4.2.2 1 Causes and treatment of infertility

IVF

Simon and Megan now have a family of three sons, but at one time it seemed as if they would have to remain childless or adopt. In 1997, after two pregnancies had ended in miscarriage and after an ectopic pregnancy, Simon and Megan had their first cycle of IVF. Megan became pregnant eventually after a frozen embryo transplant, but unfortunately miscarried. They adopted a 5-month-old baby boy – thinking that this was their only chance of being parents, but their local Primary Care Trust offered them another cycle of IVF. This was successful, and Simon and Megan now have twin boys. They also agreed to donate their remaining frozen embryos to assist other childless couples.

Asherman's syndrome

Suzanne gave birth to her first daughter, but after a week she developed a uterine infection. After unsuccessful antibiotics, a medical scan and a D&C she had no periods for over a year following the procedure. After a series of failed diagnoses, Asherman's Syndrome was suspected. This is scarring in the uterus, which had resulted from the D&C. Suzanne underwent a hysteroscopy to try to remove the scarring, but although her periods returned, they were very light. Further surgery followed, alongside a course of HRT.

The surgery had been quite severe. The result meant that her uterus was now mostly scar-free but her **endometrium** was very badly damaged and thin. Suzanne has had two unsuccessful attempts at IVF, and, even with no pregnancies, the IVF drugs helped thicken up the uterine lining.

Examiner tip

You should be able to understand what treatments to assist with fertility are trying to do. For example, you should recap hormonal action and control of the menstrual cycle when considering ovulation induction.

Causes of infertility

Currently one in seven couples in the UK has problems conceiving.

The problem of infertility could be a result of problems with the female reproductive system, problems with the male reproductive system or a result of some other factor. The following table outlines some of the potential causes of infertility in both males and females.

Females	Males
Failure to ovulate due to abnormal menstrual cycle or insufficient hormone levels	Sperm may be abnormal and fail to develop correctly in the testes, for example they might not contain tails
Blockage of the oviducts, which could be a result of a bacterial infection	Semen may contain such a low number of sperm cells that there is not enough to be successful at fertilising an egg
Endometriosis may occur which causes the uterine lining to develop outside of the uterus and may block the oviduct	Some men also produce antibodies into their own semen, which actually destroy the sperm at source
Anti-sperm antibodies may develop, which are secreted into the uterus, destroying sperm before it reaches the egg	

Table 1 Causes of infertility

Fertility treatments

There are treatments available for infertility in both males and females. Ovulation can be induced with hormone treatment, surgery can unblock oviducts and sperm ducts, and couples can also be offered methods of assisted fertilisation. Some of the most commonly used treatments available to men and women include:

- ovulation induction
- artificial insemination
- *in vitro* fertilisation
- frozen embryo replacement
- gamete intrafallopian transfer
- intracytoplasmic sperm injection
- use of sperm banks and donor sperm.

Ovulation induction

Many infertile women produce follicles that do not fully develop to form viable eggs. This is a condition called *polycystic ovarian syndrome*. It is treated by giving these women drugs that act to inhibit oestrogen. The effect is to promote the release of **GnRH** from the hypothalamus and so stimulate the release of FSH and LH from the anterior pituitary gland. This will induce ovulation and also help to develop immature follicles. LH and FSH can also be given directly into the bloodstream if other treatments fail. One possible result of the treatment is that by stimulating the development of follicles there is a high risk of multiple pregnancies.

Artificial insemination

This involves injecting semen into the top of the vagina or the uterus through a small plastic tube. The process can involve either intra-cervical insemination (ICI), or intra-uterine insemination (IUI). With ICI, the semen is collected and insemination occurs within two hours at the top of the vagina. A plastic cap is often placed in the vagina for several hours to give the sperm the chance to enter the uterus through the cervix. IUI places sperm near the oviducts and this treatment is more successful. Semen rather than sperm is inserted into the uterus using a thin plastic tube that is passed through the cervix.

How does IVF work?

