THE FACTS ON FERTILITY.

AUTUMN 2019

COMPASSION AND CUTTING EDGE SCIENCE AREAS THE KEYS TO FERTILITY TREATEMNT SUCCESS.

by Professor Kelton Tremellen, Medical Director
MB BS(Hons) PhD FRANZCOG CREI

The success of fertility treatment, like all areas of medicine, is the net result of a team effort. The doctor's clinical and technical skills, the nurse's ability to guide patients through what must initially appear as a daunting number of steps in treatment and the embryologists nurturing of the patients precious gametes and embryos. These scientists, the unsung heroes of IVF, are so critical to a successful IVF program and therefore a key factor to consider when deciding which clinic to send your patients to. Here at Repromed we have eight PhD scientists specialising in diverse areas ranging from embryology, genetic analysis of embryos, andrology and endocrinology. As a result Repromed provides the most comprehensive scientific range of Assisted Reproductive Treatment (ART) services available in South Australia, with all endocrine, embryo genetic analysis and andrology services being performed 'in house'. This ensures that Repromed can provide rapid turn around of results and have total control over service quality. No other clinic in South Australia comes close to this in terms of the depth of scientific PhD experience and breadth of treatment options.

Research is given a high priority at Repromed as we believe that it not only benefits patients' clinical care, but also enriches the work experience of our staff. Research at Repromed has been integral in the development of many clinical advances that have benefited patients around the world. In our next newsletter we will touch on one of those advances- non invasive pre-implantation genetic screening. More recently, Professor Tremellen's publication on sperm oxidative stress was recognised as a citation classic, ranked as the 9th most quoted paper in the field of andrology in the last hundred years (1). This accolade, and his invention of the male antioxidant therapy Menevit, is just one example of where Repromed staff are making a meaningful difference in reproductive medicine through their applied clinical research.

Finally, Dr Deirdre Zander-Fox (Scientific Director) and Professor Tremellen were recently awarded the runner up prize for best paper published in 2017 in the journal Reproductive Biomedicine Online (2). This journal was initiated by the Nobel Prize winning scientific pioneer of IVF- Professor Robert Edwards. It was therefore appropriate that the prize was presented to Professor Tremellen at a conference in London celebrating the 40th anniversary of the birth of Louise Brown, the world's first IVF baby.

KELTON TREMELLEN.

Fertility Specialist
Reproductive Endocrinology And Infertility Sub-specialist MBBS(Hons), PhD FRANZCOG, CREI, Grad Cert Mgmt

This prize winning research article explored the underlying mechanisms behind why miscarriage is increased in obese women - specifically does the problem lie with the embryo or the uterine environment. In order to examine this question Repromed analysed the outcomes of 125 biochemically confirmed pregnancies in which a high quality euploid (genetically normal) embryo was transferred. The primary findings were two-fold. Firstly, irrespective of the underlying cause of infertility, the rate of miscarriage of good quality embryos increased with BMI - confirming the presence of an underlying uterine pathology. Secondly, uterine endometriosis (adenomyosis) was more commonly seen in overweight and obese women compared to their lean counterparts, with adenomyosis being recognised as a risk factor for miscarriage. Fortunately, more recent work by Repromed

and Flinders University has shown that hormonal pre-treatment (ultra-long down regulation) of adenomyosis can significantly reduce the risk of miscarriage (3).

In 2019 Repromed will continue to strive to offer high quality clinical care for your patients, drawing on our leading clinical and scientific expertise, world class facilities and cutting edge research. On behalf of Repromed I would like to thank all our referrers and wish them and their patients a happy and successful year.

