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THE INFERTILE COUPLE

Evaluation begins with history of both partners, preferably interviewed separately:

Is it a primary or secondary problem for both partners

Secondary infertility does not exclude male problem

Secondary female problem - think of tubal factor

Prior fertility - how long did it take last time?

Contraceptive history

IUCD - think of tubal problem

Menstrual history - since cessation of any COC

Calculate the number of ovulations that have occurred

Most women with a regular cycle are ovulating

Symptoms of endometriosis? i.e. dysmenorrhea or dyspareunia, premenstrual spotting

How often is intercourse occurring? Any problems?

Male and female risk factors for or history of genital tract infection. Ask about any STD, Pap smear problems, pelvic inflammation, penile discharge, previous partners etc

If there has been one STD e.g. HPV, then there may have been others. Treatment such as cervical diathermy may also be relevant by its effect on cervical mucous

Previous investigations, pelvic surgery, vasectomy or tubal ligation reversal etc.

Drug history Smoking (both partners), Alcohol, Heat or Toxins especially in males

EXAMINATION AND INVESTIGATIONS proceed on the basis of hypotheses generated from the history. Is it:

Ovulation problem

Male factor

Tubal problem

Endometriosis

Or a combination of any of the above

PRENATAL TESTS: Do routine pregnancy screen on all patients i.e. Full blood examination, Rubella and Varicella immunity and Serology for syphilis, HIV and Hepatitis B. Perform a Pap Smear, if required and counsel about diet and especially Folic acid. Recommend supplements with 0.5 mg daily of folate

FERTILITY TESTS THAT CAN BE ARRANGED BY ANY DOCTOR

Commence a basal body temperature chart – see below

Arrange semen analysis for the male – but beware. Unless you can provide appropriate collection instructions, interpret the report AND counsel the male if the result is abnormal then this exercise can backfire.

Arrange a luteal phase serum progesterone (PROG). This should be midluteal i.e. 7 days before the expected menstrual period. For a 28-day cycle this is Day 21, but for a 35-day cycle it is Day 28.

A follicular phase FSH is useful for patients who may be at risk of ovarian failure i.e. >35 years of age. This is best done on Day 2 or 3 of a cycle. It is often performed with an LH estimation and oestradiol (E2).

Endocervical swab or ThinPrep or first passed urine for Chlamydia PCR if tubal disease or STD is suspected

Counsel along the lines of: “There is really no simple test that will indicate whether a man or a woman is "fertile". Rather it is a matter of evaluating the known causes of infertility and deciding which is the best way of assisting Nature to commence and/or complete its task.”

BASAL BODY TEMPERATURE CHART

The easiest and least invasive method of evaluating a woman's hormonal cycle is the charting of the basal body temperature. On waking, a woman takes her temperature orally for at least two minutes before getting out of bed, drinking or eating. She carefully records this on a chart. If ovulation occurs, a woman's temperature will normally rise by 0.4 to 0.6 degrees Centigrade during the second half of the cycle.

The basal body temperature is not a good method of identifying the best day for intercourse and the overall pattern may require specialist's interpretation. The basal body temperature chart is often used for evaluating the effectiveness of treatments to stimulate ovulation. A prolonged rise in the basal temperature may also be the first indication that pregnancy has been achieved.

Sometimes couples with fertility problems have completed a large number of basal body temperature charts over many months, even years. This can cause a degree of unnecessary stress and is not encouraged.

HYSTEROSALPINGOGRAM (HSG)

This X-ray examination is used to check both tubal patency and the internal structure of the uterus. A radio-opaque dye is injected through the cervix with screening by fluoscopy performed without anaesthesia as an outpatient. Some women may experience cramping and there is a small risk of aggravation of pelvic infection.

Normally the dye will "fill" the uterine cavity, pass along both fallopian tubes and then "spill" out of the ends where it will be visualized pooling in the peritoneal cavity. Failure of the dye to pass into one or both tube indicates either blockage or temporary spasm.

This test (like tubal insufflation during laparoscopy) is both diagnostic and therapeutic. That is to say, apart from identifying any site of a possible tubal blockage, it may also relieve minor obstruction and thus facilitate a conception in the months immediately after the procedure.

LAPAROSCOPY and HYSTEROSCOPY

A laparoscopy permits direct inspection of the ovaries, fallopian tubes and uterus. It is the only certain means by which endometriosis of the pelvis can be excluded as a factor in the fertility problem. It is usually performed as day-case surgery.

It is possible to examine the size, shape and contours of the pelvic organs. Adhesions, scarring, endometriosis or fibroids can be detected. Examination of the flower-like ends of the fallopian tubes is possible to ensure that they are capable of free movement and egg capture. The ovaries can be examined for evidence ovulation with the visualisation of a corpus luteum (or yellow body). This is a small progesterone-producing structure that forms in the ovary after the release of an egg. The patency of the tubes is tested by the injection of dye through the cervix to see if any passes out through the tubes.

