The effective treatment of infertility is dependent on an accurate diagnosis as to the cause of the problem. Options vary and include expectant management (a wait and see approach to establish if conception occurs naturally), surgical management and drug treatments allowing stimulation of the ovaries to produce multiple follicles, and retrieval and fertilisation of oocytes with replacement of resulting embryos into the uterine cavity.

It is essential that the couple themselves be involved in the decision on which treatment option to pursue. Treatment is not without its risks, particularly ovarian hyperstimulation syndrome (OHSS) as a result of drugs used for ovarian stimulation and those complications arising as a result of egg collection. Of further concern is the multiple pregnancy rate associated with fertility treatments, which not only creates a medical burden on the patient (increased risk of complications) but also a financial burden on society.

In the UK all clinics providing treatment of infertility in the form of in vitro fertilisation (IVF), donor insemination and the storage of eggs, sperm or embryos require a licence and are under the control of the Human Fertilisation and Embryology Authority (HFEA). The HFEA is a non-departmental government body.

This article describes some of the methods of fertility treatments and also a guide as to which patient groups may benefit from these forms of treatment. It then discusses drugs used in the treatment of infertility and the recent National Institute for Clinical Excellence (NICE) guidelines concerning assessment and treatment of fertility problems.

**Expectant Management**

Expectant management is generally reserved for those couples who are young in terms of reproductive age (less than 35 years old for female, male age not as important) and who may have been trying for a pregnancy for a short period of time provided major causes of infertility have been excluded.

**Surgical Management**

Surgery may be indicated for the underlying cause of infertility; for example, tubal blockage (whether by disease or by intent as in the case of sterilisation), endometriosis, fibroids or polyps. Surgical management is particularly successful for the treatment of proximal tubal disease with success rates of approximately 68 per cent at 24 months. There is the added benefit that further singleton pregnancies may be achievable. Treatment of distal tubal disease is slightly less successful with pregnancy rates quoted between 14 and 33 per cent depending on the severity of the disease. Surgery may also be used before fertility treatments to optimise chances of success, eg, in the case of significant hydrosalpinges (accumulation of fluid in the fallopian tube) where it is postulated that retrograde leakage of fluid from dilated tubes into the uterine cavity may decrease the implantation rate. There is some evidence that treatment of minimal and mild endometriosis may lead to an increase in spontaneous conception but less evidence for its use in assisted conception except for moderate and severe disease affecting the ovaries.

**Ovulation Induction**

Ovulation induction involves stimulation of the ovary by oral or injectible drugs or both. The result is to stimulate the ovary to produce usually between one and three follicles. Response is monitored by serial scans or oestradiol and luteinising hormone (LH) levels. This may be combined with sexual intercourse around the time of ovulation. Alternatively, if sperm motility or count is borderline then preparation of the sperm to extract the fast forwardly motile sperm and insemination into the uterine cavity at the time of ovulation may be appropriate.

It is important that at least one fallopian tube is open and healthy before proceeding to this form of treatment.

The use of intra-uterine insemination (IUI) in minimal or mild endometriosis with gonadotrophin stimulation appears better than no treatment or IUI alone.

**IVF**

IVF involves stimulation of the ovaries to produce multiple follicles and is monitored by serial scans or blood tests. Oocytes are then collected transvaginally under sedation, local or general anaesthetic. A prepared sample of sperm is diluted and combined with the collected oocytes to allow fertilisation to occur. The resulting embryos are then allowed to

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diverge further before subsequent transfer. This is usually performed two, three or five days after fertilisation. Recently the HFEA has limited the transfer of embryos to a maximum of two in the vast majority of cases to try to reduce the incidence of multiple births.

Couples suitable for IVF treatment may have tubal infertility because the fallopian tube is by-passed for this procedure. This form of treatment may also be a natural progression for those couples with otherwise unexplained fertility who have not been successful with IUI treatment or may be a first-line of treatment for those couples presenting later in life with infertility not wishing to pursue less definitive treatments.

Patients with a diagnosis of moderate or severe endometriosis or other female factor infertility, such as fibroids, may also benefit from IVF as first-line treatment.