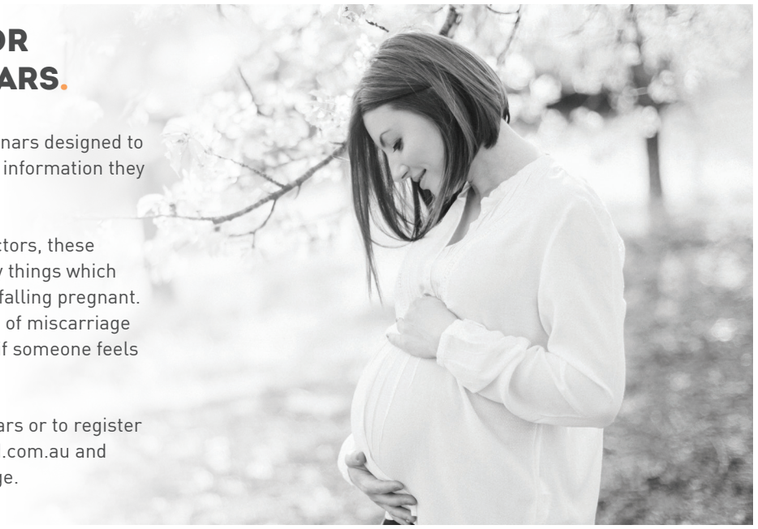
References

1. Bullock N, Ellul T, Bennett A, Steggall M, Brown G. The 100 most influential manuscripts in andrology: a bibliometric analysis. Basic Clin Androl. 2018 12;28:15.

2. Tremellen K, Pearce K, Zander-Fox D. Increased miscarriage of euploid pregnancies in obese women undergoing cryopreserved embryo transfer. Reprod Biomed Online. 2017;34(1):90-97.

3. Stanekova V, Woodman RJ, Tremellen K. The rate of euploid miscarriage is increased in the setting of adenomyosis. Hum Reprod Open. 2018; 1:1-8

FREE PREPARING FOR PREGNANCY SEMINARS.



Repromed regularly holds free seminars designed to give hopeful parents-to-be all of the information they need to start their family.

Presented by one of our Fertility Doctors, these seminars provide advice on everyday things which can increase someone's chances of falling pregnant. We also cover causes and treatment of miscarriage and infertility, and the steps to take if someone feels it is taking too long.

For details on up and coming seminars or to register simply visit our website at repromed.com.au and click on the link to our Seminars page.

ONCO-FERTILITY.

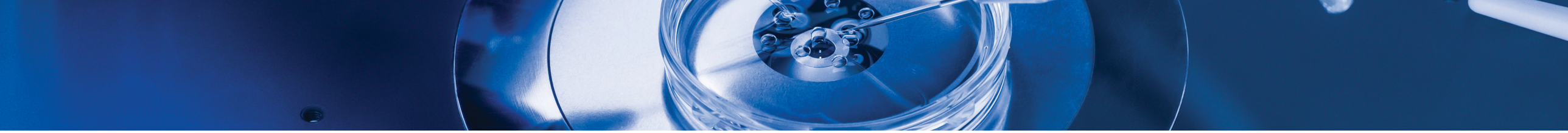
by Dr Vamsee Thalluri.

In Australia, approximately 2% of women of reproductive age are diagnosed with cancer, with 50% of these women requiring gonadotoxic treatment.

With earlier detection of cancer, as well as advancements in treatment, we are seeing significant improvements in survival rates and thus it is important we not only focus on treating the disease but also on ensuring optimal quality of life afterwards. For many women this includes the ability to start or grow their family. Unfortunately one of the potential side effects of cancer treatment is premature ovarian failure.

Treatment effects on future fertility depend on the mode of cancer treatment, the drugs used and the dose and duration of the agents used. Typically the main treatments that are associated with significant detrimental effects on fertility are the alkylating chemotherapy agents (eg Cyclophosphamide) as well as abdominal/pelvic radiation therapy.

Following a diagnosis of cancer where the patient is expected to undergo gonadotoxic treatment, counselling regarding the potential effects on



future fertility should be offered. The opportunity to proceed with fertility preservation treatment can then be discussed and the patient can decide whether it is something they wish to do.

For women the option for fertility preservation will typically mean controlled ovarian stimulation in order to freeze oocytes or embryos. Approximately 12-14 days is required to complete this process and whilst a typical IVF cycle normally starts with the patient's menses, in an emergency fertility preservation cycle where time may be of the essence, we are able to commence the stimulation immediately as part of a 'random-start protocol'.

In breast cancer there is typically a 6 week break between surgery and commencement of adjuvant chemotherapy, this is often a good time to complete a fertility preservation IVF cycle should the patient wish to do so. Research has shown that undergoing an IVF cycle for fertility preservation does not cause the cancer to progress or impede the ability to proceed straight into cancer treatment. Certainly, the decision to proceed with fertility preservation treatment is made as part of a multi-disciplinary team and in close conjunction with the treating Surgeon and/or Oncologist.

