reposition hand
28:33	Epidural + IDC Inserted, IV fluids at 100ml/hr Contracting 2:10, mild 40–60 seconds, irregular
30:38	Syntocinon infusion commenced
32:42	Syntocinon infusion now 30ml/hr FHR not audible, despite moving CTG transducer lower Patient could 'feel something low down' Baby's hand birthed down left side of face out of vagina Fetal heart rate 60, maternal pulse 60. SMO in attendance Failed attempt to reduce prolapsed arm
32:47	Fetal Scalp Electrode applied, FHR 130 Vaginal Exam: Direct Occipit-Anterior, fully dilated, moulding +, caput +, station +2 vertex beyond hand and arm
32:51	Fetal Scalp Electrode not working – removed Second attempt to reduce arm unsuccessful, FHR 120
32:53	Patient asked to push – FHR 60 on Doppler, contraction lasting > 60 seconds. Minimal descent
32:56	Consent for Ventouse, patient moved to lithotomy. Kiwi cup applied to flexion point, FHR 128 First pull with contraction, FHR 60
32:59	FHR 130 between contractions, IDC deflated Second pull with contraction, FHR 60 Consent for episiotomy, right mediolateral incision
33:02	Third pull, live baby boy birthed Umbilical cord entangled around shoulders + torso, cut Transferred to resuscitaire, HR>100, not breathing, low tone Stimulation, IPPV for 1 minute, then CPAP FiO2 100% APGARs 3, 7, 9 (1, 5, 10 min)
33:10	10IU syntocinon IM Placenta delivered whole with controlled cord traction Episiotomy and small left labial tear repaired Estimated blood loss 250mls

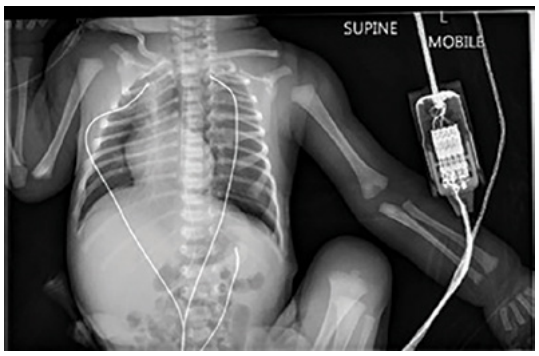

Figure 2. X-ray Day 0, left pneumothorax and greenstick fracture of the proximal radial shaft.

Discussion

Intrapartum management of compound presentation depends on patient-specific factors, and assessment by an experienced clinician is recommended. If a fetal limb is identified in early labour, this can be managed expectantly, often as the fetal head engages the pelvis the baby will withdraw the limb and labour will progress.[1] In cases of persistent presentation, the limb may be reduced back into the uterine cavity with gentle manipulation followed by a small amount of fundal pressure to reapply the presenting part. Benign noxious stimuli, such as a gentle pinch of the hand or fingertip between contractions, may also encourage withdrawal. If the fetal extremity cannot be reduced and fills the space between head and maternal sacrum it may cause a dystocia, resulting in an arrested second stage or limb prolapse.[3]

Compound presentation increases the diameter of the fetal presenting part. This has been associated with an increased number of pulls and higher traction forces during ventouse deliveries.[3] Severe maternal rectal trauma has also been described after vacuum-assisted delivery of an unidentified compound presentation.[4] Therefore, when confirming cup placement, it is important to identify a fetal limb and attempt to reduce it before applying traction. In this case, the left arm up to the elbow had prolapsed beyond the introitus. The limb was purple, swollen and the forearm was tightly wedged between the left side of the vertex and pelvis. Due to the level of descent and increasing fetal distress, a ventouse delivery was deemed to be the safest and most efficient option to expedite birth and release the entrapped arm.

Prolonged cases of limb prolapse and dystocia have been associated with fetal hypoxia, ischemic limb injury, uterine rupture and maternal hemorrhage.[2,5] A case report describes a compound presentation where the arm became ischemic and required amputation after it was entrapped between the bony pelvis and fetal head.[6] If the limb cannot be reduced, delivery must be expedited, which has traditionally been achieved through emergency caesarean section. However, second stage caesarean delivery increases the risk of bladder trauma, hypoxic fetal injury, extension tears of the uterine incision and maternal haemorrhage.[7] Prolapse of the arm may reduce the traction force required for successful cephalic ventouse delivery compared to compound presentation where the limb remains within the pelvis. Ventouse delivery of a compound presentation with a prolapsed limb has not been described previously. This case demonstrates an alternative method to caesarean section if the limb cannot be reduced and fetal distress demands immediate delivery to prevent hypoxic injury.