Various treatment protocols can be used to stimulate the ovaries. Historically most involved the use of a gonadotropin-releasing hormone (GnRH) agonist to down-regulate the ovaries. This prevents the premature release of LH and follicle stimulating hormone (FSH) by the pituitary which in turn stops follicular development in the ovary and prevents oestrogen production. This can be started on day 2 or 21 of the menstrual cycle (long protocol) or alternatively on day 1 or 2 of the menstrual cycle with FSH injections commencing the subsequent day (short or flare protocol). This then allows the ovary to be stimulated by exogenous FSH injections on a daily basis.

Alternatively, a GnRH antagonist protocol can be employed which does not involve down-regulation of the ovaries but starts with stimulation of the ovaries by means of FSH injections on day two or three of the menstrual cycle. Once adequate follicular development commences GnRH antagonist is commenced to prevent an LH surge and subsequent ovulation. The two injections are continued until sufficient follicles of adequate size are obtained when human chorionic gonadotropin (hCG) is then given to complete oocyte maturation.

Complications of IVF treatment are primarily those related to multiple births, to the oocyte retrieval process (namely infection, bleeding, damage to other structures in the pelvis) and to hyperstimulation of the ovaries by FSH.

OHSS can occur with any form of ovarian stimulation. It is characterised by the development of multiple ovarian follicles with associated high oestrogen levels and may be classified as mild, moderate or severe. Symptoms are abdominal swelling, nausea and possibly vomiting. In more severe cases there may be abdominal ascites, breathlessness secondary to pleural and cardiac effusions with haemoconcentration (increased concentration of red blood cells usually resulting from loss of fluid to the tissues) and associated thrombus formation in the deep veins or pulmonary vessels.

The exact mechanism of OHSS is still unclear and treatment will depend upon the severity but is mainly supportive for mild OHSS, ie, maintaining fluid intake and urine output. In more severe cases abdominal drainage, chest drain, intravenous fluids and anticoagulants may be necessary.

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**Natural IVF**

Natural IVF is a technique which involves monitoring a woman’s normal menstrual cycle to track a developing follicle, collecting a single oocyte and fertilising the egg with sperm. The embryo is then transferred two or three days later. This technique is associated with a significantly lower success rate since ovulation is not controlled and a single egg is collected which may not fertilise or divide.

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**Intra-cytoplasmic sperm injection (ICSI)**

Developed over 10 years ago, ICSI allows fertilisation of oocytes with low sperm numbers. The female partner undergoes IVF treatment as described above. An individual sperm is then injected through the membrane of each harvested oocyte to achieve fertilisation. This technique has revolutionised the treatment of male factor infertility. Sperm can also be retrieved by means of an operation for obstructive causes of azoospermia (absence of sperm in the semen), such as vasectomy, congenital absence of vas deferens, etc. This is known as mesenchymal sperm aspiration or testicular sperm aspiration.

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**Gamete or zygote intra-fallopian transfer**

Gamete or zygote intra-fallopian transfer are procedures performed laparoscopically and involve the transfer of unfertilised eggs and sperm or a limited number of fertilised embryos into the fallopian tube.

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**Donor treatments**

It is possible to use donor gametes or embryos for treatment. Previously, donation of gametes or embryos has been anonymous. In January 2004, however, the Department of Health released plans to change the law such that after April 2005 any children born as a result of gamete or embryo donation will be able to access the identity of the donor when they reach the age of 18. Anybody donating their gametes or embryos before April 2005 will remain anonymous.

It remains to be seen what impact this will have for those patients requiring donor gametes or embryos.
**Gonadotrophins**

Gonadotrophins are injectible forms of drug to stimulate the ovaries, namely FSH and LH. They are administered daily and have the effect of acting directly on the ovary to stimulate ovarian follicle development, overriding the normal physiological production of a single follicle. LH is used in combination with FSH for this purpose but is insufficient by itself for oocyte development.

Historically these preparations were extracted from the urine of post-menopausal women (human menopausal gonadotrophins) and contained varying proportions of FSH and LH as well as extraneous proteins. However, in more recent years, it has become possible to synthesise these hormones (recombinant FSH and LH). This has resulted in more reliable dosing (particularly in the case of filled by weight products [as opposed to using rat in vivo biological assays to determine mass]), higher purity of drug and significantly reduced the potential for contamination of drug product. This is particularly the case with the advent of prion protein disease and the fact that abnormal prion proteins have been found in the urine of patients with prion disease such as variant Creutzfeldt-Jakob disease. Indeed a vast amount of human urine (175,000 litres) is required for each batch of menopausal gonadotrophins. This is obtained from approximately 10,000 donors.