During the counselling process it must be made clear that fertility preservation treatment is not a guarantee of future children. 20-40% of women with breast cancer treated with chemotherapy will undergo early menopause and unless these women had oocytes or embryos frozen prior, they will have little choice but to consider egg donation or adoption should they wish to have children in the future.

Other options for fertility preservation include giving the patient a GnRH agonist during their chemotherapy treatment. This is thought to put the ovaries into a quiescent state and thus potentially reduce the impact on the ovarian reserve. Whilst such treatment has become rather popular in recent times the research data showing benefit remains limited and thus it is still considered to be controversial. Further prospective trials and ideally randomised controlled trials are needed to determine if GnRH agonists are an effective pharmacological treatment for the purposes of fertility preservation.

For men diagnosed with cancer, we would advise freezing sperm prior to undertaking gonadotoxic cancer treatment.

At Repromed we are dedicated to providing an Onco-Fertility service that allows counselling and clinical appointments within 24 hours if required and the opportunity for patients to proceed with fertility preservation treatment without concern for cost. Our fertility preservation treatments are offered at no out of pocket expense to the patient.

VAMSEE THALLURI.

Fertility Specialist / Gynaecologist

MBBS, MRANZCOG, CREI Fellow

Dr Thalluri completed his schooling in Adelaide and went on to study Medicine at The University of Adelaide. Having completed RANZCOG Specialist Training Program, he is now undertaking further experience to obtain the highest qualification available in Australia in the field of reproductive medicine and infertility (Certificate of Reproductive Endocrinology and Infertility – CREI).

It's extremely important to Dr Thalluri to help patients feel as comfortable as possible and guide them through what initially may seem like a very daunting process. "The first step is always to try and identify exactly what may be causing the fertility difficulties. Quite often there are reversible causes which we can treat with simple medications or a minor procedure. I believe in helping my patients conceive in the most natural way possible, using the least invasive and most cost effect treatments available. It's about offering choice and helping people achieve their dreams of having a family."

Dr Thalluri has published in peer reviewed journals and also presented at the Fertility Society of Australia's national conference.

SOUTH AUSTRALIA'S FIRST AUTOMATED SEMEN ANALYSIS MACHINE.

By Dr Deirdre Zander-Fox

Repromed is proud to have the first and only computer assisted automated semen analysis machine in South Australia.

Integrated into our Andrology Lab late last year following a vigorous validation program, this equipment which uses state-of-the-art Optoelectric Technology, enables results to be returned in 2 minutes from sample load.

Another strong clinical benefit of this new technology is the removal of operator bias when assessing results. Being a fully automated process, the machine provides a more consistent and standardised approach when providing results.

40% of couples struggling to fall pregnant will be due to problems with sperm function*. It is also widely accepted that the most effective way to assess a man's fertility potential is via a Semen Analysis.

Either referring your male patients to Repromed for a Semen Analysis test alone or referring them into Repromed's care is a strong step forward to identifying any potential fertility issues. And with our newly integrated automated Semen Analysis technology, results are returned faster and with a greater level accuracy when compared to traditional methods of assessment.

*A male can become infertile as a result of many causes. For a small minority there is a significant genetic issue causing poor sperm production, for others there are hormonal causes, infections damaging the sperm outflow channels or problems with the testis such as testicular cancer or failure of the testis to descend into the scrotum early in life (cryptorchidism). Several medications can also negatively impact on sperm production and quality. Heat can also affect male fertility however for the vast majority of men, no major factor will be identified as attributing to their infertility. In these cases "lifestyle issues" such as obesity, stress, excessive consumption of alcohol, or smoking can all have an impact on a man's fertility. Sometimes when these lifestyle factors are removed, a man will regenerate healthy sperm after approximately 3 months.

Infertility

The inability to conceive after a year of unprotected intercourse, is a common concern for both men and women as approximately 1 in 6 couples will experience difficulties when trying to conceive.

For the vast majority of couples, they will fall pregnant naturally within the first 12 months of trying however research tells us that of the couples struggling to fall pregnant, 40% will be due to problems with sperm function, so called male factor infertility.

