The **Women's** Health Council
Comhairle Shláinte na mBan

Infertility Treatments for Women

A Review of the Bio-medical Evidence

Full Report

Infertility is a medical and social condition that can cause considerable social, emotional and psychological distress. It is estimated to affect one in six couples in Ireland (CAHR, 2005); however, it is still a topic that is not widely discussed or for which help is easily accessible.

(WHC, 2009)

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A dandelion is a universal symbol for fertility - the dozens of seeds released by each flower head represent fertility and abundance. The seeds' journey illustrates a time of letting go, of starting something new.

The Women's Health Council

The Women's Health Council is a statutory body established in 1997 to advise the Minister for Health and Children on all aspects of women's health.

The mission of the Women's Health Council is to inform and influence the development of health policy to ensure the maximum health and social gain for women in Ireland. Its membership is representative of a wide range of expertise and interest in women's health.

The Women's Health Council has five functions detailed in its Statutory Instruments:

1. Advising the Minister for Health and Children on all aspects of women's health
2. Assisting the development of national and regional policies and strategies designed to increase health gain and social gain for women.
3. Developing expertise on women's health within the health services.
4. Liaising with other relevant international bodies which have similar functions as the Council.
5. Advising other Government Ministers at their request.

The work of the Women's Health Council is guided by three principles:

- Equity based on diversity – the need to develop flexible and accessible services which respond equitably to the diverse needs and situations of women.
- Quality in the provision and delivery of health services to all women throughout their lives.
- Relevance to women's health needs.

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List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Assisted Reproductive Techniques
ASRM	American Society for Reproductive Medicine
BMI	Body Mass Index
eSET	elective Single Embryo Transfer
ESHRE	European Society of Human Reproduction and Embryology
FSH	Follicle Stimulating Hormone
hCG	human Chorionic Gonadotrophin
HFEA	Human Fertilisation and Embryology Authority
HIV	Human Immunodeficiency Virus
HSG	hysterosalpingography
ICI	Intracervical Insemination
ICSI	Intracytoplasmic sperm injection
IVM	In Vitro Maturation
IUI	Intrauterine insemination
IVF	In Vitro Fertilisation
GIFT	Gamete Intrafallopian Transfer
GnRH	Gonadotrophin Releasing Hormone
LH	Luteinizing Hormone
LOD	Laparoscopic Ovarian Drilling
NCC WCH	National Collaborating Centre for Women's & Children's Health
NICE	National Institute of Clinical Excellence
OHSS	Ovarian Hyperstimulation Syndrome
PCOS	Polycystic Ovary Syndrome
PGD	Pre Implantation Genetic Diagnosis
RCT	Randomised Controlled Trial
rFSH	recombinant Follicle Stimulating Hormone
rhCG	recombinant human Chorionic Gonadotrophin
rLH	recombinant Luteinizing Hormone
SIGN	Scottish Intercollegiate Guidelines Network
UAE	Uterine Artery Embolization
UFE	Uterine Fibroid Embolization
uFSH	urinary Follicle Stimulating Hormone
uhCG	urinary human Chorionic Gonadotrophin
uLH	urinary Luteinizing Hormone
ZIFT	Zygote Intrafallopian Transfer

Often cited consequences of infertility are: depression, anxiety, sexual anxiety/difficulty, relationship problems with partner, family and friends, and an increased sense of self-blame and guilt.

(WHC, 2009)

Abstract

The use of assisted reproductive technology is increasing in Ireland. The number of babies born as a result of in vitro fertilisation has more than doubled from 135 in 2000 to 301 in 2005. The main reasons for the increase in couples seeking help for fertility problems is the trend for delaying pregnancy until later in life, the increase in obesity, and the higher rate of sexually transmitted infections. The demand for advice and treatment of fertility problems is likely to increase over the coming years.

Fertility treatments available to couples are often complex. In order to make informed decisions on fertility treatment, couples need to understand the treatment options available to them. The large volume of research on fertility treatments, which is often of poor quality, makes it difficult to access reliable, relevant and readable information. This makes the emotional decision making process even more of a challenge.

This review summarises relevant evidence from guidelines and high quality studies. To enhance the readability of the evidence, a summary of this review is also available. It should be noted however that scientific evidence is not infallible, and that knowledge in this field is constantly evolving. The evidence summarised in this review presents the consensus at the time of publishing.

This review aims to investigate the effectiveness of the types of fertility treatments in the following categories: (1) Medicines to improve fertility; (2) Surgical treatments; and (3) Assisted reproductive technology. The effectiveness of fertility treatments, and the associated risks and benefits, will be considered.

The information summarised in this review is intended to inform professional groups who have a role in caring for couples seeking advice and treatment for fertility problems. It also aims to provide couples seeking advice and treatment for fertility problems with the best available current evidence on treatments. A report on the psycho-social issues related to infertility and its treatment is also available to provide a more holistic overview of this complex issue (WHC, 2009).

One: Background to review

1.1 Why infertility is an important health issue to examine?

Infertility can cause considerable social, emotional and psychological stress. It is estimated that one in six Irish couples are considered to be infertile according to the WHO definition of infertility[1] (CAHR, 2005).

The European Society of Human Reproduction and Embryology (ESHRE) highlighted that the prevalence of infertility is increasing across the developed world. The main reasons for this is the trend for putting off pregnancy until later in life, an increase in obesity, and the higher rate of sexually transmitted infections (ESHRE, 2008). Doctors predict that these health and social changes could lead to a rapid increase in demand for fertility treatment in the coming years (HFEA, 2005).

The main reasons women postpone starting a family include: extended time spent in education; extended time spend developing career; professional stability; use of contraception; late meeting of partner; falsely reassuring information on the progress in ART; second child desire after late first pregnancy; second marriage and child desire in the redefined couple. The average age of women in Ireland having their first child is 30.6, which is higher than in the UK (28.7) and the EU average (29.6) (McGrath *et al.,* 2005). Postponement of pregnancy has led to an increase in the incidence of 'unexplained infertility' due to age-related decline in the quality of eggs and the decline in the reserves of eggs in the ovaries (RCOG, 2008).

The level of obesity in young women has been increasing, which leads to increased rates of anovulation and polycystic ovary syndrome (PCOS), as well as poorer response to fertility treatment (RCOG, 2008).

The incidence of notified cases of chlamydia infection in Ireland has increased every year from 245 cases in 1995 to 3,353 cases in 2005, although there was a slight decrease to 3,144 in 2006 (HPSC, 2008). It is estimated that around 3% of women with chlamydial infection in the lower genital tract will become infertile (Paavonenggert-Kruse, 1999).

[1] The World Health Organisation (WHO) defines infertility as a lack of conception following one year of unprotected sexual intercourse.

1.2 Why conduct this review of biomedical evidence?

The use of ART is increasing. The most recent data from the USA shows that 1.2% of all infants born in the United States are as a result of ART (Wright *et al.,* 2008). Fourteen countries in Europe record ART data in a national register[2]. The proportion of infants born as a result of ART in these 14 countries ranged between 0.2% in Latvia to 4.2% in Denmark (Andersen *et al.,* 2008).

The increasing availability worldwide of assisted reproductive technology has led to an upsurge of published literature on the effectiveness of such treatments. The large volume of evidence, which is often of poor quality, makes it difficult for the average health-care individual or couple seeking help with their fertility to obtain relevant evidence for treatment decisions (Daya, 2006).

According to a survey commissioned by the UK Human Fertilisation and Embryology Authority (HFEA), infertility is the single biggest reason for women aged 20-45 going to see their GP, apart from pregnancy itself. One of the biggest concerns of patients is the need for clear, reliable independent information on infertility (HFEA, 2005). Patient concerns in Ireland are likely to be even greater due to the lack of regulation and poor data availability from fertility clinics, compared to the UK. An up-to-date summary of the available treatments and their effectiveness would help enable couples to make informed decisions on their fertility treatment.

1.3 Aims & objectives of this review

Infertility treatment can have substantial social and emotional repercussions. For an overview of these issues, please see this report's companion publication *Infertility and its treatments: a review of psycho-social issues* (WHC, 2009). The ethical implications of infertility treatments, and the regulation of such treatments are also important issues to consider. However, this review focuses only on the biomedical evidence regarding the effectiveness of female infertility treatments.

[2] These countries are: Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Latvia, Macedonia, Norway, Slovenia, Sweden, The Netherlands and UK.

This review aims to collate and summarise high quality evidence on the various types of fertility treatment available to women in Ireland. The objectives of this review are to investigate the effectiveness of the types of fertility treatments in the following categories:

1. Medicines to improve fertility
2. Surgical treatments
3. Assisted reproductive technology

The effectiveness of fertility treatments, and the associated risks and benefits, will be considered.

