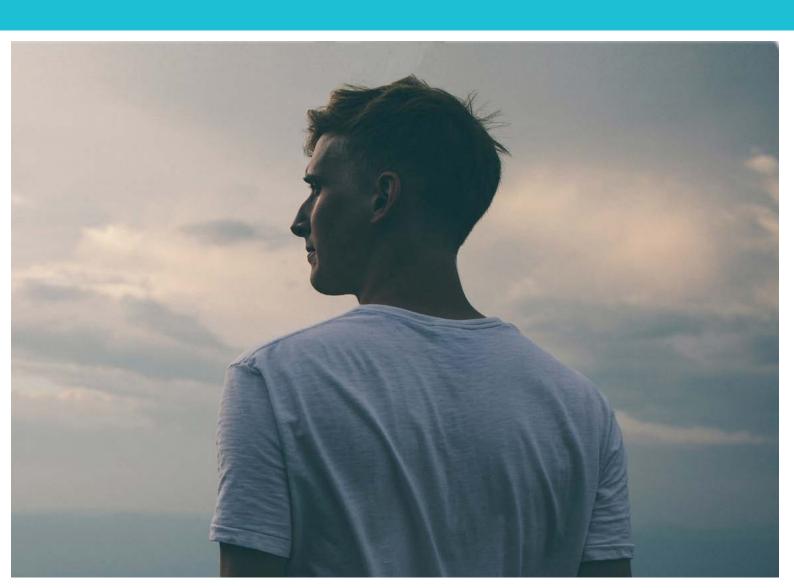


Male Infertility

A guide to causes and treatments

SA'S IVF LEADER SINCE 1982



How common is infertility in men?

Around one in six couples in Australia experience infertility so it's likely that someone you know will have faced it or even be going through treatment currently.

While it's often thought of as a female issue, in fact, one-third of infertility cases are caused by male reproductive issues, one-third by female reproductive problems and another third by both male and female reproductive challenges or by unknown factors.

The causes of male infertility are varied but in most (though not all) cases it can be treated, and couples go on to have a healthy pregnancy.

Why does it seem like infertility is in the spotlight?

If it seems that infertility is more common today than in the past, then that's because the current stats show this to be true. In the last 50 years, average human sperm concentrations dropped by 51.6%, and total sperm counts dropped by 62.3 percent, according to a 2022 review of 223 academic papers. The studies analysed sperm samples of a combined 57,000 men across 53 countries between 1973 and 2018².

Fragile Fertility

Average sperm count of men worldwide in 1973 and 2018 (million sperm per milliliter of semen)

101

1973

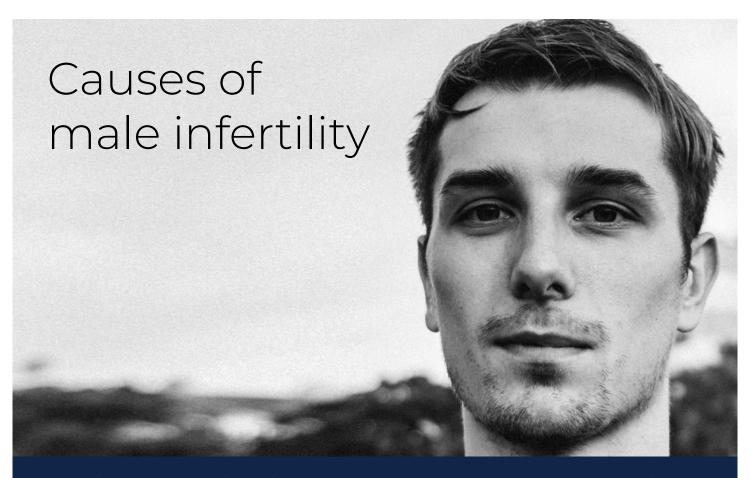
2018

Whilst more research is needed, and the cause is not agreed, it is thought to be due to a variety of factors such as men becoming fathers later in life, environmental exposure to harmful chemicals, and lifestyle factors including changes in diet, exercise, and sleep patterns. The latest thinking suggests as well that infertility is a barometer for general health with infertile men more likely to:

- Have underlying metabolic conditions and chronic disease such as diabetes, heart disease and depression.³
- Be hospitalised during their lifetime and die younger than the rest of population.⁴

We will explore the causes of male infertility and what can be done to improve sperm health as the good news is that many of the risk factors are reversible.

If you have concerns about your fertility you can book a no-obligation free chat with our patient care coordinator. Call 8155 5333 to arrange.