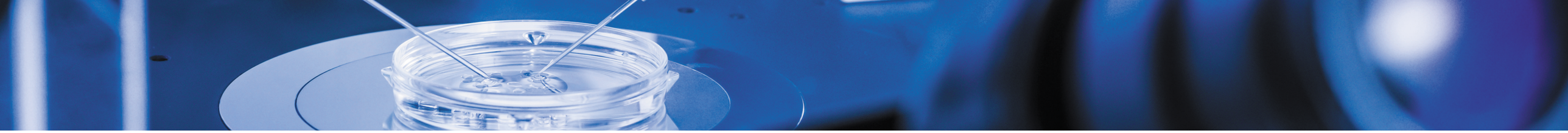
DEIRDRE ZANDER-FOX.

Scientific Director

Dr Zander-Fox is the Regional Scientific Director for the Monash IVF Group and is responsible for clinics throughout Australia and Malaysia, including Repromed. She is also a visiting research fellow and lecturer for the University of Adelaide

With a keen interest in optimising scientific technology, Dr Zander-Fox was instrumental in designing/implementing new laboratory protocols that resulted in significant increases to Repromed's pregnancy rates and was awarded the FSA-BFS Exchange Award at the World Congress of Human Reproduction.

She has a keen interest in genetics and oversees Repromed's onsite Genetics Laboratory which performs preimplantation screening/diagnosis as well as non-invasive prenatal testing (NIPT).



RECENT CHANGES TO THE GUIDELINES FOR ASSESSMENT AND MANAGEMENT OF POLYCYSTIC OVARY SYNDROME (PCOS) HAS AGAIN BROUGHT THIS CONDITION TO THE FOREFRONT.

Dr Juliette Koch helps to explain PCOS and how it can affect female fertility.

Q: What causes PCOS?

A: PCOS stands for Polycystic Ovary (or Ovarian) Syndrome and it is a hormonal disorder that affects up to 1 in 5 women world wide. Often a complex condition to identify, PCOS has several contributing symptoms however a patient does not have to have all of the symptoms to be diagnosed with PCOS. In fact, very few women have the same set of symptoms.

To date the causes of PCOS are still unknown. No single gene has been found to cause PCOS, so the link is likely to be complex and involve multiple genes however there are indicators that suggest family history, insulin resistance, lifestyle and/or environment do play a part.

Q: Is PCOS more prevalent in certain age groups?

A: Interestingly 12-18% of females of reproductive age are thought to have PCOS – therefore being able to identify them early and manage their condition will give them greater options about if and when to start a family.

Q: How does common is PCOS in families?

A: Immediate relatives (sisters or daughters for example) of females with PCOS are 50% more likely to have PCOS themselves.

Q: How does PCOS affect a female's fertility?

A: Women with PCOS often have high levels of androgens and insulin which can affect their menstrual cycle and prevent or disrupt ovulation and thus making it more difficult to conceive naturally. And some women with PCOS can have a greater risk of miscarriage.

Q: What are the symptoms of PCOS?

A: PCOS can be a complex condition to identify because there are several indicators and a patient does not have to present with all of them to be diagnosed with the condition.

Symptoms can include irregular or missing periods, growth of excessive facial or body hair, scalp hair loss, acne and/or oily skin, and sudden or unexplained continuous weight gain.

Q: The guidelines for PCOS Assessment recently changed – is that correct?

A: Yes, the international guidelines were released at the ESHRE meeting in Rome in July 2018. The guidelines were produced in collaboration with over 1600 health professionals and 1500 women and coordinated by the NHMRC and the Australian Centre for Research Excellence in PCOS in collaboration with the American Society of Reproductive Medicine and the European Society of Human Reproduction.

The aim of the guideline is to promote accurate diagnosis, optimal consistent care, prevention of complications and an improved patient experience and health outcomes for women with PCOS.

Q: What are the important updates addressed in the guidelines?

A: The importance placed on irregular cycles and hyper-androgenism. Free androgen index is suggested as the most reliable biochemical marker and doctors are encouraged to exclude other causes if the FAI is much higher than the reference range.

Whilst the guideline endorses the Rotterdam criteria in adult women, the ultrasound criteria for polycystic ovaries on ultrasound, has been modified. Polycystic ovarian morphology (PCOM) on ultrasound has been addressed and the criteria for diagnosis has increased from 12 follicles to 18 per ovary or a volume of 10mls or greater. Standardised measurement and reporting of pelvic ultrasound has been recommended. AMH has not been endorsed as a diagnostic tool. With improved standardisation of assays and large scale validation in different populations and ethnicities, AMH may be a useful tool in the future.