Two: Background information on female infertility

2.1 What is infertility?

2.1.1 Natural conception process

Natural conception occurs when sperm cells, after sexual intercourse, migrate up through the cervix and uterus and into the fallopian tubes. Somewhere along the fallopian tube the sperm will meet the egg and a single sperm will penetrate the egg and fertilise it. The fertilised egg (called a zygote) continuously divides to form a ball of cells as it travels down the fallopian tube. By the time the fertilised egg has reached the uterus it has developed into a blastocyst. A blastocyte has an inner group of cells that will become the embryo, and an outer group of cells that will attach the blastocyst to the uterus wall to form the placenta. The placenta carries oxygen and nutrients from the mother to the foetus and waste materials from the foetus to the mother. The blastocyst attaches to the lining of the uterus, where is starts to receive nourishment from the mother's bloodstream. The implantation of the blastocyst to the uterus lining usually occurs about 10 days after the sperm first penetrated the egg in the fallopian tube.

Natural conception is a complex process that relies on a number of factors in order to be successful. These factors include:

- The production of healthy sperm by the man
- The production of healthy eggs by the woman
- Unblocked fallopian tubes to allow the sperm to reach the egg
- The ability of the sperm to fertilise the egg when they meet in the fallopian tube
- The ability of the egg to move into the woman's uterus and become implanted in the uterus wall
- A good quality embryo
- Suitable hormonal environment in the woman

It should be noted that the chance of pregnancy per menstrual cycle in the most fertile couples is no higher than 33%. It is therefore unrealistic to expect a higher chance of pregnancy than this from any fertility treatment (Cahill & Wardle, 2002).

2.1.2 Definition of infertility

Infertility is has been defined as *a failure to conceive following frequent unprotected sexual intercourse for one or two years.* Diagnosis based on failure to conceive after two years is thought to give a better measure of infertility as around half of women who fail to conceive during the first year are likely to do so in the second year (NCC WHC, 2004). The term "subfertility" may be used to describe any form of reduced fertility that results in a prolonged duration of unwanted lack of conception (Gnoth *et al.,* 2005).

2.2 Causes of female infertility

For between 15% and 30% of couples no reason can be found for their fertility problem (The Practice Committee of the American Society for Reproductive Medicine, 2006a). The prevalence of different causes of female infertility is associated with age (Maheshwari *et al.,* 2008a). Women over the age of 35 are almost twice as likely to be diagnosed with unexplained and tubal factor infertility, compared with women aged under 35, however diagnosis of ovulatory dysfunction is reduced by a third in women older than 35 years (Maheshwari *et al.,* 2008). Causes of infertility and their estimated occurrence are listed in table 1, with further description provided below.

Table 1 Infertility cause and occurrence in couples

Cause of infertility	Occurrence
Sperm defects or dysfunction	30%
Ovulation failure (e.g. PCOS)	25%
Unexplained infertility	25%
Tubal infective damage (due to chlamydia infection)	20%
Endometriosis (causing damage)	5%
Failure or infrequency of sexual intercourse	5%
Cervical mucus defects or dysfunction	3%
Uterine abnormalities	Less than 1%

Total percentage exceeds 100% as 15% of couples had more than one cause of infertility. Data from (Hull *et al.,* 1985; Cahill & Wardle, 2002).

As ovulation depends on a complex balance and interaction of hormones any disturbance to this can impact ovulation. The most common cause of **ovulation failure** (the failure of the ovaries to make an egg) is **Polycystic ovary syndrome (PCOS)** (Balen & Rutherford, 2007). Polycystic literally means "many cysts". Typically, the polycystic ovary contains many small cysts (fluid filled sacs). Each small cyst represents a follicle, which contains a single egg that is attempting to develop to a stage where it is ready to be released from the ovary (ovulation). Due to a complex biochemical situation in the ovaries with PCOS the development of the follicles is stopped prematurely, resulting in a collection of small follicles and no ovulation occurring (Cedars-Sinai, 2008). The most recent consensus meeting between the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) was held in Rotterdam, the Netherlands in 2003 (The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2003). It was agreed at this meeting that PCOS is diagnosed with at least two of the three characteristics

(1) irregular or absent ovulation, (2) clinical and/or biochemical signs of excess androgen[3] (hyperandrogenism) and (3) polycystic ovaries. The prevalence of PCOS in the general population is unclear and dependent on the diagnostic criteria used. Using the criteria agreed in Rotterdam, the prevalence of PCOS is estimated to be as high as 26% among white women aged 18-25 in the UK (Michelmore *et al.,* 1999), although the symptoms are often mild (Balen & Rutherford, 2007b). Women with PCOS can successfully ovulate when managed with clomifene citrate, gonadotrophins or laparoscopic ovarian surgery in women resistant to clomifene (Balen & Rutherford, 2007b).

Other causes of ovulation disorders include malfunctions of the hypothalamus or pituitary gland, which can lead to too much or too little FSH and LH being secreted. This results in immature eggs and the ovaries being unable to ovulate properly. Scarred ovaries as a result of extensive or invasive surgery for repeated ovarian cysts can prevent ovulation occurring. Although rare, premature menopause[4] results in anovulation. Thyroid disorders such as hypothyroidism (underactive thyroid) and hyperthyroidism (overactive thyroid) may lead to menstrual irregularities and ovulation disorders. Some chronic debilitating diseases such as cancer and AIDS may lead to anovulation (failure to ovulate).

Unexplained infertility is diagnosed when the results of a standard infertility evaluation are normal (Quaas and Dokras, 2008). The guidelines for a standard infertility evaluation published by the Practice Committee of the American Society for Reproductive Medicine (2006b) includes an assessment of ovulation, an x-ray of the uterus, fallopian tubes and the area around them, tests for ovarian reserve and semen analysis.

Tubal infective damage is most commonly caused by infection of genital **chlamydia trachomatis,** which is the most common curable sexually transmitted infection worldwide (WHO, 2001). Population based studies in Europe and the USA suggest that the prevalence of chlamydia in men and women aged 15 to 42 years is 2-6% (Low *et al.,* 2007). Many infections with chlamydia cause few symptoms and may go undetected. Untreated chlamydial infection that moves up the female genital tract can cause pelvic inflammatory disease and scarring in the fallopian tubes, which can lead to tubal factor infertility (Low *et al.,* 2007, NCC WCH, 2004).

The endometrium is the tissue that lines the uterus (womb). **Endometriosis** is a chronic condition characterised by the growth of endometrial tissue in areas other than the uterine cavity, most commonly in the pelvic cavity, including the ovaries (Farquhar, 2007). Endometrial deposits within the ovary are known as endometriomatas (Hart *et al.,* 2008). Tubal damage

[3] Symptoms of hyperandrogenism include acne and hirsutism or male pattern hair growth, e.g. on the chin, upper lip and chest, and male pattern hair loss.

[4] Premature menopause is menopause that occurs before age 40 years.

can occur as a result of endometriosis. The symptoms include pelvic pain, painful periods, and pain during and after intercourse. These symptoms can vary with some women experiencing several severe symptoms and others no symptoms at all (Farquhar, 2007). There is often a poor correlation between symptoms and the surgical appearance, for example severe endometriosis identified at laproscopy may be associated with mild or no symptoms and severe symptoms such as pelvic pain may occur with only minimal or mild endometriosis identified at laparoscopy (Jacobson et al. 2002). Approximately 20-30% of women with endometriosis have subfertility (Farquhar, 2007).

Failure of infrequency of sexual intercourse may occur for various psychological reasons such as worry about poor sexual performance or emotional or financial stress, which can lead to lower libido and less frequent sexual intercourse. Physical causes include diabetes, heavy smoking or impotence in males, and pain during intercourse or infection in females.

Cervical mucus defects or dysfunction can cause sub-fertility. The cervical mucus acts by transporting and storing spermatozoa. Spermatozoa require an adequate amount of clear, fluid mucus to protect it from the acidity of the vagina and help move it to the upper genital tract. A post-coital test, carried out within one or two days of ovulation, can determine the quality of the cervical mucus and how well the sperm are functioning in the mucus. A sample of cervical mucus needs to be collected around 6-12 hours after normal unprotected intercourse (Reiss, 1998). Cervical mucus may also contain antisperm antibodies, which prevent sperm moving into the upper genital tract.

Uterine abnormalities such as adhesions (or scar tissue) polyps (a projecting mass of overgrown tissue) and submucous fibroids (non-cancerous growths found in the uterus) may cause infertility (NCC WCH, 2004).

2.3 Impact of lifestyle factors on fertility

The table below lists some lifestyle factors for which there is either convincing or probable evidence of a negative impact on fertility. Section 7.8 summarises evidence on factors that affect the outcome of ART, many of which are lifestyle factors.

Table 2 Factors impacting on fertility

Convincing evidence of impact	Probable evidence of impact
Age	Psychological stress
Smoking	Caffeine
Drug use	Alcohol
Weight	Environmental pollutants
Diet	
Physical activity	

Female **age** is the most important determinant of spontaneous conception and treatment related conception (Maheshwari *et al.,* 2008a). Fertility begins to decline in females from the age of 30, although the reduction in fertility is greatest in women in their late 30s and early 40s (Taylor, 2003). The number of competent oocytes in the ovaries declines with increasing age. For women up to 25 years old the cumulative conception rate is 60% at six months and 85% at one year, but conception rates for women aged over 35 are less than half of this (Balen & Rutherford, 2007a). Current recommendations state that women aged over 35 should be classed as having advanced reproductive age and referred more promptly for early investigations and active treatment (NICE, 2004; ASRM, 2006).