In vitro fertilisation aims to fuse oocytes and sperm outside of the body. These cells fuse and the zygote goes on to divide, forming a blastocyst. This is then artificially implanted back into the endometrium. The first successful procedure took place in 1978, and although the technology has been refined, the basic process still involves the following steps:

- a woman is 'super-ovulated' using synthetic hormones so that several follicles ripen at the same time
- an ultrasound probe of the vagina is used to locate ripe follicles in the ovaries. This is done under local or general anaesthetic
- these follicles are aspirated (sucked out using a special instrument) a few hours before ovulation
- the oocytes are removed using a suction device and placed in a test tube containing a special medium
- these oocytes are then maintained in separate test tubes at body temperature
- sperm are prepared and at least 100 000 are added to each oocyte in a small Petri dish
- after 16–20 hours, the oocytes are checked to see if they have been fertilised
- the resulting embryos are then left to develop for two to three days in the incubator
- they can then be transplanted back into the uterus.

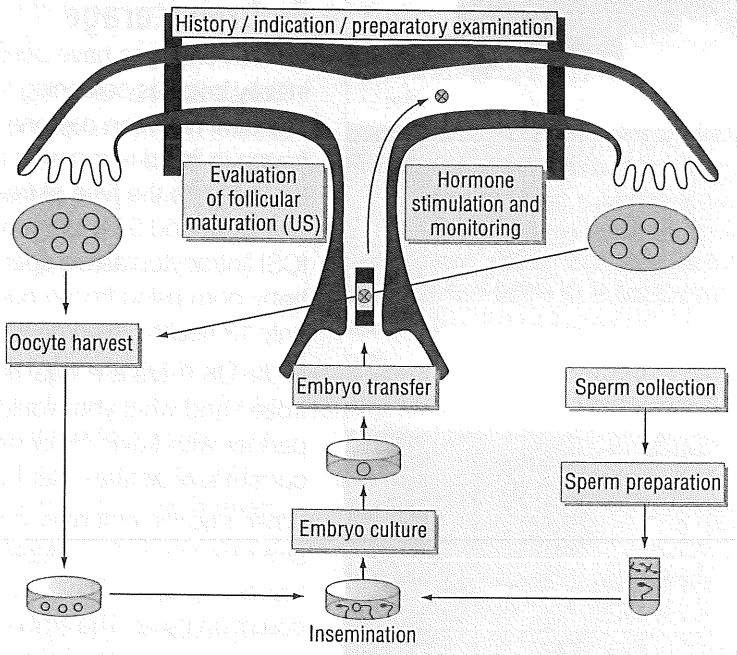

Figure 1 IVF procedure

By providing many possible embryos in the process of IVF, there is a possibility that these can be frozen and stored for later use. These embryos can be used by women who, possibly through a medical procedure such as chemotherapy, cannot produce their own eggs. Some may be donated to another infertile woman.

Alternatives and modifications to IVF

There are three possible alternatives for infertile couples that use the same principles as IVF, and also others that slightly modify it. These are explained below:

GIFT – gamete intrafallopian transfer	ZIFT – zygote intrafallopian transfer	ICSI – intracytoplasmic sperm injection
Sperm and oocytes are passed directly into the oviduct and allowed to fertilise naturally – these oocytes may have been donated	This involves a zygote being created by the process of IVF, but the zygote is implanted into the oviduct and allowed to implant naturally	IVF is given a helping hand as the sperm is injected directly into the egg, forcing fertilisation

Table 2 Alternative and modified IVF treatments

Sperm bank

Sperm has been frozen in sperm banks and used to fertilise oocytes for over 50 years. This treatment has had a good success rate and has helped infertile couples and single woman to conceive.

Since the 1950s there have been many changes to the law regarding the use of donor sperm. Currently in the UK, the identity of the sperm donor cannot be revealed to the recipients, though his physical characteristics, blood group and other information can be told in order to help in matching.

Questions

1 Explain how the use of reproductive hormones can help some infertile women.
2 Using the hormones used in fertility treatment, discuss their roles in the ovarian and menstrual cycle.
3 Explain how female antibodies may act to destroy male sperm and so prevent fertilisation.
4 Describe why it is important to screen donated sperm for diseases such as HIV.
5 Between 97% and 98% of men with cystic fibrosis may be infertile due to development problem with the sperm duct (vas deferens). Which procedure would you recommend? What other advice might you also offer?