The diagnosis of PCOS in adolescence is hampered by the frequency of irregular periods, acne and PCOM in this population. Consumer groups have emphasised the profound psychological impact of the diagnosis and the guideline emphasises the need for caution in this group. The recommendation is only to make the diagnosis at greater than 2 years post menarche and to place importance on hyperandrogenism as a key component. The recommendation in this age group is not to perform ultrasound but to do a baseline hormone profile before starting the ocp and recommending further assessment in years to come.

Assessment of complications of PCOS is important and the recommendation is baseline lipids, yearly weight, BP and 1-3 yearly glucose tolerance test based on other risk factors. All women planning pregnancy with PCOS are recommended to do an oral glucose tolerance test. Health professionals also need to consider and screen for other potential complications such as obstructive sleep apnoea and endometrial cancer, with referral to the appropriate specialist.

Q: What do the guidelines recommend as front line treatment?

A: The oral contraceptive is recommended as first line treatment for both menstrual irregularity and hyper-androgenism but no particular preparation is considered superior. Women are encouraged to use the lowest effective dose and be cautious of venous thromboembolism (VTE) with higher dose preparations or risk factors for VTE.

Metformin can be used for women with BMI →25 and women in ethnic groups which are at high risk of impaired glucose tolerance. Some good quality studies demonstrate improvement in lipids, testosterone, glucose and insulin levels with metformin.

With regards to fertility and ovulation induction, this guideline recommends the use of letrozole as a first line agent due to a superior live birth rate (40-60% higher) and lower multiple pregnancy rate than clomiphene. Second line treatment involves the use of FSH injections or laparoscopic ovarian drilling. IVF is effective for women with PCOS and multiple pregnancy can be reduced with single embryo transfer. Women with PCSOS are at increased risk of ovarian hyperstimulation and this needs to be minimised. Bariatric surgery and anti-obesity agents remain experimental.

Healthcare should be provided in partnership with women and promote self- empowerment and education. Healthy lifestyle is important to prevent long term complications and achievable goals such as 5% reduction in body weight can yield clinically relevant improvements. The guideline emphasizes the need for healthcare interactions about healthy lifestyle, diet and exercise to be respectful, patient-centered and take into account women's personal, cultural and ethnic differences.

Q: Do you have any final words on PCOS?

A: It important to understand the increased rate of depression, anxiety, eating disorders and body image problems that women with PCOS can suffer. Women with PCOS may require multidisciplinary care from their GP, specialists in endocrinology and infertility, and allied health clinicians such as psychologists, dieticians and exercise physiologists. Most importantly however, the promotion of self-care and use of peer support groups should be encouraged.

JULIETTE KOCH.

Senior Fertility Specialist / Gynaecologist

MBBS, FRANZCOG, CREI, MRepM

Born and raised in Adelaide, Dr Koch was lured by the bright lights of Sydney as a young doctor, where she was quick to find her passion for women's health whilst working at the Royal Hospital for Women.

After an obstetrics stint in Outback Australia, Dr Koch committed to specialising in Obstetrics and Gynaecology, and she has not looked back; opting to go beyond her six-year specialist training to complete a rigorous Masters in Reproductive Medicine and three-year subspecialist qualification in Reproductive Health to ensure she remains at the very forefront of her field when it comes to helping people have, or extend their family.

Most recently, Dr Koch has worked as the Deputy Director of the Department of Reproductive Medicine at the Royal Hospital for Women in Sydney, providing services in fertility, menopause and gynaecology.

Dr Koch was also a lecturer at UNSW and training supervisor for subspecialty training in infertility and endocrinology. Warm and approachable, Dr Koch is extremely thorough in her investigation and management of infertility and the emotional ups and downs along the way.

Having recently returned to Adelaide with her husband and three boys to be closer to family, and to enjoy the wonderful lifestyle that Adelaide offers. Highly qualified, but also committed to a personal, caring and thorough approach, she is a highly valued specialist within the Repromed team.

MUST HAVE CONVERSATIONS in 2019:

This year, Repromed is proud to introduce a monthly seminar program specifically for healthcare professionals that address existing and evolving trends in the field of fertility medicine and preconception care.