There is a significant association between **smoking** and reduced fertility among female smokers (NCC WCH, 2004). It has been estimated that smokers are 3.4 times more likely to take more than a year to conceive than non-smokers, and in each cycle smokers have two thirds the chance of conceiving compared with non-smokers (Taylor, 2003). A large UK longitudinal study (ALSCPAC) found that both active and passive smoking by women is associated with delayed conception (Hull *et al.,* 2000). Smoking has been found to have an adverse effect on fertility and conception as well as most phases of the development of the child in the womb and on post-natal survival (NCC WCH, 2004; Rogers, 2008). Some of the negative reproductive consequences associated with smoking include: quicker depletion of ovarian follicles, conception delay, increased risk of spontaneous miscarriage in both natural and assisted conception cycles, and increased risk of birth defects (ASRM, 2008a)

There are a number of prescribed, over-the-counter and recreational **drugs** that are known to impact on fertility. Non-steroidal anti-inflammatory drugs, commonly used to treat pain or inflammation are know to inhibit ovulation (NCC WCH, 2004). Cytotoxic chemotherapy drugs are also known to cause ovarian failure in some women. Recreational drugs such as marijuana can have an adverse effect on ovulation and cocaine appears to adversely affect tubal function (Mueller *et al.,* 1990).

The time to conceive is longer in women who are over- or under **weight** (BMI[5] of over 25 or less than 19). Obesity and overweight is associated with decreased pregnancy rates, increased requirements for gonadotrophins[6] and a higher miscarriage rate. These differences are evident at a BMI over 25 (Maheshwari *et al.,* 2007). A high BMI is also associated with adverse pregnancy outcomes such as gestational diabetes and hypertension (Chu *et al.,* 2008).

Evidence on the effect of diet composition in fertility is scarce. Several studies investigating the effect of various dietary factors on fertility have been conducted using data gathered from 17,544 women enrolled in the Nurses' Health Study II. These studies found a reduced risk of infertility due to ovulatory disorder among women whose diet favoured foods with a low glycaemic index[7] and a limited intake of nutrients that may increase insulin resistance, such as trans fatty acids (Chavarra *et al.,* 2007). This supports the hypothesis that glucose homeostasis[8] and insulin sensitivity are important determinants of ovulatory function and fertility in otherwise healthy women (Chavarra *et al.,* 2007).

Physical activity is known to be beneficial to general health. Most research conducted on physical activity and reproduction is mainly focused on athletes and vigorous exercise (Homan *et al.,* 2007). Evidence from the large Nurses' Health cohort study showed that an increase in vigorous but not moderate physical activity is associated with reduced relative risk of ovulatory infertility (Rich-Edwards *et al.,* 2002). Physical activity improves insulin sensitivity, which improves ovarian function and therefore the chance of conception (Norman *et al.,* 2004). Physical activity during pregnancy has been shown to improve maternal well being. Although there is a lack of evidence on the effects of low- and moderate-level physical activity on reproductive health, it seems reasonable to assume that, due to the general health benefits of physical activity, it would have some benefit to fertility (Homan *et al.,* 2007).

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5 BMI (Body Mass Index) is a measurement of body fat calculated from an individual's weight and height (weight in kg/ height in metres^2)

6 Two hormones necessary for ovulation are follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones are known as gonadotrophins.

7 Glycaemic Index is a numerical index given to a carbohydrate-rich food that is based on the average increase in blood glucose levels occurring after the food is eaten. Carbohydrates that break down slowly, releasing glucose gradually into the blood stream, have a low glycemic index.

8 The maintenance of glucose levels during fluctuating physiological pressures, such as eating, exercising, resting or disease.

There is some evidence that **psychological stress** negatively impacts on female reproductive performance, although due to the lack of agreement on how to define or measure "psychological stress" it is difficult to conclude any definite causal effect (Homan *et al.,* 2007).

The evidence on the association between **caffeine** and female infertility is inconsistent (NCC WHC, 2004). However, most evidence suggests that caffeine, particularly at high levels, has a negative effect on reproductive performance (Homan *et al.,* 2007). Evidence on the effect of **alcohol** on female fertility is inconsistent, although excessive alcohol consumption is harmful to the foetus (NCC WHC, 2004). Alcohol is a known teratogen[9] and its consumption has been reported to reduce fertility, although the level of consumption associated with risk is unclear (Homan *et al.,* 2007). Drinking one alcoholic drink per week has been reported to be associated with a reduced chance of conception (Hakim *et al.,* 1998). A prospective observational study of 124 women reported more than a 50% reduction in the probability of conception among participants who drank alcohol (Hakim *et al.,* 1998).

There is some evidence that **environmental pollutants** may have an adverse effect on female fertility (Homan *et al.,* 2007). There is strong evidence that heavy metals, in particular lead, impair reproductive function in females; in addition pesticides can alter hormone function and thereby cause adverse reproductive health effects (Mendola *et al.,* 2008). Further good quality studies are required to clarify the effect of environmental pollutants on female fertility.

2.4 Investigating fertility problems

It is estimated, in the general population, that 84% of women would conceive within one year of having regular unprotected sexual intercourse. This percentage is thought to increase to 92% after two year and 93% after three years (NCC WHC, 2004).

The Human Fertilisation and Embryology Authority summarises the likelihood of a couple trying to conceive naturally as:

Of 100 couples trying to conceive naturally:

- 20 will conceive within 1 month
- 70 will conceive within 6 months
- 85 will conceive within 1 year
- 90 will conceive within 18 months
- 95 will conceive within 2 years

[5] A teratogen is a drug or substance capable of interfering with the development of a fetus, causing birth defects.

Initial advice

Couples who are concerned about their fertility should be informed of the figures above and advised that sexual intercourse every 2 to 3 days optimises the chance of pregnancy. However, timing intercourse to coincide with ovulation causes stress and is not recommended (NCC WCH, 2004). Couples should be given advice on general health issues such as folic acid supplementation, rubella status, and cervical smears, and general lifestyle advice on topics including smoking cessation and weight management should be provided (NCC WCH, 2004) [See section 2.3 on the impact of lifestyle factors on fertility].

Initial assessment

Couples concerned about delays in conception should be offered an initial assessment at primary care level. This should involve a full medical, sexual and social history, a physical examination and initial medical tests (for example to check hormone levels and whether ovulation is occurring regularly). Semen tests should also be conducted at this stage to check the quality of the man's sperm.

Guidelines in the UK (CKS, 2007; NICE, 2004; NCC WCH, 2004) recommend the following areas be explored when taking a history:

- The woman's age
- Children born to the woman, and previous pregnancies and miscarriages
- Length of time trying to conceive
- Frequency of sexual intercourse
- Length of time since stopping contraception and the type of contraception
- History and symptoms that may indicate ovulatory problems, such as menstrual cycle details, galactorrhoea[10] or hirsuitism[11] , systemic disease[12] , excessive exercise, weight loss or psychological distress
- History and symptoms that may indicate tubal, uterine, or cervical factors, for example symptoms of pelvic inflammatory disease or endometriosis, a history of sexually transmitted infections or pelvic inflammatory disease, cervical smear history, previous pelvic surgery, and bleeding between periods or after intercourse
- Drug history
- Details of occupation
- Lifestyle factors that may affect fertility

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[10] Galactorrhoea is the secretion of milk from the nipples when there is no lactation. It may be associated with menstrual irregularities, a side effect of certain drugs or occasionally a sign of polycystic ovary syndrome.

[11] Hirsuitism is excessive amounts of facial or bodily hair in otherwise normally feminine women which may be a sign of an underlying hormonal abnormality.

[12] Systemic disease such as thyroid dysfunction, diabetes or inflammatory bowel disease.

Initial tests for women that may be carried out at primary care level include:

- Measuring mid-luteal phase progesterone to confirm ovulation
- Screening for chlamydia
- Gonadotrophin measurement
- Prolactin measurement
- Thyroid function tests

A physical examination should also be conducted to explore whether there are any physical difficulties that may be causing difficulty conceiving.

Referral for further investigation

Couples should be referred for further investigations if they have not conceived after 18 months, the woman is younger than 35 years and, if the history, physical examination and investigations are normal in both partners. Earlier referral is advised for couples if the woman is aged 35 years or more, or there is an abnormality in the history, examination, or investigations in either partner prompts. Such prompts in women include absent or infrequent menstrual periods, previous abdominal or pelvic surgery, pelvic inflammatory disease and sexually transmitted infection, an abnormal pelvic examination, or a known reason for infertility (such as prior treatment for cancer).