Anything that negatively impacts the numbers of sperm produced, its quality, or its motility (i.e. the ability to get to travel and reach an egg) will affect a man's fertility. In about a quarter of cases the cause can be found, however in just over 75%⁵ of cases the cause is unknown and requires much deeper investigation.

The most common causes of infertility in men include:

- Ageing
- Vasectomy
- Varicocele
- Medical treatment from chemotherapy/radiotherapy
- Chromosomal or genetic disorders, (e.g. Cystic Fibrosis)
- History of undescended testes, ambiguous genitalia at birth, trauma and/or surgery to the genital area
- Sexually transmitted disease or adult infection (e.g. mumps)
- Medications which may inhibit sperm quality (e.g. beta-blockers for motility, salazopyrin for count)
- Erectile dysfunction vascular cause or side effect of antipsychotics and anti-depressants

- Ejaculatory disorders, particularly retrograde ejaculation (sperm going backward into the bladder)
- Male obesity particularly visceral fat with increased adverse hormonal profile from conversion of androgen to oestrogen pathways
- Lifestyle choices, including the use of over the counter and recreational drugs, androgen precursors, alcohol, cigarette smoking, etc
- Exposure to occupational and environmental toxins (e.g. agrochemicals) and temperature

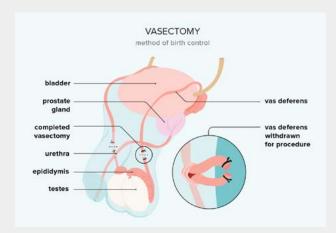
Ageing

The average age of fathers has risen significantly over the last decade. Whilst it is well-accepted that women's fertility starts to decline in the late thirties, it's generally believed that men can go on having babies till their advanced old age.

However, there is a direct correlation between paternal age and decreased sperm quality and testicular function. Further, genetic abnormalities, such as DNA mutations and chromosomal aneuploidies, and epigenetic modifications, such as the silencing of essential genes, have all been linked to paternal ageing.

Vasectomy

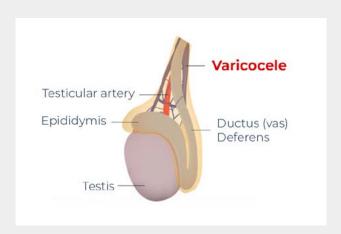
Vasectomy is a common reason we see men in the clinic.



Vasectomy surgery is generally permanent and though it may be possible to re-join the vas tubes in a reversal surgery, this does not guarantee the return of sperm in the ejaculate. The risk of failure is high and increases with the longer time between the vasectomy and the reversal surgery. If this is the case, then Surgical Sperm Retrieval (SSR) is usually the go-to option. Sperms retrieved surgically will be used for ICSI (assisted fertilisation) in an IVF treatment.

We recommend that anyone undergoing a vasectomy consider freezing sperm which has a modest cost and avoids the need to undergo future surgery.

Varicocele



Varicocele is a condition where veins in the scrotum become dilated. Men with infertility and varicocele usually have abnormal semen analysis with a low concentration and high abnormal forms.

Surgery to treat the condition may result in natural pregnancy, but this is not assured, and some may need surgical sperm retrieval and ICSI, particularly where there are other underlying conditions.

Testicular Damage

Unlike most other organs, the testicles are not well protected and can be damaged through accidental, workplace, or sporting injuries.

Possessing a single testicle does not imply a fertility difficulty however, as a normally functioning testicle can produce adequate amounts of sperm and testosterone. If the remaining testicle is functioning correctly and the spermatogenesis preserved, the man can still father a biological child.

Cryopreservation of semen (aka "sperm freezing") is important to consider in any situation where complete or a large amount of testicular tissue loss is at risk of occurring.

In the case of testicular cancers, we work with oncologists to expedite freezing to protect fertility.

Retrograde Ejaculation

Retrograde ejaculation occurs when semen passes backwards into the bladder with only a small volume of ejaculate being emitted. Individuals with diabetes or previous pelvic / prostate or bladder neck surgery are at particular risk.

Although you still reach sexual climax, there may be very little or no semen in ejaculate and large numbers of sperm will be seen in a post-coital urine specimen. While retrograde ejaculation isn't harmful, it causes infertility.

The most common method of treatment is to recover the sperm from the urine after alkalinisation. The prepared semen sample can then be used either with IUI or IVF/ICSI.

Less commonly, it can be treated with a combination of medications which increase the tone of the bladder sphincter muscle, but success is variable and often shortlived.