FSH and LH are both given subcutaneously because they are complex glycoproteins and are subject to enzymatic degradation if given enterally.

FSH is used for controlled ovarian stimulation for IUI and IVF procedures. LH is indicated for follicular development in women with severe LH and FSH deficiency and is therefore used in conjunction with FSH injections.

There are many different forms of FSH available for administration. Easiest to use are the solutions for injection which are available as pen systems similar to insulin pens. This allows fine control of administration of either 25 international units (iu) or 37.5iu increments and also allows doses to be given in a small volume decreasing pain at the site of injection. Also available are single dose vials which sometimes require reconstitution.

LH is presented as powder and solvent for reconstitution. The usual starting dose is 75iu with doses of up to 150iu depending on response as monitored by ultrasound.

Contraindications are large ovarian cysts not related to polycystic ovaries, undiagnosed vaginal bleeding and tumours of ovary, breast, uterus, pituitary or hypothalamus.

Undesirable effects are commonly bruising, pain, redness, swelling and itching at the site of injection. Thromboembolism may occur rarely.

Now that much purer forms of FSH are used there is increasing recognition that LH might be needed in some patients for normal follicular development.

**Clomifene**

Clomifene is one of the oldest drugs to be used in the treatment of infertility and is highly effective if used for appropriate cases. Generally it is given in a dose of 50–100mg in the early follicular stage of the menstrual cycle, eg, commencing on day 2 or 3. It has anti-oestrogenic properties and this has the effect of blocking the negative feedback effect of oestrogen at the level of the pituitary thereby increasing FSH production in the early part of the cycle. This, in turn, stimulates the ovary to produce follicles. As with all drugs used in infertility there is a risk that more than one follicle may be produced and that multiple pregnancy may occur. It is important to counsel patients appropriately regarding this and also to monitor patients by means of serial ultrasound and scans. Tamoxifen can also be used and it has a similar method of action.

Side effects are related to its anti-oestrogenic properties, namely menopausal symptoms. OHSS can also occur. Rarely it may cause visual problems which is a concern and also to monitor patients by means of serum and LH. This has resulted in more reliable dosing (particularly in the case of filled by weight products [as opposed to using rat in vivo biological assays to determine mass]), higher purity of drug and significantly reduced the potential for contamination of drug product. This is particularly the case with the advent of prion protein disease and the fact that abnormal prion proteins have been found in the urine of patients with prion disease such as variant Creutzfeldt-Jakob disease. Indeed a vast amount of human urine (175,000 litres) is required for each batch of menopausal gonadotrophins. This is obtained from approximately 10,000 donors.

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Now that much purer forms of FSH are used there is increasing recognition that LH might be needed in some patients for normal follicular development.

**Insulin sensitising agents**

Insulin sensitising agents can be used in the treatment of PCOS.

**Metformin**

There is increasing evidence emerging regarding the use of metformin in PCOS both with and without concomitant clomifene.

PCOS is associated with hyperinsulinaemia and insulin resistance, and therefore drugs which increase insulin sensitivity may be helpful in the treatment of PCOS.

A systematic review and meta-analysis showed that metformin is effective in achieving ovulation in women with polycystic ovaries (in 46 per cent of cases) and is more effective in terms of achieving ovulation in patients using clomifene concomitantly (76 per cent of which ovulated). Caution is needed when considering the case of pregnancy rates since not all studies followed pregnancies over 20 weeks. There appeared to be no evidence that pregnancy rates increase with metformin alone but appears to be an effect with metformin and clomifene. Currently metformin is not licensed for use in the treatment of polycystic ovaries.

**Thiazolidinediones**

Thiazolidinediones are a newer class of insulin sensitising agents which act as ligands at the level of the peroxisome proliferation-activated receptor (PPAR) which is a nuclear hormone receptor. They alter gene expression and regulation within adipocytes and also improve muscle insulin sensitivity.

Again, these drugs are not licensed for treatment of PCOS. One of the thiazolidinediones, troglitazone, was withdrawn from the market over concerns regarding acute liver failure and they remain at present a research tool.