Further investigations

When couples are referred for further investigations tubal patency tests are conducted on the woman to determine whether there is any damage (adhesions) or blockages in the fallopian tubes. A hysterosalpingography[13] or hysterosalpingo-contrast sonography (HyCoSy)[14] is carried out when there are no known comorbidities such as pelvic inflammatory disease, endometriosis, or previous ectopic pregnancy (CKS, 2007). If the woman is known to have these comorbidities a laparoscopy and dye procedure is conducted so that tubal and other pelvic abnormalities can be assessed at the same time. This diagnostic laparoscopy and dye is however, more complex and invasive, and is conduced under general anaesthetic. If an abnormality is found during the procedure, it may be possible to deal with it at the same time, and therefore avoid another operation. This operative laparoscope and dye would require additional instrument such as micro scissors to be inserted through additional holes in the abdomen.

The investigations conducted on women are generally more invasive than those carried out on the male partner. It should be noted that even after thorough investigation, no apparent reason for the inability to conceive is found in approximately one in four (25%) of couples [See table 1, page 14].

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[13] Hysterosalpingography is an x-ray of the uterus and fallopian tubes.

[14] Hysterosalpingo-contrast sonography uses ultrasound instead of x-rays to show the flow of a special contrast medium fluid through the fallopian tubes.

Three: Methodology

3.1 Search strategy

The search aimed to identify guidelines, consensus statements and reviews of best practice relating to therapies used to treat infertility in women. The search was conducted in two stages. First, the main search was conducted to identify relevant guidelines, consensus statements and high quality reviews of best practice. Second, the most recent literature and current research being conducted were searched to identify relevant high quality evidence. The sources searched are listed below. A description of these sources is available in appendix I

- NICE guidelines (http://www.nice.org.uk/)
- SIGN guidelines (http://www.sign.ac.uk/index.html)
- UK Health Technology Assessment Programme (http://www.ncchta.org/)
- Canadian Practice Guidelines Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp)
- US National Guidelines Clearinghouse (http://www.guideline.gov/)
- NHS National Library for Health ('guidance finder' & 'protocols & care pathways') (http://www.library.nhs.uk/)
- The TRIP database (http://www.tripdatabase.com/index.html)
- Cochrane Database of Systematic Reviews (CDSR) (http://www.thecochranelibrary.com)
- Database of Abstracts of Reviews of Effectiveness (DARE) (http://www.thecochranelibrary.com)
- Health Technology Assessment Database (http://www.thecochranelibrary.com)
- International Network of Agencies for Health Technology Assessment (INAHTA) (http://inahta.episerverhotell.net/)
- Centre for Research and Dissemination Reviews (CRD) (http://www.crd.york.ac.uk/crdweb/)
- Clinical Knowledge Summaries (CKS) http://www.cks.library.nhs.uk

Guidelines produced by relevant societies and agencies were sought by searching:

- Women's Health Specialist Library (http://www.library.nhs.uk/womenshealth/)

Websites that specifically focus on infertility were also searched. These included:

- ESHRE http://www.eshre.com/
- HFEA http://www.hfea.gov.uk/
- Infertility Network UK http://www.infertilitynetworkuk.com/

The keywords *"infertil*"*, and ("management" or "treatment") were used in the search strategies. The searches were not restricted by language.

Guidelines, consensus statements and reviews of best practice on therapies used to relieve menopausal symptoms published from 2000 were sought. Systematic reviews and meta-analyses published in the Cochrane library from 1997, describing the effectiveness, associated risks and/or additional benefits of treatments for infertility were sought.

The second stage of the search sought to identify very recent good quality systematic reviews, randomised controlled trials (RCTs) and longitudinal studies that described the effectiveness, associated risks and/or additional benefits of infertility treatments. The search was an iterative process using the sources below and searching the reference lists of the papers identified.

- Medline (PubMed) (http://www.ncbi.nlm.nih.gov/sites/entrez)
- Cochrane Controlled Clinical Trials (Cochrane Library)

3.2 Inclusion criteria

The titles and abstracts of the studies identified by the search were read to determine whether they were relevant to this review. The relevance of the identified studies was considered using the inclusion criteria below:

Inclusion criteria

- The study describes the effectiveness of one or more infertility treatment.
- The study describes the risks associated with one or more infertility treatment.

3.3 Quality of evidence

There are a number of different types of study, all with different strengths and limitations. The study quality relates to the degree to which bias is minimised. Bias means something that will cause a consistent deviation from the truth (Alderson & Green, 2002). The likelihood of study results being biased depends on the type of study design and the quality of methods used. Bias can also arise in research funded by an organisation with strong opinions in one direction.

Randomised Controlled Trials (RCTs) are experimental studies, and are considered the best type of study for providing evidence on the effectiveness of an intervention. Participants are randomly allocated to a control or treatment group. The randomisation process ensures participants have a pre-specified (very often equal) chance of being assigned to the control or treatment group. When an RCT is described as "double-blind", neither the participants nor

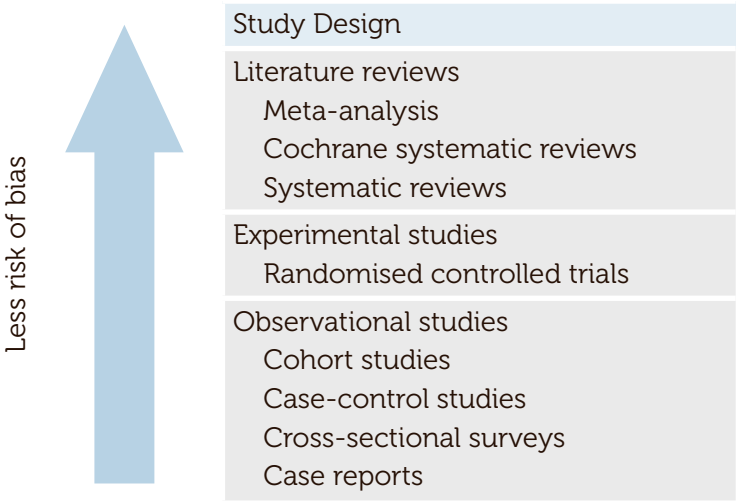
researchers know which group the participants were allocated to. A "placebo-controlled" trial includes a control group of participants who were given a placebo ("dummy pill or treatment") designed to appear the same, but have no physiological effect (Bowling, 2000). Sometimes an improvement is seen in participants receiving a placebo treatment. This is known as the "placebo affect", a known phenomenon, where by study participants receiving a placebo still show a clinical improvement, because of a belief that they are being given a drug treatment. When this is evident in the treatment group, it means that the treatment is no more affective than the placebo.

The methodological factors described above aim to reduce the risk of bias and improve the quality of the research. RCTs, if well conducted, can indicate what treatment is better, although they often cannot identify for whom it is better. This is because RCTs are often carried out on specific types of patients for a relatively short period of time, whereas in practice the treatment would be carried out on a much greater variety of patients.

Observational studies are studies where the subjects are observed in their natural state. Observational studies include cohort studies, case-control studies and cross-sectional surveys. These studies are generally more prone to bias and therefore provide weaker evidence on the effectiveness of interventions compared with RCTs (Guyatt *et al.,* 1995).

Literature reviews, if well conducted, can provide a good summary of evidence. Systematic reviews differ from traditional literature reviews as they use a replicable, scientific and transparent approach that seeks to minimise bias (NHS CRD, 2001). Cochrane systematic reviews, produced by The Cochrane Collaboration (The Cochrane Collaboration, 2005), generally focus on evidence from RCTs because of the common acceptance that RCTs will lead to the most reliable estimates of effectiveness (Higgins & Green, 2006). Cochrane reviews are therefore considered to be very good quality reviews. Finally, a meta-analysis is a study that uses statistical methods to combine the findings from several studies which all address the same question. A hierarchy of study designs is shown in Figure 1.

Figure 1: Hierarchy of study design



(Adapted from: Guyatt *et al.,* 1995)

In this review good quality evidence from guidelines relating to the menopause were initially sought. Evidence from Cochrane reviews, other systematic reviews, and RCTs was also sought. Where evidence was extremely limited or unavailable from these sources, evidence from observational studies was sought.

3.4 Reporting of infertility treatment outcomes

The most relevant outcome to couples is **live birth rate.** As this outcome adds to the time and effort required in order to collect such data, studies may report other outcomes such as ongoing pregnancy rate instead. The definition of ongoing pregnancy rate is often not consistent between studies, but in general is it used to describe a pregnancy that is less likely to miscarry (Daya, 2003). From a clinical perspective the clinical pregnancy rate is the most important outcome to consider. The **clinical pregnancy rate** is defined as a pregnancy where a foetal heartbeat is detected with an ultrasound.

Outcomes such as **ovarian hyperstimulation syndrome** (OHSS) [see section 7.9.2], **ectopic pregnancies, fetal abnormalities,** or **miscarriage** are important to examine when looking at treatment effectiveness. **Multiple births** are considered an undesirable consequence of fertility treatment, and therefore the multiple birth rates, or singleton live birth rates are important outcomes to examine (Daya, 2003). Other outcomes of importance are **cycle cancellation, low birth weight and perinatal mortality** (NCC WCH, 2004).

Most trials report pregnancy rates **per cycle,** when the most important outcome to couples is live birth rate **per couple** (Pandian et al,. 2005). Reporting of per cycle data is statistically inappropriate when it is the women who have been randomised in trial, as many women will have undergone more than one cycle (Johnson *et al.,* 2003). The Cochrane Menstrual Disorder and Subfertility group recommended studies report pregnancy and live birth rates per women/ couple (Johnson *et al.,* 2003).