Chromosomal or genetic disorders

Chromosomal or genetic disorders whilst not common, are a known cause of infertility in about 4% of infertile men.

Fortunately, genetic testing is now widely available, and a simple saliva or blood test can reliably detect the more common genetic conditions, such as:

- Klinefelter syndrome (KS) this is a genetic condition that occurs in males when they have an extra X chromosome resulting in a total of 47 chromosomes instead of the typical 46. Each year, around 200-400 boys are born with the condition in Australia. Symptoms of KS can vary widely, but common signs include small testicles and an increased risk of breast cancer as well as reduced fertility. While there is no treatment that will 'cure' Klinefelter's, some men with KS may have enough sperm to father a child through IVF with intracytoplasmic sperm injection (ICSI) where one healthy sperm is injected into an egg to hopefully form an embryo.
- Cystic fibrosis (CF) is a genetic condition that affects multiple organ systems in the body, including the reproductive organs. This condition is often associated with an absence of the vas deferens from birth. Men who carry the CF gene abnormality (ie 1 out of 2 chromosomes abnormal) may still need assistance with fertility as though they make sperm, it cannot travel to the ejaculate.

It's important to note that not all men with CF will have fertility issues and some may still be able to father children naturally. Less common chromosomal conditions that can affect fertility include:

- Y chromosome microdeletions:
 - Deletions in small areas on the Y chromosome, the male sex chromosome, have been found to be associated with male infertility. They are found in approximately 2-5% of men with severely reduced sperm counts and up to 8% with complete absence of sperm. When Y chromosome microdeletions are found, counselling is imperative. Any male baby conceived will carry the father's Y chromosome, and therefore the microdeletion.
- Kallmann syndrome: This is a rare genetic disorder that affects the development of the hypothalamus and pituitary gland. Reduced spermatogenesis and testosterone level result due to deficient secretion of pituitary hormone and insufficient testes stimulation and maturation.
- Haemochromatosis: This causes the body to absorb and store too much iron. Iron can deposit in pituitary or testes to cause testicular dysfunction.
- X-linked recessive disorders:

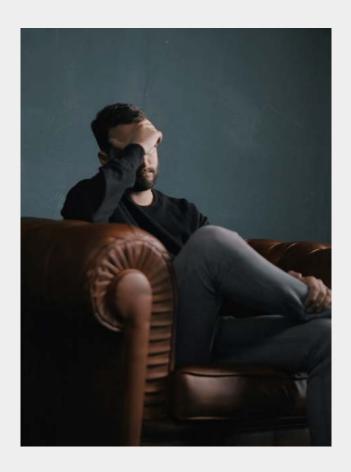
 Some X-linked recessive
 disorders, such as Fabry disease
 and Kennedy's disease can
 result in sperm dysfunction and
 infertility.

Unexplained Infertility

Vasectomy, ejaculatory problems, blockages, and genetic conditions represent less than a quarter of causes of infertility. The underlying reason for male infertility is unknown in 77% of cases.

Further, in 20% of patients who have undergone standard semen analysis tests we find no sperm, or poor-quality sperm, with no obvious cause⁷.

If you have unexplained infertility your doctor will work though a detailed medical and lifestyle history to investigate whether the underlying cause can be found. This will cover where you work, what sports you play, whether you take any drugs (prescribed or otherwise) and if you are routinely exposed (or have been in the past) to toxic chemicals. It may include blood tests to check for hormonal imbalance.



Lifestyle factors

Androgen (anabolic steroid abuse) and infertility

Androgen abuse, or the use of anabolic steroids, can have a significant impact on male fertility. Androgens are hormones that play a role in the development of male characteristics, such as muscle mass and body hair. Anabolic steroids are synthetic versions of these hormones that are often used by athletes and bodybuilders to increase muscle mass and improve athletic performance.

One of the most common ways in which anabolic steroids can affect fertility in men is by decreasing sperm count and motility. This happens because the steroids disrupt the normal balance of hormones in the body. External anabolic steroids raise blood levels of testosterone which switches off the signal to the testes to make natural testosterone. Low testosterone inside the testes is detrimental to sperm production and causes the testicles to shrink.

Long-term use of anabolic steroids can also cause the body to stop producing testosterone naturally. This can lead to a decrease in testicular function and a host of other health problems such as cardiovascular disease, liver and kidney damage. There is no evidence that intermittent cycling of drugs reduces their impact, and these effects can sometimes be irreversible.