Minor and mild endometriosis, detected during laparoscopy may be treated with diathermy. RCT has demonstrated that this improves the chance of conception in the months to follow.

Hysteroscopy involves inspection of the uterine cavity with an endoscope introduced through the cervix. It is often performed at the same time as a laparoscopy. An endometrial biopsy may be taken and minor intrauterine synechia can be divided.

ENDOMETRIAL BIOPSY

Progesterone, released only after ovulation, causes regular and predictable changes in the endometrium.

Correlation of the histological changes with the day of the woman's cycle can assist in the evaluation of both ovulation and the adequacy of the luteal phase of that cycle.

SEMEN ANALYSIS OR SPERM COUNT

This is the first and most basic test carried out on the male partner. It is desirable that the specimen be produced by masturbation after two days of abstinence. The specimen should be protected from extremes of temperature and examined within one hour of collection.

The sample produced is examined for the number of sperm present (a sperm count), the ability of the sperm to move (motility), the shape and appearance of the sperm (morphology), the total volume of the ejaculate, the chemical constituents, and the vitality of the sperm.

Sperm Count:

Any count >20 million sperm per ml is accepted as normal. However, of all the parameters, this is the one that is most likely to vary. Primarily this reflect the time since the last ejaculation but the sperm count is also influenced by such factors as any viral illness, exposure to testicular toxins and other "stressors" to the generation of sperm.

Counts of between 14 and 48 million/ml are only mildly abnormal and would generally result only in a slight delay in conception provided that the female partner is otherwise fertile. Counts consistently below 5 million/ml usually mean a more serious testicular problem exists.

It is important to recognise that no male is completely infertile unless the semen is always completely devoid of sperm. This is called azoospermia.

Motility:

Sperm motility must be assessed in a freshly collected semen sample that has not been exposed to extremes of temperature. In general, at least 30% of the sperm present should be exhibiting progressively forward movement but it is quite normal for some sperm not to be moving at all. Unless subject to computer analysis, there can be debate and observer differences in what constitutes forward progressive motility.

Those factors that affect sperm count can also affect sperm motility. One important addition is the presence of a significant concentration in the seminal fluid of antisperm antibodies that should be separately tested for. Unfortunately, the detection and interpretation of available tests for antisperm antibodies are complex and sometimes inconclusive.

Morphology: (Shape of sperm)

Of all the tests of sperm this is perhaps the one that can be most consistent from sample to sample if there is a significant testicular problem. For this parameter specialist laboratories will immobilise, stain, enlarge and examine in great detail not less than 100 individual sperm selected at random. Unfortunately, the assignment of "normal" to an individual spermatozoon is subjective and has also varied over the years in the stringency of the criteria applied.

Many men with normal testicular function and fertility will have as few as 5-12% completely normal sperm in an ejaculate if very strict criteria are applied.

If the proportion of normal sperm is consistently <3% then it is likely that a problem exists and spontaneous pregnancy is infrequent. Within the range of 3 - 9% there is a "grey zone" for which there is currently no consensus about significance nor the optimal method of treatment.

Sperm Antibodies:

Sperm immobilizing or agglutinating antibodies may be detected in seminal plasma or coating the sperm. They can also be detected in blood serum from infertile males and females.

The Importance of Repeat Semen Analysis:

The results of a semen analysis can vary spontaneously and substantially in the same man from sample to sample as a result of a multitude of known and unknown influences. It is therefore inappropriate to attach particular significance to changes from one sample to another, or indeed to any one result. If a problem is detected an infertility laboratory will require three (and sometimes four) different evaluations of semen over not less than six weeks

THE MONTHLY PROBABILITY OF PREGNANCY

One important concept for all couples who are trying to achieve pregnancy is the monthly chance of a conception occurring. Contrary to most expectations, this is not very high and only 15 - 20% at best i.e. for a healthy young male with good numbers of progressively highly motile and morphologically-normal sperm in his ejaculate who has intercourse within 24 hours of ovulation with a young female with a completely normal pelvis. This is the reason why it takes many couples 2 - 8 months to conceive after cessation of the use of condoms or a diaphragm. It may take 6 - 12 months to conceive after stopping an oral contraceptive because this contraceptive often continues to affect hypothalamic function and gonadotrophin release for a few months after its cessation. These times are shorter if the couple has achieved a pregnancy before.

If there is a lowered sperm count, poor sperm motility, "sticky" tubes or pelvic endometriosis then this monthly chance of pregnancy may be lowered by a factor of 0.75, 0.5 or greater. That is to say couples with such problems may not be infertile i.e. unable to conceive ever, but simply subfertile. It may take them longer to get pregnant than the idealised couple with normal fertility.