Pregnancy rate per cycle provides a basic estimate of the likelihood of pregnancy for one cycle of treatment. It use is limited as it provides no information on the reduction in rates that may occur with repeated cycles of treatment (Daya, 2005). As many women will have repeated ART treatment cycles, the cumulative pregnancy rate provides couples with a real view of the chances of success with fertility treatment. The **cumulative pregnancy rate for a given number of treatment cycles** provides a more useful estimate of success compared with the pregnancy rate per cycle of treatment as the probability of a successful outcome following a full course of treatment, which may include multiple cycles, is more important that the individual cycle probability (Myres *et al.,* 2008).

It should be noted that success rates of fertility treatments are often difficult to interpret. For example the live birth rate will be affected by the age of the couples and the type of infertility issues they have (HFEA, 2007/2008).

Four: Overview of infertility treatment options

Fertility treatments can be grouped into three categories:

1. Medicines to improve fertility
2. Surgical treatments
3. Assisted Reproductive Technology

The table below provides a summary of the fertility treatment options. Evidence on the effectiveness of the treatments included in table 3 is provided in sections 5, 6 and 7 of this review.

Table 3 Summary of fertility treatment options

Medicine to improve fertility	Anti-oestrogens
	Gonadotrophins
	Pulsatile gonadotrophin-releasing hormone
	Gonadotrophin-releasing hormone analogs
	Dopamine agonists
	Aromatase inhibitors (experimental)
Surgical treatments	Ovarian drilling
	Fallopian tube surgery
	Uterine surgery
	Surgery for endometriosis
Assisted reproductive technology	IUI (Intrauterine Insemination)
	IVF (In Vitro Fertilisation)
	GIFT (Gamete Intrafallopian Transfer) & ZIFT (Zygote Intrafallopian Transfer)
	ICSI (Intracytoplasmic Sperm Injection)
	Donor insemination (eggs or sperm donation)
	PGD (Pre implantation Genetic Diagnosis)
	IVM (In Vitro Maturation)
Other treatment	NaPro Technology (Natural Procreative Technology)

Medicines may be used to induce ovulation, or to stimulate the production of more than one follicle per cycle. Surgical treatment such as fallopian tube surgery may be an appropriate option in some cases. The third type of fertility treatment is assisted reproductive technology, which relates to all treatments that use methods of conception other than normal sexual intercourse. Finally, a short description of NaPro Technology is provided.

Five: Medicines to improve fertility

Medicines for inducing ovulation can be used to treat women with amenorrhea (absence of menstruation) or who ovulate irregularly (ASRM, 2006). Women who are ovulating themselves may also be treated with ovulation medicines to boost the number of follicles produced per cycle, which leads to the release of multiple eggs. This is known as superovulation, and is used along with assisted reproductive techniques. Therefore, ovulation medicines may be used:

1.) On their own to treat women with ovulatory disorders (ovulation induction), [section 5.1] or

2.) Can be used to 'boost' ovulation along with assisted reproductive techniques (superovulation) [section 5.2].

Some specific causes of infertility can be treated by medication [See section 5.3].

5.1 Medicines used in ovulation induction therapy

5.1.1 Anti-oestrogens (Clomifene citrate - Clomid®)

The anti-oestrogen clomifene citrate (Clomid®) helps stimulate ovulation in women who have infrequent or absent ovulation (ASRM, 2006). Clomifene citrate may be prescribed for women with unexplained infertility and women with polycystic ovary syndrome, and may also be used to stimulate the development of multiple eggs for use with ART such as IUI (ASRM, 2006).

Clomifene citrate works by competing with oestrogen for the oestrogen receptors in the brain. Therefore, the body is tricked into thinking there is not enough oestrogen. The pituitary gland in the brain then releases more follicle-stimulating hormone (FSH) and luteinizing hormone (LH) into the bloodstream. The high level of FSH stimulates the ovary to develop follicles that contain eggs, and the surge of LH causes the egg to be released from the mature follicle in a process called ovulation. An injection of human chorionic gonadotrophin (hCG) may be given to help trigger the release of the egg (ovulation) (ASRM, 2006). Following this, fertilisation of the released egg may be achieved through timed intercourse or IUI depending on the method considered to be most successful. One tablet of clomifene citrate is taken each day for five consecutive days, starting on or around the 5th day after menstruation begins. If the woman has no periods, a period can be induced by administering progesterone or some other progestin (ASRM, 2006). If treatment is initially unsuccessful, the dose may be increased or another medication may be added to improve the chance of ovulation and successful fertilization. The long-term effects of treatment with clomifene are unclear and usually no more than 12 cycles of clomifene are administered (NCC WCH, 2004).

Clomifene is generally well tolerated. Common symptoms occurring in approximately 10% of women treated with clomifene include hot flushes and mood swings, around 2% to 5% of women experience breast tenderness, pelvic discomfort and nausea, and less than 2% experience visual disturbances such as blurred vision or light sensitivity. These side effects usually subside after treatment stops (ASRM, 2003; Hughes *et al.,* 2000).

Tamoxifen is an anti-oestrogen that works in a similar way to clomifene citrate. It has also been used to induce ovulation, although it is not licensed in Ireland for this purpose (IPHA, 2008).

The evidence

Evidence indicates that 70-80% of women with PCOS will ovulate in response to treatment with clomifene citrate (NCC WCH, 2004; Homburg, 2005; Messinis, 2005). However, the number of women who conceive following this treatment is far lower; analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in women ovulating on clomifene citrate (Tarlatzis *et al.,* 2008).

Women with unexplained infertility who are treated with clomifene citrate have no clinical benefit compared with no treatment or placebo (Bhattacharya *et al.,* 2008; Hughes *et al.,* 2000).

Women should be informed of the side effects and risks associated with clomifene citrate treatment. Side effects may include abdominal pain, bloating, hot flushes, nausea and headaches and were experienced by 10-20% of women treated with clomifene citrate in a recent RCT (Bhattacharya *et al.,* 2008). The multiple pregnancy rate associated with clomifene citrate treatment is approximately 8-10% (Hughes *et al.,* 2000). Miscarriage rates of 13-25% have been reported in women who conceived after treatment with clomifene citrate treatment. This rate may be higher than that expected in women with normal fertility with unassisted conception, although this is not clear (Beck *et al.,* 2005).

The recent RCT by Bhattacharya et al. (2008) reported similar rates of miscarriage, ectopic pregnancy and multiple pregnancy in the women treated with clomifene citrate and those with no treatment. Reports of ovarian hyperstimulation syndrome are rare following treatment with clomifene citrate (Beck *et al.,* 2005).

A maximum of six cycles of clomifene citrate is recommended (IPHA, 2008). This relates to the number of cycles within each course of treatment. Many women require more than one course of treatment. Although most authorities suggest clomifene citrate should be given for no more than six menstrual cycles (ASRM, 2006), the review by NICE (2004) suggests there may be some benefit in receiving clomifene citrate for up to 12 cycles. However, use of

clomifene citrate for more than 12 cycles has been associated with an 11% increased risk of ovarian cancer (Rossing *et al.,* 1994) and is not advised (NICE, 2004).

Approximately 15-40% of women fail to ovulate and are resistant to clomifene citrate (Beck *et al.,* 2005). Resistance to clomifene citrate is associated with an increased BMI, although weight loss programmes can improve the response to treatment (NCC WCH, 2004).

5.1.2 Gonadotrophins

For ovarian stimulation

Two hormones necessary for ovulation are follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones are known as gonadotrophins. There are a number of medications used to treat infertility that contain gonadotrophins. FSH is a small protein that would be destroyed by digestive enzymes in the stomach if taken orally; therefore gonadotrophins are given by injection under the skin or into muscle.

Various gonadotrophin preparations can be used to stimulate follicle growth. The main preparation used is human menopausal gonadotrophin (hMG), which contains both LH and FSH. Pure FSH is also available, derived from urine or as a recombinant form. These preparations can stimulate follicular development alone. Recombinant luteinizing hormone (rLH) is also available. Treatment with rFSH and rLH can be used as an alternative to hMG. These preparations are described below:

- hMG (human menopausal gonadotrophin) contains natural FSH and LH extracted and purified from the urine of postmenopausal women who have high levels of these hormones.
- uFSH (urinary follicle stimulating hormone) contains FSH derived from purified urine of postmenopausal women.
- rFSH (recombinant follicle stimulating hormone) contains FSH produced in the laboratory using DNA technology.
- rLH (recombinant luteinizing hormone) contains LH produced in the laboratory using DNA technology.