Anabolic steroids are best avoided in anyone seeking to become a parent.

Recreational drug use

Use of recreational drugs is one of the leading factors that we see in male infertility, but one that mostly can be reversed by ceasing usage. Marijuana may help relaxation, but it has an unfortunately potent effect on sperm, reducing concentration, motility, and morphology which renders men infertile.

Cocaine and methamphetamines use have a similar effect and they also cause oxidative stress, leading to DNA damage in sperm. Additionally, methamphetamine use can affect the hormonal balance in the body, leading to a decrease in testosterone production, which can negatively impact sperm production.

The good news is that these effects, in all but the most long-term or heavy users can be reversed be stopping drug use.

Heavy mobile phone use

Some recent studies have shown a correlation between heavy use of mobile phones and low sperm motility and sperm count, however there is no clear evidence for the cause. The electromagnetic radiation is emitted by mobile phones is non-ionising, low frequency radio waves, which are not believed to damage DNA but they can be absorbed by the body.

So, while there is no clear-cut evidence, using earphones and minimising heavy use such as streaming is a sensible precaution.

Prescription medications

Certain common prescription medications can affect sperm production and function which poses a dilemma as they are necessary for your health, so it may not always be possible to stop them quickly.

Antidepressants

Some antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) have been linked to lower sperm count, decreased motility, and higher DNA fragmentation all of which can lead to lower chances of conception. They can also cause anorgasmia – the inability to achieve orgasmand erectile dysfunction.

Anabolic Steroids

Long-term use of anabolic steroids can also cause the body to stop producing testosterone naturally. This can lead to a decrease in testicular function and a host of other health problems such as cardiovascular disease, liver and kidney damage. There is no evidence that intermittent cycling of drugs reduces their impact, and these effects can sometimes be irreversible.

Blood Pressure

Some blood pressure medications, specifically thiazide diuretics (Chlorothiazide (Diuril) Chlorthalidone (Chlorthalid, Hygroton, Thalitone) Hydrochlorothiazide (Oretic, Microzide, HydroDiuril, Hydro, HCTZ, Esidrix), have been associated with decreased sperm count and reduced sperm motility.

Spironolactone (Aldactone, Spiractin) reduces testosterone and increases its conversion to estrogen.

Opiates

The long-term use (and misuse) of opiates such as morphine and oxycodone for pain management can affect pituitary hormones which stimulate spermatogenesis (FSH & LH) and subsequently lower testosterone levels inside the testes causing reduced fertility. In some cases, it is possible to switch to a different type of drug so if you are taking medications containing opiates, talk to your GP or pain specialist and let him/her know you are trying to conceive.

Over the counter (OTC) medications:

Some OTC medications have been associated with decreased sperm count and motility including nonsteroidal anti-inflammatory drugs (such as ibuprofen), antihistamines (e.g. Diphenhydramine (Benadryl) and Promethazine (Phenergan), and proton pump inhibitors such as Esomeprazole (Nexium) and Omeprazole (Prilosec).

While for most people taking these in small amounts will cause no harm, long term usage can lead to impaired sperm.

It is important to inform your fertility doctor of what medications you are taking and discuss their possible effect on fertility.

Occupational/environmental exposure to toxins

Certain chemicals have been linked to decreased sperm production. As part of our pre-clinic and consultation forms, we will check whether you have exposure to chemicals through your job or hobbies.

Some examples of chemicals that can have a negative impact on male fertility include:

- Pesticides such as organochlorines and organophosphates
- Heavy metals such as lead, cadmium, and mercury that can be found in mining, smelting, welding, and the construction industries.
- Solvents such as benzene used in the production of rubber, dyes and plastics – and toluene which is used in the manufacturing of paints, thinners, and glues can damage sperm and lead to decreased fertility.
- Phthalates which are chemicals are used in a variety of everyday consumer products, such as plastics and personal care products, and that have been linked to decreased sperm count and motility.
- Bisphenol A and S (BPA and BPS): These are chemicals used in many consumer products such as food packaging, water bottles, and even some dental sealants.

BPA is being phased out of many products however is being replaced with BPS, which some studies⁶ show has even more toxic effects on the reproductive organs. Much more research is needed, but we suggest that avoiding plastic as much as possible is the safest route.

■ Polychlorinated biphenyls (PCBs) were widely used in the past in industrial and commercial applications and are amongst a broader group of harmful chemicals known as persistent organic pollutants (POPs) or "forever chemicals". Even though banned in Australian since 1975, they persist in the environment and animals and can bioaccumulate through the food chain.