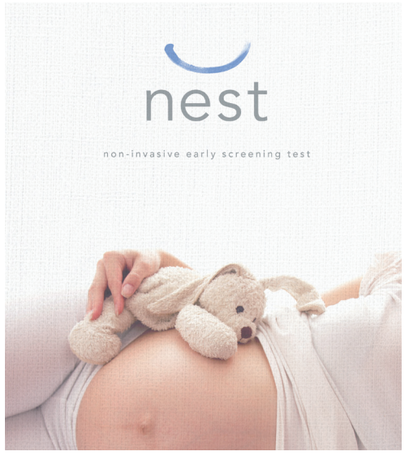
'Must Have Conversations' is a series of 1 hour clinical updates presented by a Repromed Doctor at our Dulwich clinic.

Upcoming sessions will discuss topics such as Pre-conception Genetic Screening and Creating Families using Donor Gametes.

Following each seminar there is an opportunity to ask questions and tour our facilities. The evening also includes a light supper.

There is no cost to attend and RSVP is either via our website or by texting Stephanie Pollock (Mbp 0419854722) or Sue Opie (Mbp 0411 523 528).

NEST UPDATE: MEDICARE ONLY SCAN



Performed in South Australia by Repromed's world class genetic scientists - **nest** represents a major Australian advancement in prenatal screening.

Nest (Non Invasive Prenatal Screening Test) may be requested as early as 10 weeks gestation. This highly sensitive and specific blood test screens for fetal chromosomal abnormalities, specifically Trisomy 21, 18, 13 and common sex chromosome aneuploidies.

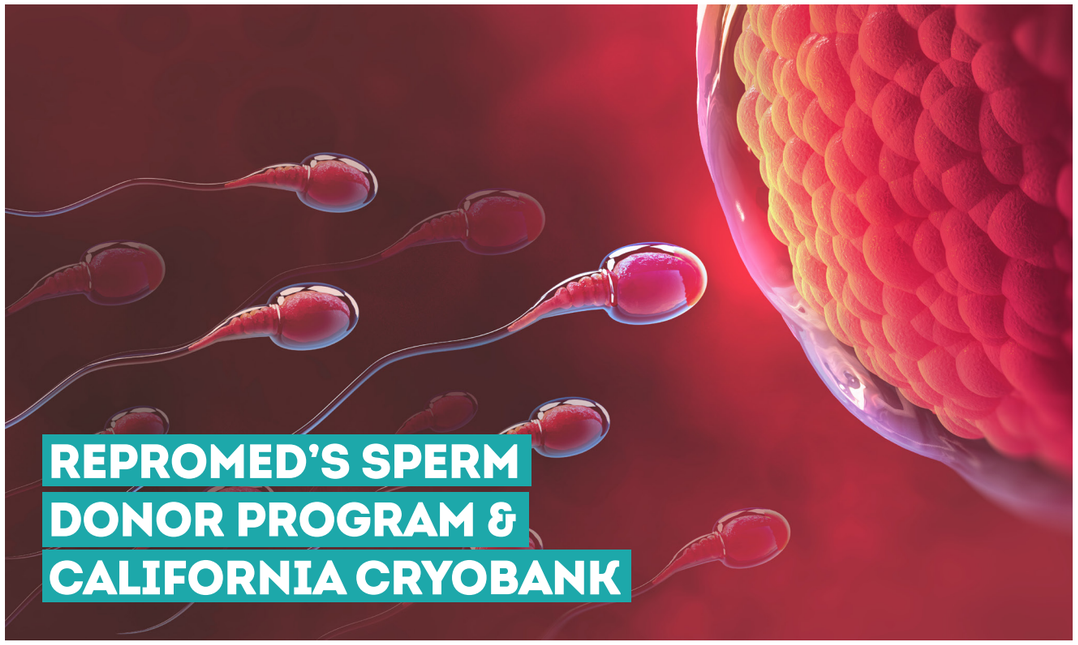
nest utilises whole genome sequencing technology and has the lowest test failure rate of any NIPT test performed in Australia.

nest is not restricted by maternal BMI, ethnicity or donor egg conception.

With **nest** 99.9% of your patients will receive a result.

Results are reported within 3-5 business days from receipt of sample and our genetic counselling service is available to assist you with interpreting of your results - at no additional cost.

To request a **nest** information pack (containing resources for you as a requesting clinician as well as supporting information for your patients) please contact **nest** laboratories today on 08 8333 8172.