4.2.2 (2) Fertility treatments continued

Embryo storage

Human embryos have been successfully frozen and thawed since 1983. Embryo storage initially involves screening for HIV and hepatitis B and C. The embryos can be frozen at any time between day one and day six inclusive. They may then be stored unharmed, frozen in liquid nitrogen at temperatures of –300 °C, for 50 years or more. But the current law restricts the time of freezing to between five and 10 years. With oocytes, the survival rate is around 50% but the fertilisation rate using conventional methods is low. But, using ICSI (intracytoplasmic sperm injection), the fertilisation rate is much improved. The first baby born using frozen oocytes was in 1986, but the success rate in 1997 resulted in only 13 healthy children from 212 transfers!

In the UK there is a legal requirement to state how long you would like your embryos frozen and what you would like to happen to them. If the couple separate and one partner withdraws his or her consent to the ongoing storage of the embryos, then the current law dictates that the embryos are removed from storage.

When freezing embryos, couples have the choice of using their own embryos, donating embryos to another couple undergoing fertility treatment, or donating the embryos to a research project. The frozen embryo cycle is relatively non-invasive compared to an egg collection cycle. The embryos can be replaced in a natural cycle if the time of ovulation can be monitored easily. Failing this, a 'controlled cycle' is used and hormonal tablets or nasal sprays are used to prepare the endometrium for implantation. The development of the endometrium is monitored by ultrasound. When the endometrium is the correct thickness, and providing both partners give consent, embryos can be thawed for transplantation.

Examiner tip

You need to read questions carefully and watch the terms that you use in the answers. Also, oocytes, sperm and embryos can all be stored frozen.

Figure 1 Storage of embryos

Vanishing twin syndrome

Occasionally a twin observed during ultrasound in the early stages of development will disappear during later pregnancy. This is called a vanishing twin. The developing fetus has died during the pregnancy and has been reabsorbed by the woman's body. This can occur as a result of chromosomal abnormality, fetal development problem or a fault with the placenta.

If the fetus dies early on in the pregnancy then there are usually no health worries for the mother. But if the death occurs during the later stages of development it can result in infection, premature labour and death of the other fetus.

Multiple pregnancy

Multiple pregnancies occur when more than one fetus develop simultaneously in the womb.

These pregnancies occur naturally in about 1 in every 100 births. This natural incidence has been upset by current advances in fertility treatments. When women are given hormone treatment that acts to increase follicle development, this has the effect of creating a state of *super-ovulation*, which leads to the release of many **secondary oocytes** into the oviducts and the possibility of a multiple pregnancy.

Most multiple pregnancies produce twins – identical or fraternal. Identical twins occur as a result of the splitting of a single fertilised zygote into two separate individuals. Fraternal twins occur when two eggs are fertilised by separate sperm.

When twins fail to separate completely, the result is Siamese (or conjoined) twins.

Risks involved in multiple pregnancies

Women who are pregnant with more than one fetus run a higher risk to their health than those who carry a single fetus. Their unborn children are also at a higher risk of problems such as low birth weight (less than 2500 g) and premature birth. They are also at a higher risk of being stillborn. For mothers, there is an increased risk of high blood pressure and **pre-eclampsia**, anaemia, haemorrhage, and early labour, and more chance of needing a Caesarean section. Although the risk of mortality in pregnancy is small, it is double for women expecting twins than for those expecting just one child.

If multiple pregnancies are a result of fertility treatment, a choice can be made to selectively reduce the number of fetuses. This is known as *fetal reduction*. The abortion of one or more fetuses can be carried out to increase the chances of survival for the other developing fetuses. This procedure does risk all of the fetuses and some women may miscarry or enter premature labour. It is a difficult and emotional decision for all involved.

Clinics will transfer a maximum of two embryos per IVF cycle if the woman is aged 39 or under, or three if the woman is over 40 and using her own eggs.

Examiner tip

You should re-read the section you studied on antibody structure. Remember that antibodies have variable and constant regions. The variable region is specific to the antigen and here, the hCG is the antigen.