Rather than exhaustively pursuing fertility tests and looking for “the cause for infertility” modern practice uses the monthly chance of fertility as an indication to assist the reproductive process. The monthly probability of pregnancy is calculated from the number of months in which ovulation occurred and there was a reasonable possibility of a conception because intercourse was occurring at appropriate intervals (two or three times a week) and no contraceptives were used. *In short, the most important "test" of fertility is the length of time that the couple has had for pregnancy but it did not occur.*

If the monthly chance of pregnancy is below 5%, then it is appropriate to consider assisted reproduction. This equates to about “two years of trying” but this by no means dictates that earlier evaluation or intervention is not appropriate under certain circumstances. The most common of these is *the increasing age of the female partner*.

Age and Fertility

The chance of becoming pregnant in any one month is about 20 percent in women less than 30 years of age, but only 5 percent in women more than 40. There are several explanations for this. They include such medical conditons as hypertension or diabetes, changes in ovarian function and alterations in the chromosomes of eggs released by the ovaries. By the time a woman is 35 or 40, she has also had more time to develop such gynaecological disorders as endometriosis which decrease fertility in ways that are not completely understood.

Ageing doesn't just affect women. Though perhaps not as abrupt or noticeable as menopause is for women, changes in fertility and sexual functioning do occur in men as they age. The testes tend to get slightly smaller and softer with age. Semen quality and sperm morphology (shape) and motility (movement) all tend to decline. Overall it is estimated that male fertility declines about 30% between the ages of 30 to 50 years.

Sexual functioning in men may also change with ageing. Often there is a slight decrease in a man's testosterone level which can cause a decrease in libido. Men may have difficulty achieving and/or maintaining erections as they age. Illness, stress or reactions to medications, all of which tend to occur more frequently as men get older, can accelerate these changes in testosterone, libido and sexual functioning.

Despite these changes, there is no maximum age at which men are not capable of conceiving a child, as evidenced by occasions when men in their 60s and 70s conceive with younger partners.

Table 1 Rate of Miscarriage by Maternal Age

Age in Years	Spontaneous Miscarriage (%)
15 – 19	9.9
20 – 24	9.5
25 – 29	10.0
30 – 34	11.7
35 – 39	17.7
40 – 44	33.8
>45	53.2

Ovarian changes

In order to understand the effect of age on the ovary it is necessary to review the process by which ovulation occurs. The hypothalamus and pituitary gland orchestrate the events leading to ovulation and regular menstruation. The hypothalamus stimulates the pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones are secreted into the bloodstream and control the growth of eggs (oocytes) and the production of the female hormones, oestradiol and progesterone by the ovaries.

Table 2 Risk of Baby with Chromosomal Abnormality by Maternal Age		
Mother's Age at expected date of delivery (Years)	Chance of live-born baby with Down's Syndrome	Chance of live-born baby a chromosomal abnormality
20 – 24	1:1420	1:500
25 – 30	1:1250	1:480
31 – 34	1:1140	1:420
35	1:384	1:179
36	1:307	1:149
37	1:242	1:124
38	1:189	1:105
39	1:146	1:81
40	1:112	1:64
41	1:85	1:49
42	1:65	1:39
43	1:49	1:31
44	1:37	1:24
45	1:30	1:21
46	1:23	1:16
47	1:18	1:13
48	1:14	1:10
49	1:11	1:8

Most women have about 300,000 eggs in their ovaries at puberty. For each egg that matures and is released (ovulated) during a menstrual cycle, at least 500 to 1000 do not fully mature and are reabsorbed by the body. By the time a woman reaches menopause, typically between the age of 40 and 56 years, there are only several thousand eggs remaining. These remaining eggs generally do not respond well to the secretion of FSH and LH. The levels of these hormones in the bloodstream increase in an attempt to stimulate the ovaries. *An elevated blood FSH level early in the menstrual cycle (Day 2 - 5) suggests that the ovary is not responding normally to the pituitary. This lack of ovarian responsiveness is indirect evidence of poor egg quality.*

Another hormone that can be measured at any stage in the cycle and called antimullerian hormone (or AMH) is produced by the cluster of granulosa cells in the primordial follicle that nourish the developing oocyte. *Measurement of AMH or the ultrasonic evaluation of primordial follicles* are additional means of determining a woman's remaining reserve of eggs.

The decrease in the ovary's response to FSH and LH from the pituitary gland results in a lowering of oestrogen and progesterone produced by the ovary.

The menstrual cycle may first become shorter but, owing to the complex processes by which menstruation occurs, longer cycles and heavier bleeding may also occur. Because oestrogen and progesterone are critical for the normal development of the endometrium, any reduction in these hormones with age will decrease the chance of pregnancy.