For follicular maturation

Final maturation of the follicle and the release of the egg are triggered by a surge of LH. Blood tests and ultrasound of the ovaries are used to monitor the growth of the follicles, and to determine when mature eggs have developed inside the follicles. When this stage is

reached, an injection is given of gonadotrophin drugs, which cause the dominant follicle to release its egg (this process is known as ovulation). Until recently, urinary human chorionic gonadotrophin (uhCG) was used to trigger the release of the egg, although DNA technology now provides recombinant human chorionic gonadotrophin (rhCG) and recombinant luteinizing hormone (rLH) as alternatives to uhCG. These drugs are described below:

- uhCG (urinary human chorionic gonadotrophin) has a biological activity similar to LH, although is also contains FSH. It is produced in pregnant women and extracted from the urine.
- rhCG (recombinant human chorionic gonadotrophin) is produced in the laboratory using DNA technology.
- uLH (urinary luteinizing hormone) contains LH derived from purified urine of postmenopausal women.
- rLH (recombinant luteinizing hormone) contains LH produced in the laboratory using DNA technology.

To summarise the process, a women with low hormone levels who is not ovulating can have daily injections of hMG or rFSH for around 12 days to stimulate follicle growth. When blood tests and ultrasound of the ovaries indicate that mature eggs have developed inside the follicles, a single injection of hCG, rhCG or rLH is given to trigger the dominant follicle to release the egg.

Gonadotrophins can be used to stimulate the production of eggs in women who have problems ovulating, or can be used for superovulation along with ART such as IVF, GIFT or IUI treatment. An injection of hCG may be given to some women being treated with clomifene citrate to help trigger release of the egg.

Side effects of gonadotrophins include a higher risk of miscarriage, ovarian hyperstimulation syndrome and multiple pregnancies. Other possible side effects include headaches, abdominal pain or bloating, breast tenderness, swelling or rash at the injection site and mood swings (ASRM, 2006).

The evidence

For the approximate 20-40% of women with PCOS who fail to conceive after treatment with clomifene citrate, an alternative option is treatment with gonadotrophins (Myers *et al.,* 2008).

The Cochrane review by Cantineau et al. (2007) found ovarian stimulation with gonadotrophins increases pregnancy rates significantly compared to anti-oestrogens, without effecting adverse outcomes. The general view is that gonadotrophins result in significant

higher multiple pregnancy rates compared to clomifene citrate, although the evidence in the Cochrane review could not support this. The authors of the Cochrane review conclude that although anti-oestrogens seem to be cost effective in IUI programmes, they appear to be less effective compared to gonadotrophins.

The evidence shows there is no difference between urinary and recombinant gonadotrophins regarding live birth rate, pregnancy rate, multiple pregnancy rate, miscarriage rate or OHSS rate (Al-Inany *et al.,* 2005). Findings from one large RCT showed no significant difference between uhCG and rhCG in clinical pregnancy rates (25% with uhCG compared to 33% with rhCG), live birth rates (23% with uhCG compared to 27% with rhCG), and incidence of OHSS (7% with uhCG compared to 6% with rhCG) (ERHCGSG, 2000). However, rhCG may be more acceptable to patients due to a significantly higher number of mature oocytes retrieved (9.4 with rhCG compared to 7.1 with uhCG), and significantly fewer adverse events (23% with rhCG compared to 45% with uhCG) (ERHCGSG, 2000). There is also no convincing evidence of a difference between urinary FHS (uFSH) and recombinant FSH (rFSH) (Cantineau *et al.,* 2007). The advantages of recombinant gonadotrophins include the purity, availability and consistency between different batches of the drug, although the cost is higher compared with urinary gonadotrophins (Bayram *et al.,* 2001).

When comparing different types of gonadotrophins, evidence from nine RCTs showed there is no evidence to indicate whether FSH or hMG is better, although the trials were too small to make any firm conclusions (Cantineau *et al.,* 2007).

When comparing gonadotrophins alone with gonadotrophins plus GnRH-agonists no significant difference in pregnancy rate, miscarriage rate or OHSS rate. However, data from three RCTs showed a statistically significant higher multiple pregnancy rates per pregnancy (4.5 times higher) when a GnRH agonist had been added (Cantineau *et al.,* 2007). The high cost and increased risk of multiple pregnancies associated with GnRH-agonists in IUI programmes, along with no improvement on the chances of conception, makes the use of GnRH-agonists in this setting not advisable.

When gonadotrophins alone were compared with gonadotrophins plus GnRH-antagonists a statistically significant difference was found in live birth rates in one small RCT with 82 women; 38% of women who received the GnRH-antagonist and 17% of the women who receive the gonadotrophins alone had a live birth (Gómez-Palomares *et al.,* 2005). However, the combined results from five RCTs indicated no benefit in adding a GnRH-antagonist compared to gonadotrophins alone (Cantineau *et al.,* 2007). Slightly more multiple pregnancies occurred with GnRH-antagonists added to gonadotrophins compared to gonadotrophins alone, although the difference was not significant (Cantineau *et al.,* 2007).

Results from four RCTs indicate no benefit in treatment outcomes when doubling the dose of gonadotrophins per day from 75IU to 150IU, although the risk of multiple pregnancies in doing this is significantly increased and the rate of OHSS is significantly higher with a more aggressive ovarian stimulation protocol (Cantineau *et al.,* 2007).

5.1.3 Pulsatile gonadotrophin-releasing hormone

Gonadotrophin releasing hormone (GnRH) is released at regular intervals of around every 60-120 minutes during the follicular phase in a normal menstrual cycle (Bayram *et al.,* 2003). The pulsatile release of GnRH from the hypothalamus[15] in the brain into the blood stream stimulates the pituitary gland[16] to secrete LH and FSH. If a woman is deficient in GnRH, it can be administered to her using a special pump. The pump, which is attached to a belt and worn on the body at all times, helps to mimic the natural pattern of GnRH release. The pump administers a small, regular dose of GnRH through a needle placed under the skin, or into a blood vessel (ASRM, 2006). Infections and locally allergic reactions around the site of the needle may occur, although sterile procedures and changing the needle once or twice a week can limit the risk of infection (Mattle *et al.,* 2008). Possible side effects include stomach pains, sickness and nausea, heavy periods and headaches (HFEA, 2007/2008).

The evidence

The evidence is limited regarding the effectiveness of pulsatile gonadotrophin-releasing hormone. The four RCTs involving 57 women identified in the Cochrane review by Bayram et al. (2003) were too small, of short duration and were of low quality. Therefore, no conclusions could be made on the effectiveness of pulsatile gonadotrophin-releasing hormone based on the evidence available. The data does suggest that pulsatile GnRH may be useful in women who are resistant to clomifene citrate (Bayram *et al.,* 2003).

5.1.4 Gonadotrophin-releasing hormone analogues (GnRH-agonists/ GnRH-antagonists)

Gonadotrophin-releasing hormone (GnRH) agonists can be used along with gonadotrophins to achieve pituitary downregulation and help control the cycle during ovarian stimulation. However, they are not widely used to induce ovulation in women with ovulatory disorders. GnRH analogues are mainly used with assisted reproductive technologies and are discussed in more detail in section 5.2.3.

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[15] The hypothalamus regulates the functions of the pituitary gland in the brain by directing the pituitary to stop or start production of its hormones.

[16] The pituitary gland produces various hormones essential for growth, metabolism, reproduction, and vascular control.

5.1.5 Dopamine agonists

Some women ovulate irregularly due to too much of the hormone prolactin being released from the pituitary gland. This is known as hyperprolactinaemia. High levels of prolactin suppress the pulses of GnRH and therefore prevent ovulation. This results in irregular ovulation and infrequent menstruation, or may result in menstruation stopping completely (ASRM, 2007). The incidence of increased prolactin level in infertile but ovulatory women ranges between 3.8% and 11.5% (CKS, 2007). The dopamine agonists bromacriptine (Parlodel®) and cabergoline (Dostinex®) which are taken orally, may be used to treat this condition, as it reduces the secretion of prolactin, thereby allowing the ovaries to work properly. Possible side effects of the treatment include headaches, drowsiness, dizziness, nasal congestion and nausea (IPHA, 2008).

The evidence

Hyperprolactinemia can be treated by dopamine agonists. Treatment with bromocriptine is an established, inexpensive and safe option, although some women may become resistant or intolerant to this therapy (Crosignani, 2006). Significantly more patients treated with bromocriptine become resistant (18.4%) compared with those treated with cabergoline (10%) (Vilar *et al.,* 2008). The newer dopamine agonist, cabergoline, is better tolerated and is more effective in restoring ovulation and increasing pregnancy rates (Crosignani, 2006). Side effects associated with bromocriptine include nausea, headache, dizziness, abdominal pain and tiredness. Such symptoms may also occur with cabergoline use, although they tend to be milder and less frequent (Crosignani, 2006). Two RCTs published in the mid 1990s found 72% of the women treated with cabergoline had ovulatory cycles or became pregnant during treatment and 48% to 52% of women treated with bromocriptine had ovulatory cycles or became pregnant (Pascal-Vigneron *et al.,* 1995; Webster *et al.,* 1994).

One RCT with 100 women who had PCOS and were resistant to clomifene citrate found there were no significant differences in ovulation or pregnancy rate in women treated with clomifene citrate only and those treated with clomifene citrate and bromocriptine (Parsanezhad *et al.,* 2004).