**Aromatase inhibitors**

Aromatase enzyme is responsible for the conversion of androgen to oestrogen. Inhibition of this enzyme leads to a decrease in the levels of oestrogen which in the early follicular phase of the menstrual cycle prevents negative feedback of oestrogen at the level of the pituitary and hence leads to an increase in FSH levels and ultimately ovarian stimulation. An increase in androgen levels may also have a synergistic effect with the central effects of decreased oestrogen production to enhance the ovarian response to FSH stimulation. There is good evidence that clomifene-resistant PCOS patients ovulate with this drug but more trials are needed.
DRUGS TO PREVENT A PREMATURE LH SURGE

Drugs can also be used to prevent a premature LH surge and control the timing of ovulation.

GnRH agonists GnRH agonists are used for down-regulation before IVF cycles to prevent premature ovulation. They are also used in the treatment of fibroids to shrink the size and minimise blood loss. They are available in injectable form (daily and depot) and as nasal preparations. Generally subcutaneous administration gives higher and more consistent serum levels and is recommended. For IVF cycles agonists are given for two weeks, and sometimes longer, before down-regulation is achieved. Response is monitored by means of blood tests and ultrasound scan.

Contraindications are pregnancy, undiagnosed vaginal bleeding and known hypersensitivity.

Undesirable effects are those related to the fall in oestrogen levels as a result of pituitary desensitisation, such as hot flushes, sweating, loss of libido and vaginal dryness. GnRH agonists can stimulate the release of histamine directly from mast cells leading to an acute hypersensitivity reaction, but this is rare. More common reactions are redness and itching and skin rash at the site of injection. Other side effects include breast tenderness, dry skin, acne, sleep disturbance, tiredness, musculoskeletal discomfort and dry eyes. There may rarely be a deterioration of control of blood pressure and reduction in glucose tolerance.

GnRH antagonists GnRH antagonists are a class of drugs that act at the level of the pituitary gland to block the action of luteinising hormone releasing hormone (LHRH) and hence LH to prevent ovulation.

They are given subcutaneously and are commenced around day 5 or 6 of FSH stimulation. They have almost instant suppressive effect and should be taken at the same time each day to prevent an LH surge. The benefit of using this type of drug for IVF cycles is that the total cycle length from start of FSH injections to egg collection is approximately 10 to 12 days compared with 28 days for agonist IVF cycles. Patients also avoid the menopausal symptoms associated with agonist use.

Special features for 2005

Have we covered your area of practice recently?

Hospital Pharmacist is currently compiling its list of special features for the first part of 2005. We would welcome suggestions from hospital pharmacists about topics you would like to see included. Suitable subjects for special features are generally disease areas and aspects of hospital pharmacy practice, but consideration will be given to any suggestions made. Please also let us know if you would be willing to write an article on your proposed topic.

Suggestions should be directed to Gareth Jones (e-mail gareth.jones@pharmj.org.uk or hospital.pharmacist@pharmj.org.uk or telephone 020 7572 2425)

Special feature topics in the past 18 months include:

- Leukaemias
- Bespoke pharmacy
- Transplantation
- Obstetrics
- Epilepsy
- Aseptic preparation
- Antimicrobial management
- Anaesthesia and surgical pain relief
- Parkinson’s disease
- Renal failure
- Chronic heart failure
- Bipolar disorder
- Colorectal cancer
- Care of the elderly
- Infectious diseases
Contraindications are pregnancy and moderate renal and hepatic impairment.
Undesirable effects are few but nausea, headache and injection site reactions are the most common and rarely hypersensitivity reactions occur.

**DRUGS TO TRIGGER OVULATION**

Normally ovulation is initiated by a surge in LH hormone in response to rising oestradiol levels. During down-regulated cycles this surge is prevented and is initiated by means of hCG injection. Structurally hCG and LH are similar and both act on theca lutein cells (cells that line the corpus luteum) to initiate maturation of the oocyte.