Full reference list available online

Maternal diaphragmatic hernia in pregnancy

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Case Description

A 38-year-old woman, G4P3, presented at 36+1 with intermittent upper abdominal pain and heartburn. She denied any vomiting, changes in bowel habit or recent abdominal trauma. She had recently completed a course of oral antibiotics for a urinary tract infection.

Her past obstetric history included two vaginal births followed by a caesarean section for placenta praevia. She was planning a vaginal birth in this pregnancy. She also had an elevated BMI of 40, chronic hypertension, previous renal stones and laparoscopic gastric sleeve since the birth of her youngest child.

On admission, she had normal vital signs and a soft abdomen. Cardiorespiratory examinations were not performed at the time. Her full blood count, liver function tests and urine dipstick were all normal. She was started on regular omeprazole and buscopan for presumed gastric reflux with initial improvement, therefore she self-discharged prior to imaging.

The following day she re-presented with a recurrence of severe pain, localising to the left flank. She had a renal tract ultrasound, which excluded obstructing renal stones. Despite now requiring IV morphine for her pain, she was haemodynamically stable and her abdomen remained soft. However, she was found to have absence of breath sounds in the left lung field on chest auscultation.

Repeat blood tests showed a CRP rise from 3 to 104. Chest X-ray (CXR) showed a bowel herniation into the left hemithorax with mediastinal shift to the right (Figure 1). CT chest and abdomen confirmed a complete collapse of the left lung due to the large, left posteromedial diaphragmatic hernia with intrathoracic transverse colon.

Given the severity of pain and increasing respiratory distress, the joint decision between obstetrics and general surgical teams was to proceed for combined caesarean section and subsequent reduction and assessment of the diaphragmatic hernia (DH). An uncomplicated caesarean section was performed under combined spinal-epidural anaesthesia via pfannestiel incision and baby was delivered in good condition.

Following closure of the uterotomy, the general surgeons identified a 2cm DH. They attempted to reduce the herniated bowel with gentle traction; however, this was limited secondary to patient discomfort. Therefore, the surgery was converted to general anaesthesia and additional midline vertical incision was made to reduce the herniated contents.

Following reduction, the transverse colon was noted to be distended with multiple serosal tears. Therefore, an extended right hemicolectomy was performed given the unhealthy appearing bowel concerning for ischemia.

Histological findings were consistent with early ischemic changes with areas of serositis and mural fibrosis. At the end of surgery, the anaesthetist placed a chest drain in the left chest as there was a breach in the parietal pleura causing hydropneumothorax.

The mother required extended hospital admission following her surgery. However, she made a good recovery with rapid improvement to her cardiorespiratory symptoms.

Discussion

DH in pregnancy are rare, with less than 50 cases reported in literature between 1959 and 2016.[1] Early diagnosis and management are critical to avoid life-threatening complications including respiratory failure and bowel obstruction.

The majority of DH are mostly congenital, affecting 1 in 3000 births.[2] They are usually diagnosed antenatally and repaired in the neonatal period. Acquired DH result from increased intra-abdominal pressure, most commonly due to penetrating and blunt abdominal trauma which compromises diaphragmatic integrity and allows abdominal organs to enter the chest cavity. Diaphragmatic defects occur more frequently on the left than the right. This is attributable to the protection provided by the liver.

In this case report, we describe a rare case of acquired maternal diaphragmatic hernia manifesting late in pregnancy. The patient's previous gastric sleeve operation was thought to prevent herniation of the stomach through the hernia. It is likely the hernia manifested on a basis of pre-existing anatomical weakness, exacerbated by increased intra-abdominal pressure in pregnancy.