Changes to South Australian Legislation in March 2017 has meant that a person can not be refused fertility treatment based on their sexual orientation, gender identity, marital status or religious beliefs.

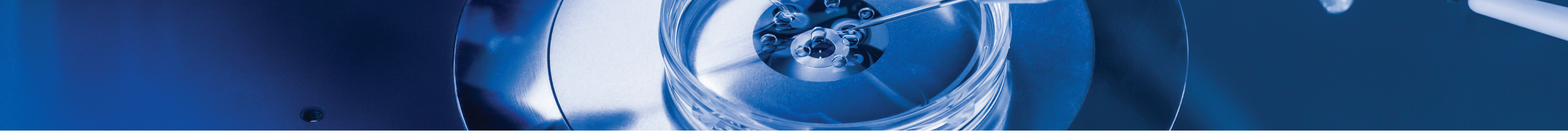
Women now no longer need a medical diagnosis of infertility to be considered for fertility treatment. This has given single females wishing to solo parent and same sex female couples the opportunity to become parents with the use of donor sperm.

In South Australia, Repromed has exclusive access to California Cyrobank, who has over 40 years of reproductive experience, for high quality, ID disclosure sperm donors who comply with Australian guidelines.

Repromed – who has the longest serving donor program in South Australia, has a dedicated Donor Team who work with both recruited donors and recipients. Our counsellors provide in-house ANZICA certified counselling, as well as our on-site doctors, nurses, day surgery, laboratory, blood taking and ultrasound services – ensures Repromed is fully equip to treat women with our donor program up to the average age of natural menopause which is taken to be 52 yrs.

QUICK FACTS:

- A child born as a result of donation is considered to be a child of the Recipient/s under South Australian Law, Family Relations Act 1975. The Donor has no legal parenting rights or responsibility (including financial) for the child.
- Both parents (if in a relationship), or just the mother's (if solo parenting) will be named on the birth certificate - donor's details are never listed.
- All Clinic Recruited Sperm Donors must be prepared to be contacted annually by Repromed to ensure their contact and medical details are up to date.
- All donors must be able to be identified to a donor conceived child from the age of 18 (at the child request).



WHAT IS A TUBAL PATENCY STUDY (HyCoSy)?

A Tubal Patency Study or HyCoSy is an ultrasound procedure which checks whether the fallopian tubes are 'open' or 'blocked'. HyCoSy stands for Hysterosalpingo-Contrast Sonography. This is low risk procedure that is performed in our ultrasound rooms at Dulwich. It is often used in preference to an HSG as no ionising radiation is required to perform the examination and it gives more information about the uterine cavity. A full pelvic ultrasound including a check for deep infiltrating endometriosisis is also performed at the same time.

The examination starts with a normal vaginal ultrasound to assess the uterus, ovaries and pelvis. Saline is then injected to check the uterine cavity and tubes. This allows us to accurately assess the shape of the uterine cavity and whether there is anything protruding into the cavity such as a polyp or fibroid or any intrauterine adhesions (Ashermans syndrome). By then watching the saline flow through the tubes we are able to assess if they are patent. The results of this test may direct the type of treatment that is required if a patient is having trouble falling pregnant.

During this procedure you may also wish to request for your patients to have a Lipiodol Flush. Lipiodol contains poppy seed oil and has a fertility promoting effect. It has been shown that it may increase a patient's chances of successful implantation in particular in patients with unexplained infertility or endometriosis, by up to 40%.

JANE WOOLCOCK.

FRANZCOG, COGU, DDU, BMBS(Hons), BMus, BSc

Dr Woolcock who is an Obstetrician and Gynaecologist with subspecialty qualifications in Ultrasound (COGU).

Specialising in laparoscopic 'key-hole' surgery and the complete excision of severe endometriosis, she is also a subspecialist in women's ultrasound, and offers a full range of diagnostic ultrasound and prenatal screening.

Dr Woolcock is also a staff specialist Obstetrician, Gynaecologist & Ultrasonologist at the Women's and Children's Hospital in addition to regularly operating at both Calvary North Adelaide Hospital and Burnside War Memorial Hospital. As a senior lecturer at the University of Adelaide, Dr Woolcock has many publications in peer-review journals and is currently Co-Chairman of the Australian Association of Obstetric and Gynaecological Ultrasound.

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