Changes in Eggs and Sperm

Whereas new sperm are generated daily from stem cells in the testis, all women are born with a fixed number of eggs which are held in a state of arrested maturation until the hours before each ovulation. The final stage of maturation involves a division and a halving of the chromosome number. This step is increasingly prone to error as the woman ages. The result is a greater risk of a chromosomal abnormality which, in turn, results in a greater risk of a miscarriage because this is the most common reason for this form of pregnancy loss.

The majority of abnormal conceptions are recognised by nature and miscarried, usually before the 12th week of pregnancy. A woman's chance of a miscarriage increases with age as shown in Table 1. However, these errors in chromosome number also result in a greater risk of Down's syndrome and this also has a direct relation to maternal age as shown in Table 2.

The source of the decreased pregnancy rates in older women is thought to be due, in large part, to the increase in the number of eggs with chromosomal problems. When donor eggs are collected from women in their 20s and 30s, fertilised and placed in the uterus of a woman more than 40, then the rate of pregnancy in the older woman is much higher than she could expect if she had used her own eggs. The success of this egg donation confirms that egg quality is the primary barrier to pregnancy in older women. Unfortunately, there is nothing that a woman can do to prevent the age-related decline in egg quality.

Paternal age has much less of an effect on the risk of such chromosomal disorders as Down's syndrome but there is a small risk of other genetic disorders for men of advanced years. These are the autosomal dominant conditions an example of which is dwarfism.

Finally, there are changes in the eggs from ovaries with advancing age which make them less capable of fertilisation by sperm both in vivo (natural conceptions) and in vitro (test tube conception or IVF).

MALE FACTOR INFERTILITY

In not less than 30% of couples the male is primarily responsible for the delay in conception. When increasing age and milder forms of semen problems are taken into account, the male is a contributing factor in about 50% of instances.

Declining Male Fertility and Testicular Toxins

There is reasonable evidence to conclude that, for many industrialized countries, sperm counts (and more probably sperm quality) are declining. This has been linked to increasing exposure to chemicals and toxins in our increasingly complex environment. A wide variety of compounds are implicated including heavy metals, plastic by products, benzene derivatives and many more.

It is quite probable that some men are genetically more susceptible than others to these toxins.

For some it may be the interaction of several substances and, whilst it may not be possible to avoid some toxins, for others positive steps can be taken. For example, it is known that nicotine from cigarette smoke directly affects testosterone-producing cells in the testes, and this results in sperm of abnormal appearance and decreased motility. Marijuana use has also been associated with reduced fertility. Inappropriate alcohol use not only affects male sexual function but is also associated with decreased sperm production.

Men whose occupations, recreation or clothing result in scrotal heating may also have impaired sperm function. The generation of sperm (referred to as spermatogenesis) occurs best at a temperature that is less than that of the core body. This is why a scrotal sac is almost universal in mammals (the elephant is one of the few interesting exceptions!)

Failure of Spermatogenesis

Testicular disease can result in the complete absence of sperm in the semen. This condition is generally not associated with a reduction in testosterone or sexual function. In many instances the cause is unknown, although it sometimes results from an infection in the testes, for example the mumps virus contracted after puberty. For other men it seems that the cells responsible for spermatogenesis have been absent from birth. Some of these are associated with chromosomal additions, rearrangements or missing portions e.g. Klinefelders syndrome 47XXY

In most instances failure of spermatogenesis is permanent and irreversible but, for some, for example after chemotherapy, regeneration can sometimes occur.

Hormone Deficiencies

Deficiencies or overproduction of hormones involved in sperm production are infrequent but may be treatable. Evaluation of male factor infertility often involves the measurement if FSH, LH, Prolactin, Testosterone and sometimes Thyroid hormones. *If FSH is high then this usually implies a failure of spermatogenesis. If there is azospermia and FSH is normal then this implies obstruction in the male genital tract.*

For example, if FSH is elevated, it may indicate that few or no sperm are produced in the testes. This cannot usually be treated but, if there are any sperm in the testes at all, then assisted conception may be possible.

Duct Obstruction

The epididymis is one vulnerable site for obstruction because it is a very fine and coiled tube (about 8 metres long in fact). The vas deferens is another tube that can become blocked. Infections, including sexually transmitted disease, injury, or surgery can scar the delicate tubules of the epididymis or obstruct the vas. The vas may be absent (a birth defect) or severed in a vasectomy. If the obstruction is complete on both sides for any of these reasons, the semen will contain no sperm even though the testes are still producing sperm normally.

Antisperm Antibodies

Antisperm antibodies may form when sperm are exposed to the male immune system. This can occur when sperms are extravasated beyond the blood-sperm barrier, for example, after vasectomy when antibodies develop in about 70 percent of men. Other causes include infection and trauma.

The antibodies can attach to different parts of the sperm and either reduce motility or impair fertilisation. These antibodies usually cause no other health problems.