Adults with DH can present with a variety of symptoms relating to abdominal viscera herniating into the pleural cavity. Symptoms can include chest

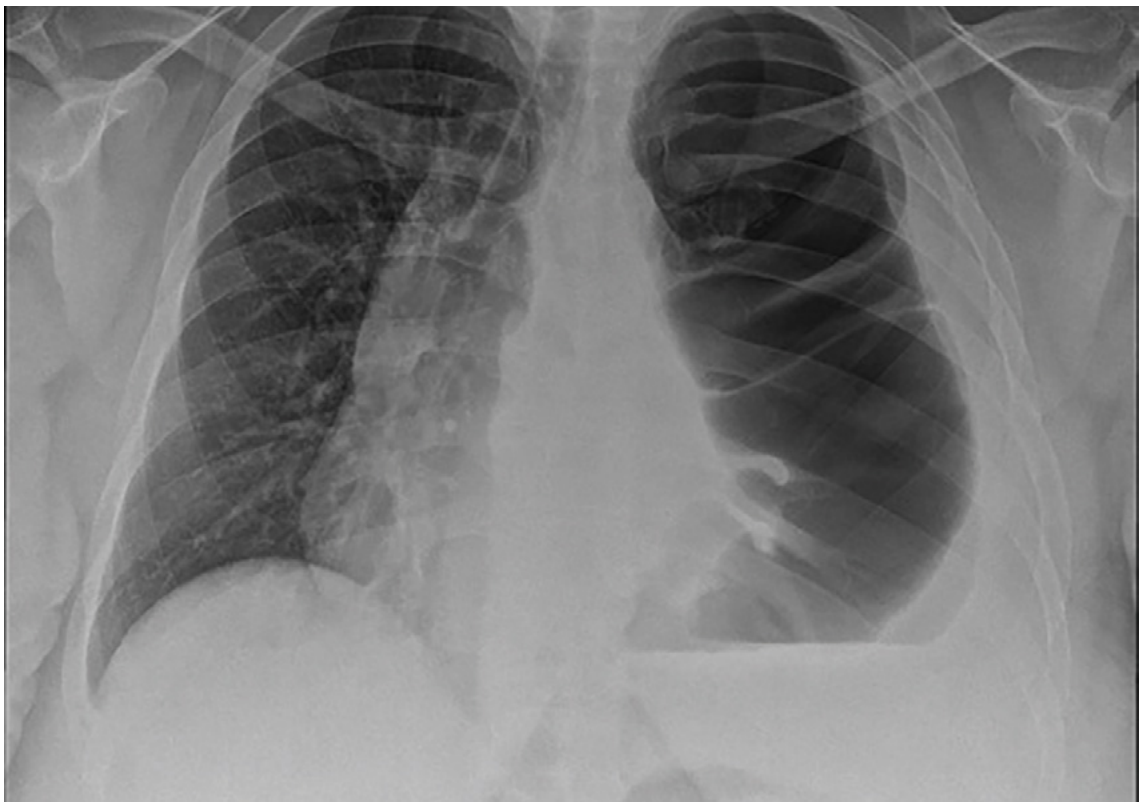

Figure 1. CXR demonstrating bowel loops with haustral folds herniating into the left hemithorax with marked mediastinal shift to the right.

pain, shortness of breath, heartburn, abdominal pain, nausea, vomiting, and the inability to pass flatus or stool. These are often non-specific and are commonly reported complaints during pregnancy, making diagnosis challenging. Therefore, it is important to perform generalised review of systems in all those presenting with an unclear diagnosis. On physical examination, reduced breath sounds on the ipsilateral side is the most common finding for DH.[3] Failure to respond to antacids, antispasmodics and dietary changes should also raise the suspicion of underlying bowel pathology.

Imaging modalities useful in evaluating DH include CXR, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). CT is considered the gold standard, as it can both localise the exact defect while also demonstrating the extent of herniated organs involved. CXR has a sensitivity of 70% as pleural effusion and pneumothorax often mimic the findings seen with DH.[4] MRI may be appropriate when patients are haemodynamically stable and have relative contraindications to CT such as contrast allergies or pregnancy. In this case, a CT scan was performed given the worsening symptoms and cardiorespiratory involvement. It also allowed assessment of the bowel.

Surgical management of DH is advised as the diaphragm is in a constant state of movement during respiration. Therefore, a diaphragmatic defect rarely heals without intervention.[5] Timing of surgery for pregnant women depends on the severity of symptoms and the gestational age. Symptomatic women with investigations demonstrating bowel compromise or cardiorespiratory involvement should proceed with emergent DH repair without consideration of gestational age. In asymptomatic women, elective surgery can be planned for the late first or second trimester. In third trimester, DH repair should take place simultaneously with caesarean section to avoid anaesthesia-related complications.[6] Between 24–34 gestational weeks, it is possible to consider steroid treatment and nasogastric decompression until the patient can be transferred to a tertiary hospital and surgery can be planned.