It's important to be aware of the potential risks associated with these chemicals and avoid unnecessary exposure as much as possible. This can be done by using personal protective equipment, avoiding certain products that contain these chemicals or using products that are labelled as 'BPA/BPS free'.



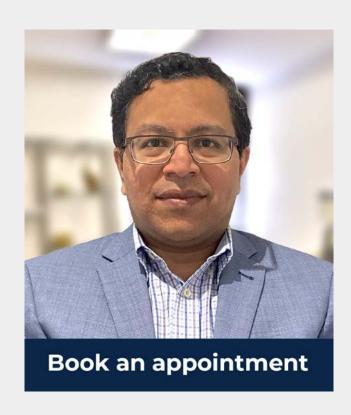
Hormonal imbalance

When fertility hormones are mentioned, we tend to think about women, however in men hormones also play a key role in creating healthy sperm.

The main hormones that have an impact on sperm production and that we may test for are:

- **Testosterone:** This is the primary male sex hormone, and it plays a key role in sperm production and maturation. Low levels of testosterone can lead to decreased sperm production and quality as well as decreased libido.
- Follicle-stimulating hormone (FSH): This hormone stimulates the primordial cells to increase proliferation and increase production of sperm in the testes. Low levels of FSH can lead to severely reduced sperm numbers.
- Luteinizing hormone (LH):
 This hormone stimulates the production of testosterone in the testes. Low levels of LH can lead to decreased testosterone levels and decreased sperm production.
- **Prolactin:** This hormone is secreted by the pituitary gland and can affect sperm production if levels are too high by suppressing FSH and LH and indirectly lowering testosterone.

- **Thyroid hormones:** Thyroid hormones are important for overall health, including sperm production. Abnormal thyroid hormone levels can affect sperm production.
- Estrogen: Estrogen is a hormone typically associated with females, but men also produce it in small amounts particularly in central adipose (i.e fat) tissue. High levels of estrogen can decrease sperm count, motility and morphology.



At Flinders Fertility we have an experienced endocrinologist,

<u>Associate Professor Vasant Shenoy</u> who can test, diagnose and treat male factor hormone conditions.

Treatments for Male infertility



The treatment for infertility depends on the underlying cause.

Often making lifestyle changes such as losing weight, quitting smoking or drugs, and avoiding exposure to toxins can help improve sperm count and overall fertility without further intervention.

If sperm counts are low but not absent, sperm can be retrieved and used for simple procedures like Intrauterine insemination (IUI), IVF or preserved via sperm banking for future use.

If the underlying cause is found to be hormonal, an endocrinologist may prescribe medication to rebalance.

Where sperm is still in the testes, but cannot be ejaculated (eg vasectomies, retrograde ejaculation, obstruction of ejaculatory pathway), we may recommend one of surgical sperm retrieval (SSR) procedures, a procedure called Testicular Sperm Extraction (TESE). This involves taking a small tissue sample under local anaesthetic and examining it under a microscope to find and extract sperm. Men often have non-uniform sperm production throughout the testicle with pockets of spermatogenesis.

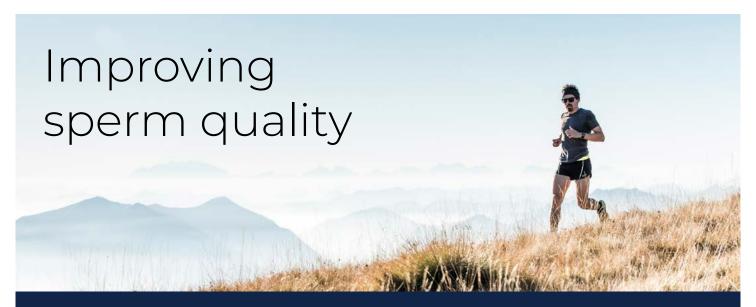
In some cases, a slightly more invasive procedure called open testicular biopsy is used.

The extracted sperm can then be injected directly into their partner's egg using a technique called intracytoplasmic sperm injection (ICSI).

Where sperm are present, but they are abnormal, we may instead 'wash and prep' the semen sample in the lab to select healthy sperm and directly inject the sperm into the egg using an IVF procedure known as ICSI.

It's important to note that in some cases, infertility may be caused by a combination of factors or may be unexplained. In these cases, a combination of treatments may be necessary to achieve a successful pregnancy.

It's also important to note that not all infertility can be treated, and in some cases, couples may need to consider alternative options such as adoption, fostering, or using a sperm donor.



