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IVF AND ICSI - THE ESSENTIALS

WHAT IS IVF AND ET?

In vitro fertilisation (IVF) is the procedure by which eggs are taken from a woman's ovaries and placed with the man's sperm in a test tube or culture dish ie in vitro in order to facilitate fertilisation. The result is an embryo that is then returned to the woman's uterus (womb) during a procedure referred to as embryo transfer (ET). IVF and ET bypass the functions of the fallopian tubes (oviducts) during natural conception. The first birth after IVF and ET occurred in 1978.

WHAT IS ICSI?

Intracytoplasmic sperm injection (ICSI) refers to a special form of IVF in which individual spermatozoa are injected into an egg in order to commence the fertilisation process. It is required when there are very few or poorly motile sperm available from the male partner. It may even assist some men who have no sperm at all in the ejaculate. However, in contrast to IVF after which thousands of babies around the world have been born, babies conceived with the assistance of ICSI were not born until the 1990's.

WHAT IS ACTUALLY INVOLVED IN IVF & ICSI?

The first step is to administer hormone injections to the woman in order to stimulate the ovaries to produce a number of eggs. This increases the likelihood that one or more eggs or embryos will be available to return to the uterus. It is possible to forego the use of these hormones in a process that is called "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 embryos is returned to the uterus. Natural cycle IVF therefore is not very cost effective.

During the first few days of each woman's natural monthly cycle the ovaries usually prepare a number of follicles that contain immature oocytes (eggs) for further development and eventual release of just one mature oocyte about 14 days later. Human follicle stimulating hormone (FSH) is used in 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 it is necessary to monitor the response of the ovaries by blood tests which measure ovarian hormones (principally oestrogen) and to perform ultrasound scans to record the number and size of follicles which are developing. During this period another drug called a GnRH (Gonadotrophin Releasing Hormone) agonist is usually simultaneously administered to regulate the pituitary gland and prevent a premature or inappropriate release of the eggs. For most women it is desirable to first administer the GnRH agonist to suppress the pituitary (and the ovaries) and then commence FSH in order to promote the development of a synchronised group of follicles.

Most women self-administer their FSH by subcutaneous injections in the same way that diabetics administer insulin. Attendance to the Fertility Centre is required for only a few days during this period for blood tests and scans. Women who live at a distance may arrange to have blood samples sent to the hospital by courier and scans performed locally in order to monitor the early days of the stimulated cycle.

When the follicles are judged to be appropriately mature, a final injection (HCG or Human Chorionic Gonadotrophin) is administered to prepare the oocytes for collection. The egg collection takes place 36-38 hours after this injection and requires a minor surgical procedure that can be carried out at the Fertility Centre.

The oocytes are usually collected by a process called vaginal ovary 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 upper portion of the vagina and into the ovarian follicles. The 2-10ml of fluid from each follicle is removed under low pressure and examined for the presence of an egg. Sometimes fluid is flushed through the follicle in order to dislodge the oocyte from the sidewall where it has developed. All of the follicles

are emptied and the woman is usually fit to leave the hospital within 2-4 hours.

The husband is given at least 36 hours notice of the time of egg collection and is asked to provide a semen sample at the Fertility Centre about three hours after the collection of the oocytes. Some time is spent harvesting the best sperm from this semen sample and a short period of in vitro maturation is required before the sperm are ready to be added to the eggs.

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 and ready to receive sperm. The eggs are examined 18-24 hours later for evidence of fertilisation. If the eggs have fertilised, the embryos as they are now called, 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

For this to occur an embryo is returned to the uterus. This process is called embryo transfer and is done simply on a walk-in and walk-out basis taking 1-2 hours at most. A speculum is passed into the vagina in order to expose the neck of the womb (cervix). This is very similar to having a cervical smear. A fine and soft catheter is then placed through the cervix and the embryo deposited with a tiny drop of fluid.

The woman may return home and to normal activities the same day but may require vaginal pessaries of a natural hormone called progesterone or further injections of HCG for the next 10-14 days in order to help support any implanting pregnancy. A pregnancy test can be performed on the 16th day after the embryo transfer if a period has not occurred before then.

WHAT IS THE CHANCE OF PREGNANCY?