Varicocele

Varicocele refers to varicosity in the veins around the testes. It may be felt as a very soft swelling in the scrotum examined in the standing position or during a Valsalva manoeuvre. Unilateral or bilateral varicoceles is present in approximately 15 percent of all men. A varicocele poses no threat to a man's health and usually causes no discomfort. Though varicoceles are associated with infertility (approximately one-third of men with infertility will have a varicocele), the majority of men with a varicocele do not have significant fertility problems so the practice of varicocele ligation has fallen into disfavor.

Infection

Infections in the epididymis, seminal vesicles, or prostate gland may cause few or no symptoms, but can impair infertility.

Ejaculation Problems

Premature ejaculation may be an infertility problem. Some men also experience erection failure or anejaculation, especially during the "on demand" pressure that infertility treatments may require. During retrograde ejaculation semen is released backward into the bladder. This condition may be congenital i.e. present from birth but may also occur with diabetes, multiple sclerosis, or trauma to the bladder neck, including prostate surgery.

Stress

Physical stress, as from a minor illness with fever, severe trauma or a "binge" of alcohol, cigarettes or drugs can affect sperm numbers and function. These problems are usually only temporary ones but they can also be one reason for conflicting reports from semen analyses. It is also the reason why evaluation of male fertility may take some weeks or months. Psychological stress may occasionally interfere with male sexual drive, erection, and ejaculation.

MANAGEMENT OF THE INFERTILE COUPLE

Whilst contemporary management of infertility often involves assisting conception by a variety of techniques with a confusing litany acronyms (IVF, IUI, AIH, ICSI etc.), during which time a couple's monthly probability of pregnancy can be enhanced five to tenfold, medical treatment of some disorders of ovulation and spermatogenesis, as well as surgical correction of anatomical pathology in the genital tract of both males and females, all remain important options in the management of infertility. Such services are increasingly offered at specialist centres with

multidisciplinary contributions from gynaecologists, urologists, endocrinologist, andrologists, laboratory biologists, nurses and counsellors.

Induction of Ovulation (and Spermatogenesis)

As a practicing gynaecologist with a specialty interest in infertility for many years, my greatest pleasure was to have a young and healthy couple present with infrequent menstrual periods as their only problem because this usually represents a hypothalamic disorder of ovulation that can be overcome by the oral administration of a drug with a high probability of success. Often the problem was masked by years of use of a combined oral contraceptive. For a while, this disorder was given its own name, post-pill amenorrhoea, until this was recognized as a part of the spectrum of disorders called Polycystic Ovarian Syndrome (PCOS), which has a genetic basis and affects 5 – 20% of the female population.

Clomiphene Citrate

Clomiphene citrate, sold as Clomid or Serophene is similar in structure to oestradiol but it acts as a long-acting anti-oestrogen when it binds to receptors in the hypothalamus. If administered as a short course (usually five days) at the beginning of a cycle, this drug manages to induce the hypothalamus to release GnRH which, in turn, stimulates the release of FSH from the anterior pituitary, thus initiating the whole endocrine cascade resulting in ovulation. The response can be monitored with a basal body temperature chart, blood tests for progesterone in the second half of the cycle (and sometimes oestrogen in the first half of the cycle) or pelvic ultrasound for visualization of ovulatory follicles. Several cycles may be required to find the correct dose for the individual patient. This drug should be discontinued as sole therapy after 6 – 12 cycles of successful ovulation without conception as it is likely that other infertility factors are operative. For some patients with PCOS, enhancement of the effects of clomiphene citrate occurs with the daily administration of the oral hypoglycaemic drug, Metformin whilst weight loss for those with obesity is an important part of the regime.

Unfortunately clomiphene citrate is rarely successful in the treatment of males with a failure of spermatogenesis. This is because, unlike females, the problem usually arises either in the testes or sometimes the anterior pituitary and not the hypothalamus.

Unwanted effects of Clomid include hot flushes (about 10%), mastalgia, tiredness, feeling bloated or light headed, headaches, nausea, anorexia, myalgia, mood swings with anxiety and depression and blurred or double vision (1-3%). Painful ovulation is not uncommon. There is a small risk of ovarian hyperstimulation syndrome (see below) and the chance of a multiple pregnancy is 5 or 6-fold higher than the background rate of 1:80. However, this means a twin rate of only 6-8%, whilst triplets and higher order multiples are rare.

There is no convincing evidence that clomiphene citrate has any long term risks of ovarian or breast cancer despite theoretical concerns that relate to the biology and endocrine dependency of these cancers. There is some evidence that, if Clomid is given after a conception has occurred, then it can cause miscarriage. The drug also has an anti-fertility effect because it acts as an anti-oestrogen on cervical mucous. This is avoided by using it only early in the cycle and not around the time of ovulation. The rate of ectopic pregnancy is slightly higher after ovulation induction but whether this is due to the drug used or other factors associated with the infertility is uncertain. There is no evidence that the rate of birth deformities is higher than normal when Clomid is used.