There are several things you can do to improve the quality of your sperm:

- Maintain a healthy lifestyle: Eating a balanced diet, getting regular exercise, and avoiding smoking and excessive alcohol consumption can all help to improve sperm health.
- Maintain a healthy weight: Being overweight or obese can negatively impact sperm health, so maintaining a healthy weight can help to improve it.
- Avoid toxins: Exposure to certain toxins, such as pesticides and heavy metals, can harm sperm health. Try to avoid exposure to these toxins as much as possible.
- Manage stress: Stress can negatively impact sperm health, so finding ways to manage stress, such as through exercise, meditation, or therapy, can help to improve it.
- Avoid overheating the testicles:
 The testicles need to be slightly cooler than the rest of the body for sperm production, so avoid prolonged use of saunas, hot tubs, or tight clothing that may overheat the testicles. Keep your laptop off your lap!

Certain medications, such as testosterone replacement therapy and some antidepressants, can negatively impact sperm health. If you're taking any medications, talk to

Avoid harmful medications:

your doctor about any potential impacts they may have on your fertility.



- Minimise mobile phone use or use headphones to avoid heat and electromagnetic radiation
- Keep an eye on your overall health: Regular check-ups to identify and treat any underlying health conditions that may affect sperm health is a good idea.

Diet

There is no specific "fertility diet" for men, but maintaining a healthy diet that is balanced and nutrient-dense can be beneficial for sperm health. Some specific foods and nutrients that have been shown to be beneficial for male fertility include:

- Foods that are rich in antioxidants, such as fruits and vegetables, can help protect sperm from damage caused by free radicals. Some of the best sources of antioxidants include berries, leafy greens, and brightly coloured fruits and vegetables.
- Omega-3 fatty acids which are healthy fats that improve sperm health and increase sperm count. Good sources of omega-3s include fatty fish such as salmon, mackerel, and sardines, as well as flaxseeds, chia seeds, and walnuts.



Zinc which is important for sperm production and can help improve sperm count and motility. Good sources of zinc include oysters, beef, poultry, and legumes.



- Selenium: Selenium helps to protect sperm cells from oxidative stress, which can help to maintain their quality and function. Eating just two brazil nuts meets your daily selenium needs.
- Vitamin C: This can help protect sperm from damage. Good sources of vitamin C include oranges, strawberries, kiwi, and capsicums.



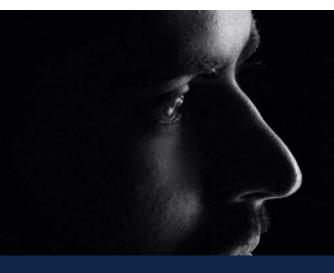
Vitamin D: Vitamin D is important for sperm production and can help improve sperm count and motility. Good sources of vitamin D include fatty fish, egg yolks, and fortified foods such as milk and cereal.



■ Folic acid isn't just for women, it is important for sperm health and can help improve sperm count and motility. Good sources of folic acid include leafy greens, fortified grains, and legumes.

It's also important to limit the intake of processed foods, saturated fats, and added sugars as they can negatively affect sperm health.

The emotional impact of infertility



An infertility diagnosis can be devastating. Men report feeling a wide range of emotions such as:

- Shock and disbelief: Many men may be surprised to learn that they have infertility issues and may have trouble accepting the diagnosis.
- Grief and loss: Infertility can be a difficult and emotional journey. Men may feel a sense of loss and grief over the idea of not being able to have biological children.
- Anger and frustration: Men may feel angry and frustrated with their bodies for not working as they should and may also be frustrated with the lack of control they have over the situation.
- Isolation and loneliness: Men may feel isolated and alone with their feelings and may not know who to talk to about their diagnosis.

- Anxiety and depression: Men may also experience anxiety and depression as a result of the diagnosis and the uncertainty of their future.
- Hope: Some men may find hope and positivity in the fact that there are assisted reproductive technologies such as IVF and ICSI, which may help them to father a child.

It's important to seek emotional support and counselling if necessary, especially if you don't have friends or family you can confide in. Flinders Fertility has counsellors available for patients who need some additional support, and appointments are free of charge. We also recommend checking the healthymale website which is full of great information on all things related to male health – not just fertility.

Book an appointment

If you are concerned about your fertility, you can <u>book a fertility chat</u> to run through your options, or <u>make an appointment</u> with a Flinders Fertility doctor.

Clinical review by Assoc. Prof. Vasant Shenoy and Dr Susie Kim

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