Our experience indicates that between 20 and 50% of couples (that is a range of one in every five to one in every two) 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 (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, the number of eggs (and embryos) that are generated in a cycle of ovarian stimulation and the number of embryos transferred.

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.

When put another way and in the case of most couples, IVF/ICSI can increase the odds of getting pregnant about 40-fold in the month that a treatment is carried out. However, the decision whether to commence or continue with IVF is a personal one which takes into account an individual's needs and priorities and the alternatives. It is a decision to be made with your partner, your family, and with the professional advice of your doctor.

ONE EMBRYO OR MORE?

The pregnancy rate is increased as the number of eggs or embryos transferred is increased but so is the rate of multiple pregnancy ie twins and triplets. For most women only *one* embryo will be transferred.

For women under 38 years, there is now no material difference in the chance of achieving pregnancy whether one or two embryos are transferred. However, the chance of a twin pregnancy is very high following the transfer of two embryos - and with twins there is a much higher risk of pregnancy complications, including miscarriage, birth defects, or in later pregnancy, the death of one or both twins.

WILL THE BABY BE NORMAL?

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 for the past 25 years. 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 more than a decade of studies 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. In fact 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.

Tests are available during pregnancy that can safely screen for and test for such major abnormalities as Down syndrome.

If ICSI is used for in vitro fertilisation by men with severely impaired fertility then there is evidence that some male offspring may inherit the same fertility problem.

WHAT ARE THE HEALTH RISKS INVOLVED?

As with most things we undertake in life, there are risks associated with attempting conception by IVF. Ovarian stimulation with fertility drugs causes the ovaries to enlarge with multiple follicles. This is referred to as hyperstimulation syndrome. Some women experience pain from this and there can be abdominal swelling, vomiting and internal fluid disturbances that require admission to hospital and specialist treatment. Hyperstimulation syndrome is always self-limiting and only in very rare circumstances will it result in long term sequelae.

The procedure of egg recovery is by operation that carries with it all the risks inherent with minor surgery. There is a small risk of damaging a blood vessel and causing internal bleeding or injury to the bowel or bladder. During vaginal ovarian puncture it is possible to introduce infection and cause a pelvic abscess. There are the discomforts and complications of the procedure that is usually carried out with sedation and pain relieving drugs only ie not general anaesthesia.

If sperm extraction from the testis is required for ICSI then there is a small risk of haemorrhage into the testis or scrotum. The risks are similar to those described above but are probably lower because the testis are essentially external organs in contrast to the ovaries.

If a pregnancy does occur there are all the risks associated with pregnancy, including the possibility of miscarriage or ectopic pregnancy. If more than one embryo is transferred then there is the possibility of twins or triplets.
Perhaps the greatest risk to health occurs from the emotional stresses associated with such an intense program. IVF carries an inherent potential for success or bitter disappointment. Counselling is provided as a part of the IVF program through this Centre.

WHAT IMPACT WILL THE PROGRAM HAVE ON OUR EVERYDAY LIVES?

We encourage everyone on our programs to continue with their normal life, as this is the best way to deal with the extra stresses. You will only need to be away from work for a short time each treatment cycle: rarely more than a couple of days for women and a couple of hours for men.

Cost of Assisted Conception

Detailed information about the costs associated with each of the methods of assisted conception is available from this Centre or the Nurse Co-ordinator SIVF, Coffs Harbour Phone 02 6659 4429. Financial assistance is not generally available for fertility services through this Centre.

Limitations to Treatment

In general the female partner needs to be less than 45 years of age and the male less than 55 years of age and HIV free. The treating doctor has a responsibility to safeguard the welfare of any child born (including the need of that child for a father). There is no waiting period required before commencing treatment for self-funding patients. However, we are concerned that you are fully informed about the processes and treatment that you will be undertaking. Therefore it is necessary for both partners to be seen by the treating gynaecologist and a nurse. If you are using donor sperm or eggs then more extensive preparation with a counsellor is required.

Other Options

First and foremost you should discuss with your fertility specialist the chance of a normal conception with time. You may wish to compare your monthly probability of a spontaneous conception with that offered by a cycle of assisted conception. Surgical or other medical treatments may be available. Some couples consider the options of staying childless, adoption or fostering. For some others there may be a need for donor eggs, donated embryos or surrogacy.