5.1.6 Aromatase inhibitors (experimental)

Aromatase inhibitors are mainly used to treat breast cancer in postmenopausal women. They work by reducing circulating estradiol[17] levels and reducing the negative feedback that stimulates an increase in pituitary gonadotropin output. As a result, ovarian function increases. Studies show that administering aromatase inhibitors to women during the follicular phase results in the development of mature follicles which, when coupled with human chorionic gonadotrophin (hCG) could be shown to ovulate. Aromatase inhibitors are currently being

[17] Estradiol is the most potent natural oestrogenic hormone secreted by the ovaries.

explored for use in ovarian stimulation. It is thought that aromatase inhibitors used alone result in the development of one or two mature follicles and a very low risk of OHSS and multiple pregnancies; when used in addition to FSH, superovulation should be achieved (Casper & Mitwally, 2006). The aromatase inhibitors letrozole (Femara®) and anastrozole (Arimidex®) are currently the most widely investigated for use in ovulation induction.

The evidence

The Cochrane review by Cantineau et al. (2007) found no significant difference between aromatase inhibitors and anti-oestrogens regarding pregnancy rates, multiple pregnancy rates or miscarriage rates. The evidence was too scarce to determine whether there was any difference in live birth rates or the incidence of OHSS. A recent RCT including 220 infertile women with clomifene citrate resistant PCOS found very similar numbers of women ovulated with letrozole (62%) and anastrozole (63.4%) treatment and similar numbers of women became pregnant with letrozole (12.1%) and anastrozole (15.1%) treatment (Badawy *et al.,* 2008a).

A recent systematic review and meta-analysis of nine studies concluded that letrozole is as effective as other methods of ovulation induction (Requena *et al.,* 2008). For ovarian stimulation with IUI less FSH is required when letrozole is used, which limits the effect of letrozole on the endometrium. During IVF treatment, the use of letrozole may reduce the amount of gonadotrophins administered, and therefore reduce the cost of the IVF treatment cycle (Requena *et al.,* 2008). Further large RCTs are required to investigate the usefulness of aromatase inhibitors in the treatment of infertility.

5.2 Medicines used in superovulation therapy along with ART

5.2.1 Anti-oestrogens (Clomifene citrate – Clomid®)

Clomifene citrate may be prescribed for women with unexplained infertility and women with polycystic ovary syndrome, and may also be used to stimulate the development of multiple eggs for use with ART such as IUI (ASRM, 2006) [See section 5.1.1 for the evidence on the effectiveness of clomifene citrate].

5.2.2 Gonadotrophins

Gonadotrophins can be used to stimulate the production of eggs in women who have problems ovulating, or can be used for superovulation along with ART such as IVF, GIFT or IUI treatment [See section 5.1.2 for a description of gonadotrophins and the evidence of their effectiveness].

5.2.3 Gonadotrophin-releasing hormone analogues (GnRH-agonists/ GnRH-antagonists)

Approximately 8% to 20% of IVF cycles have to be cancelled due to inadequate follicular development and premature surges of luteinizing hormone among women receiving gonadotrophins (Hughes *et al.,* 1992). As GnRH-analogues are ineffective when taken orally, they are taken by injection or nasal spray. GnRH-analogues are often used to prevent spontaneous ovulation when gonadotrophins are given to women undergoing IVF. The pituitary gland in the base of the brain secretes the hormones - luteinizing hormone (LH) and follicle stimulating hormone (FSH). Ovulation is triggered by a surge of LH. When the ovaries are stimulated using medication, the timing of the LH surge may be altered. A premature surge of LH can lead to ovulation before the follicles reach the optimal diameter for triggering ovulation by human chorionic gonadotrophin (hCG) injection. If ovulation occurs too early the eggs are likely to be of poorer quality and therefore less useful in ART such as IUI, IVF or GIFT. GnRH analogues are used to temporarily shut-down the pituitary hormones that control ovulation. This is known as pituitary down-regulation and allows control over the events in the fertility cycle.

GnRH-agonists and GnRH-antagonists work in different ways, but both are used to stop ovulation occurring too early by suppressing the release of gonadotrophins.

GnRH-agonists work by supplying a constant rather than the natural pulsatile pattern of GnRH, which over-stimulates the pituitary gland to release more LH and FSH than normal. After a few days of being over-stimulated, the pituitary gland temporarily shuts down and stops releasing LH and FSH, thus preventing ovulation. There are a number of ways of administering GnRH-agonist that differ according to the length of time they are administered (long or short protocols) and the dose given (short acting daily doses or long-acting depot doses).

The more recently emerged treatment with GnRH-antagonists work by blocking the effect of GnRH on the pituitary gland. While GnRH-agonists act over several days to stop ovulation, GnRH-antagonists stops the pituitary from making LH within an hour or two, and therefore does not have to be used for as many days as an GnRH-agonist. GnRH-antagonists allow treatment cycles to be shorter (less than one month) and avoids oestrogen withdrawal effects associated with the use of GnRH-agonists. Therefore, GnRH-antagonists may be preferred by women (NCC WCH, 2004).

GnRH analogues are most commonly used with gonadotrophins to achieve pituitary down-regulation and help control the cycle in ovarian stimulation during IVF treatment.

The evidence

A meta-analysis of 17 RCTs concluded that the use of GnRH-agonists during IVF treatment significantly increased the clinical pregnancy rate by up to 127%, reduced the number of cycles that had to be cancelled by 67%, and made no difference to the multiple pregnancy rate or spontaneous abortions compared with other ovulation induction treatments that did not use GnRH-agonists (Hughes *et al.,* 1992). When GnRH-antagonists are used, there is a significant decrease in gonadotrophin requirements and a significant decrease in the risk of OHSS compared with the use of GnRH-agonists (Myers *et al.,* 2008), therefore side effects are less compared with GnRH-agonists.

The long protocol involves administering GnRH-agonists for at least 14 to 18 days to stop ovarian activity before administering gonadotrophins. In short protocols, GnRH-agonists are administered for approximately 10-14 days, and about 3 days in ultra-short protocols. A Cochrane review published in 2000 that included 26 RCTs concluded that the long protocol results in better clinical pregnancy rates compared with short and ultra-short protocols for GnRH-agonists use in IVF and GIFT cycles (Daya, 2000). This Cochrane review is currently being updated and should be available later in 2009 (Maheshwari, *et al.,* 2008b). Some evidence published since 2000 indicates that long and short protocols have similar biological effect, for example one RCT including 142 women reported pregnancy rates[18] of around 17% per started cycle for long and short GnRH-agonist protocols (Hohmann *et al.,* 2003). Other studies have also concluded that as the effectiveness of short and long GnRH-agonist protocols are similar, the short protocol is preferable as it requires fewer injections, has fewer side effects and less discomfort for the woman, and is more cost effective (Ho et al. 2008; Ye et al. 2001).

There are two ways of administering GnRH-agonist in the long protocol; a daily dose of GnRH-agonist administered by nasal spray, a long-action dose administered by injection (depot). A Cochrane review including six RCTs found no difference between daily and depot administration of GnRH-agonist regarding clinical pregnancy rates or adverse effects such as abortion rates, multiple pregnancies or OHSS incidence rate (Albuquerque *et al.,* 2005). Depot administration of GnRH-agonist required more gonadotrophins and a longer duration of ovarian stimulation compared with daily administration of GnRH-agonist which make it the more expensive option (Albuquerque *et al.,* 2005).

The review by Myers et al. (2008) found three RCTs that showed pre-treatment with an oral contraceptive, to help schedule when to start the stimulation cycle, followed by a GnRH-antagonist, resulted in lower pregnancy rates, significantly lower in one RCT. A more recent systematic review and meta-analysis concluded there was no statistically significant difference

[18] Pregnancy rate defined as a positive heart beat on ultrasound at 12 weeks gestation.

in pregnancy rates between patients pre-treated with the oral contraceptive pill and those who were not (Griesinger *et al.,* 2008), although more evidence is required to make any strong conclusions.

Side effects experienced by women undergoing ovarian stimulation with GnRH-agonist and gonadotrophins for IVF experienced tiredness, depression, irritability headache, nausea, swelling and abdominal pain (Tapanainen *et al.,* 1993).

5.3 Medicines used in to treat specific causes of infertility

5.3.1 Uterine fibroids

Uterine fibroids may be treated with GnRH analogues. GnRH analogues work by controlling the bleeding and reducing the size of the fibroids (Lethaby *et al.,* 2001). However, when treatment is stopped, the fibroids re-grow and symptoms recur in the majority of women [See section 5.1.4 and 5.2.3 for more details on GnRH-analogues].

GnRH analogues are the most widely used medical treatment for uterine fibroids (Sankaran & Manyonda, 2008). Although they effectively reduce bleeding and decrease fibroid size, they can only be used for up to six months as they can cause thinning of the bones (Gupta *et al.,* 2006; RCR & RCOG, 2000). It is estimated that up to 6% of bone mineral density might be lost in the first six months of GnRH therapy (Taylor & Gomel, 2008). Therefore, their main use is for reducing fibroid size before surgery, to make the operation easier (Sankaran & Manyonda, 2008) [See section 6.3 Uterine surgery].