Hyperprolactinaemia

Males and females with hyperprolictinaemia have problems of ovulation and spermatogenesis. Both may be assisted with the dopaminergic family of drugs that includes carbergoline and bromocriptine. Hyperprolactinaemia is often caused by small adenomas in the anterior pituitary which will shrink with such medical therapy although macro tumours with other pressure effects require surgery.

Gonadotrophins and GnRH

A few men and women with disorders of the anterior pituitary, for example after surgery for tumours, will ovulate after injections of FSH (and HCG which acts as an LH surrogate). Those with congenital absence of GnRH (Kallman's syndrome) may respond to an infusion of this polypeptide but this must be administered in a pulsatile manner so as to simulate its endocrine release from the hypothalamus. Continuous administration of GnRH results in down regulation of its receptors so that long-acting GnRH analogues are effective antigonadotrophins used in the treatment of such endocrine-dependent disorders as prostatic cancer and endometriosis.

Most women whose ovulation disorder fails to respond to Clomid will move on to the use of FSH and HCG but usually in the form of IVF because it is difficult to control the rate of multiple ovulation and multiple pregnancy with this therapy.

Female Surgery

Surgery has an important role in the treatment of female infertility caused by endometriosis. All medical options for the management of this condition, although the treatment of choice when pelvic pain is the only symptom, inhibit ovulation and delay conception further. Surgery ranges from simple diathermy or laser to superficial endometriosis through to extensive peritoneal removal with plastic reconstructive procedures. All are best performed laparoscopically. Removal of a single endometrioma from one ovary, which may be the only manifestation of endometriosis, sometimes restores fertility quite rapidly. The role of agents to prevent adhesions in the pelvis after surgery for any reason is controversial.

Surgery is less successful in the management of tubal disease after salpingitis, probably because of the damage to the delicate ciliated endothelium of these organs. A variety of hysteroscopic and fluoroscopic probes are sometimes used to unblock obstructions at the uterine ends of the fallopian tubes that have not been flushed by hysterosalpingogram or dye studies with laparoscopy. Sometimes fimbriopasty to reopen that distal end of the tubes is successful provided that the tube is not distorted into a large hydrosalpinx.

IVF was developed primarily to "bypass" the role of the fallopian tubes in reproduction. However, one or more commonly two, large hydrosalpinxes reduce the rate of conception, even when IVF and embryo transfer is used, so surgical removal of such "useless tubes" is sometimes performed prior to assisting conception.

Hysteroscopic, and less commonly open surgery are important if there are intrauterine adhesions, polyps, submucous fibroids or even congenital septa. Intramural fibroids greater than 5 cm in diameter may also interfere with the success of IVF so they are often removed surgically as well.

Female surgery is most useful if reversal of tubal sterilization is required. Provided that there is a good length of fallopian tube with a fimbrial end preserved microscopic reanastomosis, whether performed as an open procedure or laparoscopically, restores fertility in more than 85% of women, albeit with an increased risk of subsequent ectopic pregnancy.

Male Surgery

Reversal of male sterilization (vasectomy) by way of contrast to that in females is less successful in restoring fertility. In this instance it is the length of time that has elapsed from the time of the vasectomy that is important. Reversal after 12 – 18 months restores fertility for up to 80% of couples but this falls to 50% after 5 or more years. Although the microscopic surgery to restore vas patency is often successful, the sperm in the ejaculate lack the capacity to fertilise eggs, even during IVF, and this is more common if there are high levels of male anti sperm antibodies.

A better option for some males with vasectomy is the direct extraction of sperm from the epididymis. PESA, or Percutaneous Epididymal Sperm Aspiration, involves the aspiration of sperm directly from the epididymis using only local anaesthesia. When sperm cannot be obtained by PESA then the other procedure, known as testicular sperm extraction (TESE), obtains sperm by means of a biopsy of the testis itself. This procedure is also performed under local anaesthesia and removes a small thread of tissue from the testis via a needle biopsy. These options are recommended if there is advancing female age (time running out) or other female factors that would make IVF desirable are extant.

PESA has the advantage of usually producing sufficient sperm to make freezing and storage a realistic option. TESE, however, may need to be repeated in each cycle that a couple is attempting conception although, as for PESA, sperm freezing is sometimes possible. Some fertility services provide the option of sperm freezing and storage as a backup before vasectomy.

After both procedures, and the collection of eggs from the female partner for IVF, direct intracytoplamic injection of sperm into the ova is required. This process is referred to ICSI. *It has become the principal means of treating most forms of male factor infertility*. If sperm in any number (just a few are required) can be obtained from the testis or epididymis many men are able to father conceptions with IVF/ICSI when it was not possible before such technology was developed in the last decade of the last century.