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DRUGS FOR IVF AND ICSI

Why are Drugs Used?

Most women being treated with IVF, ICSI or ovulation induction take fertility drugs to aid the growth of follicles (the small ovarian cysts in which the eggs develop). The aim in administering these drugs is to promote the growth of more than one follicle in order to retrieve more than one egg.

It has been shown that the likelihood of pregnancy increases with the number of embryos which are transferred to the uterus after IVF and eggs to the tubes with GIFT. However, the greater chance of pregnancy with multiple embryo transfer must be balanced against the risk of multiple pregnancy ie. twins or triplets and the risks associated with hyperstimulation (stimulation which is greater than normal) of the ovaries. It is also necessary to program the development of eggs so that recovery can occur at an optimal time in their development.

It is possible to perform IVF without the use of drugs to stimulate the ovaries. This is termed "natural cycle" IVF. However, you need to be aware that there is a risk that the single egg produced during the natural cycle will not be recovered and that the rate of pregnancy after a single embryo transfer is currently only about 15%. The biggest disadvantage of natural cycle IVF is that there is no possibility of storing frozen embryos yet the “out of pocket costs” are similar to those of a stimulated cycle. In this respect natural cycle IVF is simply not cost efficient.

Drugs Used

The currently used drugs are Lucrin or Syneral (a GnRH analogue), Follicle Stimulating Hormone or FSH (Gonal F, Puregon, Pergonal, Metrodin or Humegon) and Human Chorionic Gonadotrophin or HCG (Profasi or Pregnyl). Clomid was the original drug used for IVF cycles and is still used sometimes.

Lucrin or Syneral suppresses the release of hormones from the pituitary gland which normally controls both follicle growth and ovulation. In a normal menstrual cycle, the pituitary gland hormones regulate the maturation of just one follicle. By inhibiting the pituitary hormone release of the natural gonadotropins, FSH and LH (with Synarel or Lucrin) and regulating follicle growth (with administered FSH) and ovulation (with HCG) we have greater control of these processes.

Most women will need Lucrin or Syneral for three weeks commencing one week before the period in the month that they wish to collect eggs for IVF. Synarel is administered twice daily as a nasal spray and Lucrin is given once daily as an injection.

FSH is given daily as an injection and is usually administered over 12 or 14 days before the eggs are sufficiently developed for collection.

What about Side Effects?

It is not possible to guarantee that any drug is 100% free of side effects and 100% safe in both the short and long term. As for many things we undertake in life it is a matter of weighing the possible benefits ie. pregnancy and a baby, against the known and unknown risks. The following information is intended to provide a short summary of the known side effects and disadvantages of the drugs which are used in IVF and GIFT.

Lucrin and Syneral

Synarel (Nafarelin acetate) and Lucrin (Leuprorelin acetate) are synthetic proteins closely related to a hormone responsible for the release of two hormones (FSH and LH) from the pituitary gland. When administered on a daily basis they have the effect of blocking the pituitary release of LH and thereby preventing a premature release of eggs. Synarel and Lucrin and related drugs are also used for the treatment of endometriosis and uterine fibroids.

Because Lucrin and Syneral are discontinued before conception occurs and since they will be cleared from the body within a few days it seems unlikely that they could have any effect on a developing embryo.

Apart from their effect in causing ovarian enlargement (see ovarian hyperstimulation below) the other side effects from Lucrin and Syneral are relatively minor. The following symptoms (in decreasing order of frequency) have been reported by some women on our programs:

> Sore breasts, tiredness, feeling bloated or light headed, headaches, nausea, loss of appetite, muscle aches and pains, mood swings with anxiety and depression.

A few women have developed itchiness and swelling at the injection site. Major allergic reactions are rare.

It is difficult to know whether all of these symptoms are due to the Lucrin or Syneral or to the stresses associated with the program.

Follicle Stimulating Hormone (FSH)

FSH is the natural body hormone produced by the pituitary and responsible for stimulation of egg development in the ovaries. Whilst once extracted from human pituitary glands this hormone is now biologically produced by genetically altered bacteria or extracted from the urine of women who are past reproductive age and whose ovaries are no longer responding to their pituitary gland. Under these circumstances there is an increase in the production of FSH and LH by the pituitary and some of these finds its way into the urine. Extraction of vast amounts of urine is required to recover these natural hormones.