With regards to the mode of delivery, we recommended caesarean section for our woman due to the increased risk of cardiorespiratory compromise during labour with known mediastinal shift and left lung collapse. Kurzel and Naunheim[6] studied 17 case reports of women with DH in pregnancy, and they advised against vaginal delivery under any circumstance due to the risk of bowel strangulation when the woman is bearing down.

Conclusion

Diagnosing DH in pregnancy is challenging given the non-specific symptoms which mimic normal pregnancy, resulting in delays in treatment. Therefore, a high index of suspicion is required when reviewing women with recurrent non-specific symptoms as DH is associated with high maternal and fetal mortality rates.

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2020 Honours recipients

Professor Helena Teede
Honorary Fellowship

Awarded for the extraordinary contribution Helena has made to women's health, through her research, leadership, and mentorship of College Fellows. In particular, her research and exceptional leadership in the development of an acclaimed international PCOS guideline, which has made the investigation and management of this condition much improved for patients, not only in this country but worldwide.

Dr Celia Devenish
The RANZCOG Presidents Medal

Awarded for the extraordinary contribution Celia has made to the work of the College over many years. In particular, her extensive work on College committees, The RANZCOG Council and Board and dedication to medical education, spanning more than 25 years. The Board also acknowledges Celia's service to teaching and incredible commitment to mentoring and supporting trainees.

Dr Ian Page
Distinguished Service Medal

Awarded for the significant contribution Ian has made to the work of the College over many years. In particular, his work on numerous College committees and the RANZCOG Council over the past 15 years. The Board also recognises Ian's tireless dedication to progressing and advocating for women's health particularly in New Zealand.

A/Prof Edward Weaver
Distinguished Service Medal

Awarded for the extraordinary contribution Ted has made to the work of the College over many years. In particular, his extensive work on The RANZCOG Council, Board and College committees over the last 20 years, which continues to this day. The Board also acknowledges Ted's incredible commitment to teaching, mentoring, and supporting trainees as well as his continued contribution to improving maternity services and maternal safety in Queensland.

A/Prof Ian Pettigrew
Distinguished Service Medal

Awarded for the extraordinary contribution Ian has made to the work of the College notably, his work on numerous Committees and The RANZCOG Council as well as Ian's significant contribution and commitment as a teacher, mentor and passionate advocate for regional obstetrics and gynaecological services.

Professor Grant Montgomery
RANZCOG Excellence in Women's Health Award

Awarded for Grant's extraordinary contribution to women's health as a world leading researcher in the field of genetics and genomics in the area of reproductive science. The Board particularly notes Grant's work in endometriosis, which has reshaped global views on the aetiology of this disease.

Dr Susan Jacobs
RANZCOG Excellence in Women's Health Award

Awarded for Susan's extraordinary contribution to women's health over many years, in particular, her dedication to improving the health and wellbeing of indigenous women and longstanding commitment and advocacy work in the care of women with psychosocial vulnerabilities.

A/Prof Chris Benness
RANZCOG Excellence in Women's Health Award

Awarded for Chris's extraordinary contribution to women's health over many years, in particular, his dedication to the Urogynaecological Subspecialty, training gynaecologists from developing countries in Urogynaecological skills. The Board also recognises Chris's commitment and dedication to providing gynaecological services to women in regional NSW for nearly 20 years.

Professor Bev Lawton
RANZCOG Māori Women's Health Award

Awarded for Bev's extraordinary contribution to Māori women's health in the field of cervical cancer prevention in Aotearoa. In particular, the Board recognises her advocacy and research in HPV self-testing, aiming to increase cervical screening uptake for Māori women.

Smear your Mea Charitable Trust c/o Mr Eruera Keepa
RANZCOG Māori Women's Health Award

Awarded for the extraordinary contribution to Māori women's health in cervical cancer prevention through the extremely successful Smear Your Mea campaign, raising awareness of cervical cancer in Māori communities and encouraging women to have a smear test.

Obituary

Dr John Cunningham Anderson
1940–2020

'Few if any graduates from the 1965 year have achieved such distinction or influence in the practice of their chosen specialty or have advanced the prestige and cachet of the Sydney University Medical School as John Cunningham Anderson (known as Jock to his friends, family and acquaintances)' is a quote from his 50th year reunion book.