Refinements and improvements in IVF and ICSI means that the surgical management of most other forms of male infertility (principally that of epididymal obstructive disease) has been relegated to history.

ASSISTED CONCEPTION

Many couples with infertility are treated by one of several means of assisting the conception by various extracorporeal means. All medical graduates need a working knowledge of the processes, chances of success, possible outcomes and risks as well as the cost of such interventions. The popular press is often concerned with the more sensational and controversial aspects of this industry including the use of donors of sperm and eggs, access to the technology by lesbian couples and single women, the use of surrogates and the fate of excess embryos that includes their use as a source of human stem cells.

What is Involved

Ovarian stimulation with FSH, and less commonly with clomiphene citrate is used to increase the likelihood that one or more eggs or embryos will be available to return to the uterus. It is possible to forego ovarian stimulation with "Natural Cycle IVF". However, the chance of pregnancy that occurs with Natural Cycle IVF is significantly less than that which arises if a number of eggs are collected and the best embryo is returned to the uterus. Natural cycle IVF therefore is not very cost effective.

During the first few days of each woman's reproductive cycle the ovaries usually prepare a cohort of 10 – 50 follicles for further development but limitations in the supply of FSH usually means that only one follicle outstrips the others and just one mature oocyte is released about 14 days later. Exogenous human FSH, produced by genetically altered bacteria in vitro or extracted from the urine of postmenopausal women, is used prior to IVF/ICSI to support the development of a number of follicles so that, at the time of attempted egg recovery, more than one mature oocyte can be collected.

During the 10-12 days of FSH treatment ovarian response is monitored by measures of blood oestradiol and transvaginal ultrasound that record the number and size of follicles that are developing. During this period a GnRH agonist is usually simultaneously administered to prevent an LH surge and unregulated ovulation. Indeed, for most women the GnRH agonist (and sometimes an antagonist) is used to suppress the pituitary in the luteal phase of a cycle preceding that planned for egg collection in order to promote the development of a synchronised group of follicles with FSH.

When the follicles are judged to be appropriately mature, a final injection of HCG, acting as an LH surrogate, is administered to prepare the oocytes for collection 36-38 hours later. The oocytes are usually collected transvaginal ovarian puncture and aspiration under ultrasound control. For this purpose a slender probe is introduced into the vagina and the ovaries with their fluid-filled follicles can then be visualized on a monitor screen. Local or general anaesthesia is used before passing a needle through the vaginal wall and into the ovarian follicles. The 2-10ml of fluid from each follicle is removed under low pressure and examined immediately by an attending biologist. Sometimes fluid is flushed through the follicle in order to dislodge the oocyte. All of the follicles are emptied and the woman is usually fit to leave hospital within 2-4 hours.

The male partner is asked to provide semen about three hours after the collection of the oocytes. A variety of in vitro steps are required to harvest activated sperm that have the capacity to fertilise eggs (capacitated sperm). For IVF all of the eggs and a selected sample of sperm are incubated together but for ICSI individual sperm are chosen and injected with microscopic assistance into those eggs that are mature.

The eggs are examined 18-24 hours later for evidence of fertilisation. If the eggs have fertilised, the embryos are monitored in an incubator for a further two to four days in order to pick those that appear best and fastest developing. These are the ones most likely to result in a successful pregnancy

Embryos are returned to the uterus by the process called embryo transfer. A speculum is passed into the vagina in order to expose the cervix. A fine and soft catheter is used to deposit the embryo(s) in a tiny drop of fluid.

Because of ongoing pituitary suppression by the administered GnRH agonist, luteal support with progesterone pessaries or further injections of HCG is required to support any implanting pregnancy. A pregnancy test can be performed on the 16th day after the embryo transfer if menstruation has not occurred.

Chance of Pregnancy

Between 20 and 50% of couples who commence a cycle of IVF treatment will be pregnant at the end of it. However, the chance of pregnancy depends on the age of the woman (40-50% for women 25 - 38 years, 30% at age 38 – 39 years and less than 8% for women aged 40 years or greater), whether one or both partner is smoking and the number of healthy eggs (and embryos) that are generated in a cycle of ovarian stimulation..

When considering the success of IVF and ICSI several important facts need to be taken into account as follows:

- Because a certain number of pregnancies are lost by miscarriage or stillbirth the "take home baby rate" is less than the initial pregnancy rate.

- If there are "extra embryos" available for freezing and transfer in a subsequent month then the accumulated pregnancy rate from a single cycle of ovarian stimulation and egg recovery can be substantially better. Eventual success may depend on the number of times embryos (fresh or frozen/thawed) are transferred to the uterus.

- Unless certain adverse factors are identified, this chance of success will be the same in each subsequent cycle of treatment that is attempted.