FSH is given by a daily injection in order to promote the growth of several ovarian follicles. Since it is usually given in association with Lucrin and Syneral, FSH may be responsible for some of the side effects noted above.

Human Chorionic Gonadotrophin (HCG)

Profasi, Pregnyl and Ovidrel are three brand names for human chorionic gonadotrophin (HCG) also used during a cycle of IVF or ICSI. It is actually a pregnancy hormone, produced by

the trophoblast (placenta) and recovered from the urine of pregnant women in a similar manner to that of FSH. Because it is closely related to luteinising hormone (LH) it is used during a cycle of assisted conception in order to promote the final maturation of the eggs.

Administration of HCG about 36 hours before attempted egg recovery ensures that the eggs are obtained at an optimal state of development.

HCG is also administered for several days after embryo transfer because it stimulates the ovary to produce progesterone. Progesterone is a hormone necessary for the support and nurturing of an early embryo.

Because women are exposed to high levels of HCG for relatively long periods during pregnancy, it is not thought that HCG is harmful to either the woman herself or a developing baby.

OVARIAN HYPERSTIMULATION

The most common serious complication of the drugs used for IVF and ICSI is well recognised. It relates to the stimulation of multiple follicles (small cysts) which causes the ovaries to enlarge to several times their normal size. This results in lower abdominal discomfort, a bloated feeling and sometimes distension of the abdomen or discomfort during intercourse. Because many of these cysts are emptied during the egg recovery procedure, problems relating to the development of multiple cysts do not seem to be quite as serious during IVF or ICSI as that which occurs during ovulation induction with FSH.

During your cycle of IVF or ICSI the degree of ovarian stimulation will be monitored by blood tests and ultrasound scans. If there is a risk that too many ovarian follicles are developing then that cycle will be cancelled and another will be planned with a reduced dose of drugs.

However, despite careful monitoring, there are a few women who will develop continuing problems from the ovarian enlargement for a few days or weeks after the completion of their treatment cycle. This may be more likely to continue if the cycle is successful and a pregnancy is continuing. The symptoms arising from the hyperstimulation syndrome include low abdominal pain, abdominal swelling and sometimes vomiting with a risk of dehydration. In rare circumstances large shifts of water may result in fluid accumulation within the abdomen (ascites) or the chest (hydrothorax). There may also be thickening of blood and a risk of spontaneous blood clotting. This has, for a few women, resulted in cerebral infarction ie stroke, major arterial thrombosis and even death. This very rare but serious complication requires vigorous and intensive treatment.

FERTILITY DRUGS AND CANCER

It has been argued that the use of ovulation inducing drugs such as Clomid and FSH may increase a woman's lifetime risk of ovarian cancer. This is based on two observations. Firstly, women who take the contraceptive pill and thereby suppress ovulation over a long period of time have a lower incidence of ovarian cancer. Secondly, ovarian cancer has occurred in some women who have used FSH and Clomid. However, it is worth noting that about one woman in 100 will develop an ovarian cancer in a lifetime. Women with fertility problems have a higher risk of ovarian cancer then others and it is uncertain how much this contributes to the apparent increased risk of ovarian cancer in these women who have used ovulation inducing drugs. No increased risk of ovarian cancer was found in a large study if many thousands of women who have undergone IVF in Australia over almost 20 years.

There have also been claims that the high oestrogen levels which are generated in women during ovarian stimulation with HMG may trigger breast cancer since it is known that some breast cancers are stimulated to grow by oestrogen. Women who breast feed for long periods of time have a lower risk of breast cancer and it is known that breast feeding suppresses the ovarian production of oestrogen. However, it is not certain that oestrogen actually causes a breast cancer and, because breast cancer is very common (about one woman in every 12 will develop this cancer in a lifetime), it is not surprising that some women who received FSH have subsequently developed breast cancer. Scrutiny of cancer registries in Australia has not uncovered any excess of women with breast or ovarian cancer who have also been treated on a Fertility Program.
Recent reviews suggest Clomid is NO better than Placebo in unexplained infertility.

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