Premature birth

Premature birth is the birth of a baby before the standard period of the 40-week pregnancy is completed. Babies born any time before the thirty-seventh week of pregnancy are classed as premature. By being born premature the baby has a risk of developing certain health problems. These are outlined in Table 1.

Advances in medical care and technology have meant that the age when a fetus can survive prematurely is actually quite low. The age above which prematurely born fetuses have a good chance of surviving is considered to be about 24 weeks. However, babies born this early are at considerable risk of brain damage because the lungs are not sufficiently developed to supply the brain with adequate oxygen.

- poor neurological development
- congenital heart defects due to a failure of the child's ductus arteriosus to close after birth
- *respiratory distress syndrome* or chronic lung disease
- gastrointestinal and metabolic problems such as hypoglycaemia or feeding problems
- blood problems such as anaemia or jaundice
- infections of the urinary tract.

Table 1 Possible problems of premature birth

Pregnancy testing

There are tests that can be used very early on in pregnancy which can detect whether or not an oocyte has been fertilised by a sperm. If the woman has been receiving fertility treatment or has a history of multiple pregnancies, the outcome of this test will be vital in preparing the couple for the potentially difficult time to come. Most pregnancy tests use **monoclonal antibodies** or MABS, to detect the presence of the hormone **human chorionic gonadotrophin** (HCG) in the mother's urine. The test is described in Table 2.

- the pregnancy stick is dipped into the mother's urine – an early morning sample is normally used as this will have the highest concentration of the hormone
- any HCG in the urine will bind to specific antibodies held on the stick
- these antibodies are bound to a colour bead and form a HCG–antibody–colour complex
- the urine then seeps up the stick until it reaches a region of fixed immobilised antibodies
- these antibodies bind to the HCG–antibody complex if it is present, giving a coloured band – this is the mark of a positive result for pregnancy
- a further band is used as a control, and will give colour with the antibody alone. This is a control and shows the test is working.

Table 2 Pregnancy testing

Biological, ethical and economic arguments in fertility treatment

In Table 3 there are some arguments for and against fertility treatments from three very different perspectives. It is important to be objective when considering reasons why people might seek help through fertility treatment and the effects such treatment might have on the couple or on the individuals born to the treatment.

Biological	Ethical	Economic
There have been huge scientific advances in assisted fertilisation This is partly due to a decline in the fertility of couples in modern times Reasons for this include the increasing age of women at the time of marriage and childbearing. Also there has been an increase in the incidence of sexually transmitted diseases that damage the reproductive tract in both men and women There have been overall decreasing sperm counts in men worldwide in the last few decades. The reasons for this are unclear but could be due to environmental pollution or to the stresses of modern life	Assisting fertilisation raises issues regarding the question of embryo research. What time limits should be placed on this research? Furthermore, when does life begin and what are the rights of an embryo? There are issues around sperm donor banks and the future child's right to access to information about his or her genetic background and mode of conception World religions also differ on the ethical implications of such treatment. For example, to the Catholic Church, artificial insemination by IVF is not acceptable. Procreation without sexual union in considered unnatural. In Judaism, however, IVF is accepted as necessary to heal the illness of infertility	Infertility treatment is expensive and because success is not guaranteed there can often be no specific end point to treatment Assisted reproductive techniques, such as IVF, have made treatment even more expensive because so much expertise and technology is needed for these procedures Couples need to consider the cost-effectiveness of each treatment option. For example, it is true that an IVF cycle is four times as expensive as an IUI cycle, but the chance of a pregnancy is also four times as great What is more, most insurance companies take the view that infertility is not a medical problem, so many couples are reluctant to claim for medical expenses for treatment. There is also evidence of a 'postcode' lottery with conditions for offering IVF and the numbers of cycles offered on the NHS varying between authorities

Table 3 Arguments for and against fertility treatments

Questions

1 Discuss the ethical implications around the storage of frozen embryos.
2 Suggest why embryos are stored only for a limited time period such as 5 or 10 years.
3 Explain how antibodies might detect the presence of chemicals such as the hormone HCG.
4 What might be an advantage of a vanishing twin to the mother and remaining fetus in early pregnancy?