Jock was born at Kilmarnock near Glasgow in 1940 and migrated to Australia with his family in 1956. He came to medical school at the University of Sydney from Homebush Boys High School with a strong interest in engineering. On graduating in 1965, he did his junior medical training at Western Suburbs and Bankstown Hospitals and his senior specialty training in Obstetrics and Gynaecology at The Women's Hospital Crown Street gaining his Membership of the Royal College of Obstetricians and Gynaecologists (MRCOG) in 1972, his Diploma of Diagnostic Ultrasound (DDU) in 1977, his RANZCOG Fellowship (FRANZCOG) in 1979, Fellowship of the Royal College of Obstetricians and Gynaecologists (FRCOG) in 1984 and Credentialing in Obstetrical and Gynaecological Ultrasound (COGU) in 1991. Jock also held a commission in the army reserve as a medical officer in the rank of captain from 1971 until 1978, during which time he made two tours of duty to Papua New Guinea involved in malaria research.

Jock returned to his native Glasgow in 1973 to pursue training in Obstetrical and Gynaecological Ultrasound from its founding father, Professor Ian Donald, and was one of the first to be qualified in this field. He returned to The Women's Hospital Crown Street in 1974 as Deputy Medical Superintendent and was appointed Acting Medical Superintendent in 1976. During this period, he established an ultrasound department in the hospital. He developed an interest in the developing field of prenatal diagnosis and was involved in the first amniocentesis performed in Sydney and later pioneered fetoscopic blood sampling for the diagnosis of thalassaemia.

After the closure of Crown Street, he was appointed as a Visiting Medial Officer at King George V Hospital for Mothers and Babies/Royal Prince Alfred Hospital in 1982 where he helped set up the Fetal Medicine Department in 1987 and develop Chorionic Villus Sampling for first trimester diagnosis as well as the development of a multidisciplinary team for the monitoring and management of high-risk pregnancies. As well as continuing to practice as an obstetrician, Jock also established a specialised obstetrical and gynaecological ultrasound practice outside the hospital which was to become Sydney Ultrasound for Women, with sites throughout the metropolitan area.

Dr John (Jock) Cunningham Anderson

Jock's leisure time (what there was of it) was at this time taken up by his passion for aeronautics where he held a pilot's licence and a Command Instrument Rating on multi-engined aircraft for many years. He also hand built two Rutan designed aeroplanes, from the drawings, which he did in the garage of his home. He started with a single engine model but later progressed to the twin-engined Defiant, which was a major engineering feat. As well as this, he enjoyed playing squash and tennis and was a keen and highly skilled angler.

With the development of In Vitro Fertilisation (IVF), Jock's ultrasound and engineering expertise was sought by Prof Robert Jansen, with whom he later established Sydney IVF (Genea) in 1984, to develop the first transvaginal phased array ultrasound probe and needle guide in collaboration with engineers at General Electric. This was ground-breaking technology which enabled safe transvaginal ultrasound-guided outpatient ovum retrieval, no longer requiring general anaesthesia, a development which revolutionised the industry. He also transformed neonatal humidicribs into transport incubators, the prototypes of the equipment routinely used in IVF theatres and laboratories today as well as designing specialised embryo transfer catheters along with Prof Jansen.

Jock published widely and as well as writing multiple articles on ultrasound, prenatal diagnosis and IVF over the years, he also edited a comprehensive textbook on Gynaecologic Imaging for Churchill Livingston which was published in 1999 and remains a definitive work in the field. Teaching was another of Jock's great passions with a multitude of local and international presentations to his name and involvement in training both medical students and trainee doctors throughout his career. In recognition of these efforts, RANZCOG appointed him as chairman of the Ultrasound Subspecialty Committee from 1994 until 1998 and after his retirement in 2008, awarded him its highest honour, the Distinguished Service Medal in 2012.

Jock is survived by his wife Janette and his six children as well as six grandchildren. He will be sadly missed by his family, friends and colleagues as well as the innumerable patients for whom his expertise and ingenuity has made a difference over the years.

Dr Tom Boogert

Remembering Our Fellows

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

- **Dr Erhard (Harry) Tischler**, NSW
  17 November 2020

RANZCOG members awarded Honours on Australia Day

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

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

Prof Michael Chapman – For significant service to medical education, and to obstetrics and gynaecology.

Dr Michael Humphrey – For significant service to medicine, particularly to obstetrics and gynaecology.

Dr Jeffrey Tan – For significant service to gynaecological medicine, and to cervical cancer research.

Prof Jan Dickinson – For significant service to medical education, and to maternal fetal medicine.

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

Dr Alison Brand – For significant service to medicine, to gynaecology, and to medical organisations.

Medal (OAM) Of The Order Of Australia In The General Division

Dr Susan English-Donkers – For service to the youth of Timor-Leste, to women, and to medicine.