In the early days of IVF, when pregnancy rates were typically 50% or more lower than they are today, the chance of pregnancy was boosted by increasing the number of embryos transferred. However this practice also increases the rate of multiple pregnancy. For most women only *one* embryo is now recommended, particularly if it is transferred at the blastocyst stage after 5 days of in vitro observation when the best can be chosen.

What are the Risks

The most common serious complication of the drugs used for IVF and ICSI is well recognised. It relates to the stimulation of multiple follicles which causes the ovaries to enlarge to several times their normal size. Despite monitoring, abandonment of some cycles and freezing all embryos to allow the ovaries to recover in some instances, about 5% of women develop symptoms of the Ovarian Hyperstimulation Syndrome (OHSS) and 1% require hospitalization. Severe OHSS causes low abdominal pain, abdominal swelling and sometimes vomiting with a risk of dehydration. Abdominal ascites or hydrothorax can occur. There is hypercoaguable blood and a risk of thromboembolism. Fatalities have occurred.

About 1% of women undergoing transvaginal egg collection experience such serious unwanted outcomes as haematoma, haemorrhage and infection. There is a similar risk of adverse male outcomes arising from PESA and TESE.

The drugs used to stimulate ovulation have side effects similar to those listed above for clomiphene citrate. There is no epidemiological evidence of an increased risk of ovarian or breast cancer or premature menopause (ovarian depletion). A few women treated with human FSH of pituitary origin developed HIV infection many decades ago but synthetic and urinary FSH is free of such risks.

The outcome for pregnancies and the children born as a result of IVF has been the subject of evaluation in many countries of the world from the time of inception of the practice. There is now sufficient data to unequivocally state that babies born after conventional IVF are no different to those conceived naturally.

The same reassurance cannot be given with respect to children born as a result of sperm microinjection or ICSI. After two decades of study there is still a debate about the rate of birth defects that occur. In broad terms however, 97% of babies born as a result of ICSI are normal and some 3% will have a chromosomal problem or significant abnormality diagnosed at some time after their birth. This compares quite favourably with the 2% rate of abnormalities that occur in pregnancies that are conceived naturally or with the assistance of conventional IVF. If ICSI is used for in vitro fertilisation by men with severely impaired fertility then there is evidence that some male offspring will inherit the same fertility problem.

Rates of ectopic pregnancy are increased after IVF but the rate of miscarriage is more related to the age of the woman than to any in vitro process. Monochorionic twin pregnancy rates are increased after the transfer of one embryo especially when ICSI has been used. Perhaps this is related to puncture and damage to the zona pellucida. Pre term birth, Caesarean section and perinatal mortality is more common after IVF even when the effects of multiple pregnancy and maternal age are taken into account but it is difficult to correct for other factors which lead to the need for assisted conception.

Cost of Assisted Conception

Assisted conception is cost effective when compared to many other forms of treatment for infertility. Medicare supports the cost of IVF and the extra cost of ICSI. Human FSH and related drugs are very expensive but are provided without cost in Australia. Most Fertility Centres have out-of-pocket costs that are detailed on their websites. There are very few options available through public hospitals.

Perhaps the greatest risk to health occurs from the emotional stresses associated with such an intense program. Assisted conception carries an inherent potential for success or bitter disappointment. Counselling is often provided as a part the program.

OTHER OPTIONS

Modern technology allows couples many more options than were possible in the past. However, these treatments may have significant financial, emotional and social demands.

Donated eggs and sperm are options for women and men respectively when they are incapable of provided their own gametes for the purpose of assisting conception.

For women over 40 who have not succeeded with other therapies and those with premature menopause or absent ovaries (e.g. Turner's syndrome) eggs from a younger woman are more likely to result in pregnancy and less likely to miscarry even when carried by that older woman. The process of egg donation can involve either a known donor, such as a relative or friend, or an anonymous donor. Egg donors need to undergo the processes of ovarian hyperstimulation and egg recovery with all those attendant risks and discomforts but the process is a lot simpler for donors of male gametes.

Surrogacy occurs when a woman agrees to become pregnant for a couple (traditional or otherwise) using the male partner's sperm and her own egg (traditional surrogate) or using the male partner's sperm and the female partner's egg (gestational carrier). She also agrees to give up the baby to the couple at birth. Surrogacy is the only option for women who have had a hysterectomy or cannot become pregnant for other medical reasons. Surrogacy is illegal in some states and Medicare will not pay for IVF treatment related to surrogacy.

Adoption and foster care is another means of experiencing parenthood. Legislation regarding couple's eligibility and opportunities for overseas adoption change from time to time. Most fertility counsellors will canvas current options.

Some couples decide that the best option is **not to undergo infertility treatment** but to remain childless (or childfree!). Some need to grieve their loss and look at alternative ways to achieve personal growth. Some pursue a new career, a charity, a hobby or adopt a special project. Both partners may need to discuss what is best for them. A counsellor can help to explore the issues.

M Brinsmead February 2015