In a similar way to gonadotrophin manufacture, recombinant preparations of this drug are available and appear to show comparable pregnancy rates. Urinary derived drug are available and appear to show comparable pregnancy rates. Urinary derived products are still popular and commonly a triggering dose of 10,000iu hCG is given after stopping it is routine to supplement the luteal phase by progesterone, usually in the form of suppositories although progesterone is also available in gel, injection and oral forms. First pass metabolism of progesterone generally prevents the oral route from being used. A typical IVF protocol would normally start progesterone supplementation at the time of egg collection or up to three days after this time and would normally continue until the time of pregnancy test around 14 days after egg collection.

**LUTEAL PHASE SUPPORT DRUGS**

Due to the use of GnRH agonists and antagonists to prevent premature LH surges it has become routine use to supplement the luteal phase of the treatment cycle with progesterone. Normally progesterone levels peak approximately four days post-ovulation and then plateau for a week. The role of progesterone (in combination with oestradiol) is to support the endometrium during early pregnancy. The corpus luteum requires continuous stimulation by LH to produce progesterone. Due to the fact that the blocking effects of GnRH agonists last for up to 10 days after stopping it is routine to supplement the luteal phase by progesterone, usually in the form of suppositories although progesterone is also available in gel, injection and oral forms. First pass metabolism of progesterone generally prevents the oral route from being used. A typical IVF protocol would normally start progesterone supplementation at the time of egg collection or up to three days after this time and would normally continue until the time of pregnancy test around 14 days after egg collection.

**Panel 1: Financial impact of increased fertility services**

- A financial analysis of the clinical guidelines has estimated that the demand for IVF cycles will increase by approximately 80 per cent (costing an additional £83.9m). The increase in the number of babies needing neonatal intensive care (NICU) as a result of this would be 1,885 leading to an rise in NICU costs of £5.9m.
- The impact of current HFEA guidelines to limit the number of embryos transferred to two embryos is estimated to reduce the overall number of babies born by 7.4 per cent (from couples already eligible to receive treatment) and a reduction in the number of babies needing admission to NICU by 562 per year. This would lead to £1.8m saving per year.
- The net increase in NICU costs would be £4.1m.
- The total estimated reduction in cost for unstimulated IUI treatments and reducing costs of using HSG for tubal assessment and not laparoscopy would save £7m in total.
- The total impact of this guideline would therefore be an additional cost of £81m to the NHS.

**NICE GUIDELINES**

In February 2004 NICE issued a clinical guideline on fertility treatment. The aim of this guideline was to reduce the variability in terms of access to fertility treatments across England, which was largely determined by where people lived (the postcode lottery) and to provide guidance based on best evidence for the care of couples with infertility from primary care to tertiary care. Seven key priorities for implementation were also identified:

- Before undergoing uterine instrumentation women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique.
- Women who are not known to have co-morbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered a hysterosalpingogram (HSG) to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion and it is less invasive and makes more efficient use of resources than laparoscopy.
- Couples with mild male factor fertility problems, unexplained fertility problems or minimal to mild endometriosis should be offered up to six cycles of intra-uterine insemination because this increases the chance of pregnancy.
- Couples in which the woman is aged 23–39 years at the time of treatment and who have an identified cause for their fertility problems (such as azoospermia or bilateral tubal occlusion) or who have infertility of at least three years’ duration should be offered up to three stimulated cycles of IVF treatment.
- Human menopausal gonadotrophin, urinary FSH and recombinant FSH are equally effective in achieving a live birth when used following pituitary down-regulation as part of IVF treatment. Consideration should be given to minimising cost when prescribing.
- Couples should be informed that the chance of multiple pregnancies following IVF treatment depends on the number of embryos transferred per cycle of treatment. To balance the chance of a live birth and the risk of multiple pregnancy and its consequences, no more than two embryos should be transferred during any one cycle of IVF treatment.
- Embryos not transferred during a stimulated IVF treatment cycle may be suitable for freezing. If two or more embryos are frozen then they should be transferred before the next stimulated treatment cycle because this will minimise ovulation and egg collection, both of which carry risks for the woman and use more resources.

Clearly if IVF becomes a more widely available treatment this will have cost implications for the NHS. Predicted cost implications are outlined in Panel 1. Debate will continue as to whether treatment of infertility is a justified use of NHS resources.

**REFERENCES**

2. Johnson NP, Mak W, Sowter MC. Laparoscopic salpingectomy for women with hydrosalpinges enhances the success of IVF. Cochrane Library 2002; issue 1.