5.3.2 Endometriosis

As endometriosis appears to be an oestrogen dependent condition, treatment with ovulation suppression agents such as oral contraceptives may be useful in some cases.

Using medication to stop ovulation and the production of oestrogen for up to six months is effective in relieving pain caused by endometriosis, but it does not appear to improve fertility (Hughes *et al.,* 2007).

Six: Surgical treatments

Sometimes the cause of infertility can be treated by an operation. For example, surgery is an option for some patients with tubal damage, PCOS, adhesions, endometriosis and uterine abnormalities. Since the development of ART, surgical treatments to improve fertility have become unnecessary and therefore much less common, as IVF, for example, is unaffected by blockages in the fallopian tubes. However, women may still be treated with tubal surgery if the doctor considers the outcome will be good or if IVF is not available to the couple (Ahmad *et al.,* 2006).

6.1 Ovarian drilling (surgical method of ovulation induction)

Women with PCOS have difficulty ovulating. Approximately 20-40% of women with PCOS fail to conceive after treatment with clomifene citrate (Myers *et al.,* 2008). Ovulation can be induced surgically by a procedure called ovarian drilling or ovarian diathermy. This procedure is useful in women with PCOS who are resistant to treatment to clomifene treatment (NCC WCH, 2004). Ovarian drilling is conducted laparoscopically (keyhole surgery) through a small incision at the navel. Several small incisions are made on the surface of the ovary using heat or a laser. This process helps to correct hormone abnormalities and trigger ovulation (NCC WCH, 2004).

The evidence

Laparoscopic ovarian drilling (LOD) with diathermy is usually the second-line treatment for ovulation induction in women with PCOS who are resistant to clomifene citrate treatment. A recent RCT including 65 women with PCOS showed that treatment with clomifene citrate is more effective than LOD; with pregnancies occurring in 44% of women treated with clomifene citrate and in 27% of women treated with LOD (Amer *et al.,* 2009). However the live birth rates were only slightly higher in the clomifene citrate group (56%) compared with the LOD group (46%). A recent review of the literature reported spontaneous ovulation rates varied between 30% and 90% and pregnancy rates varied between 13% and 88% after LOD in women who were resistant to clomifene citrate. The reasons for the wide range of rates is likely to include the small number of women in some of the studies and short-term follow-up, and the variations in LOD procedures (for example the number and depth of punctures made) (Seow, K-M *et al.,* 2008).

The effectiveness of LOD appears to be significantly reduced in women older than 35 years, regarding ovulation rate, pregnancy rate and abortion rate (Palomba *et al.,* 2006). Approximately 20-30% of anovulatory women with PCOS fail to respond to LOD (Hughes *et al.,* 2000). Women with PCOS with a BMI of 35kg/m^2 or over, marked hyperandrogenism[19] and/or have been infertile for over three years appear to be poorer responders to LOD (Amer *et al.,* 2004).

[19] Hyperandrogenism is a condition characterized by excessive secretion of androgens (males sex hormones).

A Cochrane review of nine RCTs compared the effectiveness of LOD (with or without medical ovulation induction) to ovulation induction with gonadotrophins for women with PCOS and clomifene resistance (Farquhar *et al.,* 2007). The review found no difference in pregnancy or ovulation outcomes after 12 months follow-up between the two treatments, however, multiple pregnancy rates were higher among women treated with gonadotrophins whereas they were almost non-existent in women who conceived following LOD (Farquhar *et al.,* 2007). It is recommended that women with PCOS who have not responded to clomifene citrate should be offered LOD because it is as effective as gonadotrophin treatment and is not associated with an increased risk of multiple pregnancies (NCC WCH, 2004).

The most common adverse effect of LOD is post-operative adhesions, although the reported incidence in studies varies widely from 0% to 100% (Seow *et al.,* 2008). There is also a risk that LOD will affect ovarian reserve and potentially lead to ovarian failure and premature menopause (Seow *et al.,* 2008). Further evidence is currently required to determine the long-term effects of LOD on the ovary such as the potential benefits (repeated spontaneous ovulations and further pregnancies) and the potential risks (premature ovarian failure) (Farquhar *et al.,* 2007). There is evidence from some small studies that improvements in menstrual regularity and reproductive performance is still apparent up to nine or ten years after the procedure (Amer et al, 2002; Mohiuddin *et al.,* 2007). There is also some evidence that LOD reduces miscarriage rate by approximately 17% in women with PCOS who are resistant to clomifene citrate (Amer et al, 2002).

Three small RCTs included in the Cochrane review by Farquhar et al. (2007) found no difference between ovulation rates or pregnancy rates between LOD of one ovary compared with drilling both ovaries. A recent small RCT found that LOD of one ovary was as effective as drilling both ovaries, and was quicker to perform and likely to be associated with fewer complications (Youssef & Atallah, 2007). Benefits have been shown with as few as four punctures per ovary (Tarlatzis *et al.,* 2008) although more evidence is required to determine the optimum number of holes (Farquhar *et al.,* 2007). The number of punctures should be kept as low as possible as more punctures may induce ovarian failure (Seow, K-M *et al.,* 2008).

The new technique of ovarian drilling using ultrasound to guide the needle was recently compared in an RCT with traditional laparoscopic electrosurgical drilling for 163 patients with polycystic ovary syndrome (Badawy *et al.,* 2008b). No significant difference was found between the two groups regarding pregnancy outcomes such as resumption of regular menstruation, regular ovulation and pregnancy rates. The pregnancy rate among women treated with the traditional laparoscopic electrosurgical drilling was 24.7%, and 21.9% among those treated with ultrasound-guided ovarian needle drilling. This new procedure is quick to conduct and patients recover rapidly, making it an attractive alternative to the traditional laparoscopic electrosurgical drilling procedure.

6.2 Fallopian tube surgery

A blockage or damage inside the fallopian tubes (or salpinges) can be treated using various surgical procedures depending on the location of blockage and type of damage. A **hysterosalpingography** (HSG) is a procedure that can be used to diagnose problems in the uterus or fallopian tubes. It involves taking x-rays of the reproductive tract after a radio-opaque solution (or dye) is injected through a catheter placed in the cervix. The HSG procedure may also be considered as a treatment. The dye can be used to 'flush' the fallopian tubes to remove any blockages (Johnson *et al.,* 2007). Tubal flushing can be carried out with oil-soluble or water-soluble dye.

The introduction of IVF led to a reduced requirement for tubal surgery, however for couples who decide against IVF treatment for personal reasons, tubal surgery may be the only other treatment option available to them (Pandian *et al.,* 2008). The options for couples with tubal infertility are expectant management (waiting to become pregnant without treatment), IVF and tubal surgery.

Tubal damage is often caused by a pelvic infection which can destroy cells lining the tubes and result in adhesions or scars. Sexually transmitted infections such as chlamydia or gonorrhoea, infection after a pregnancy termination or miscarriage, or the use of intra-uterine contraceptive devices can result in damage to the fallopian tubes. Endometriosis can also result in damage to the fallopian tubes. Scar tissue within the tubes impedes the movement of eggs from the ovary to the uterus, and is associated with an increased risk of ectopic pregnancies (pregnancies outside the uterus).

Salpingolysis or **fimbriolysis** can be done by laparotomy (through the abdomen) along with the use of a microscope to magnify the area or by laparoscopy (minimally invasive surgery though small holes). Salpingolysis and fimbriolysis involve releasing the fallopian tubes from adhesions by cutting the adhesions out, usually using electrosurgery (also known as surgical diathermy). This involves using an electric current to heat a thin electrocautery needle that destroys the scar tissue.

When the end of a fallopian tube is damaged, watery fluid may build-up within the tube causing a hydrosalpinx. If left untreated hydrosalpinx can cause infertility and can cause treatment with IVF to fail. A **salpingostomy** may be carried out to form a new opening in the tube. This new opening replaces the normal opening in the fallopian tube through which the egg released by an ovary is collected. This procedure can be done by laparatomy or laparoscopy. A **salpingectomy** may be used to treat an ectopic pregnancy or an infection in the fallopian tube, although the more conservative procedure – salpingostomy, may be the preferred option.

Tubal anastomosis involves surgically removing a blocked section of a tube and then rejoining the freshly open ends that were on either side of the removed section. This procedure can be carried out to treat unintentional blockages (caused for example by infection), or to reverse intentional blockages (in women who have been sterilised).

If the blockage in the fallopian tubes is limited, treatment by conducting a **tubal canalisation** procedure may be appropriate. This process involves pushing a wire or catheter through the blockage to open it up. The procedure is done by passing a wire or catheter up through the vagina and through the cervix and uterus, into the fallopian tube. The physician is guided through this process by fluoroscopy[20] or via a hysteroscope[21].

Table 4 Procedures for treating tubal subfertility

Type of procedure	Description
Hysterosalpingography (HSG)	A special X-ray procedure in which a small amount of fluid is injected into the uterus and fallopian tubes to detect abnormal changes in their size and shape or to determine whether the tubes are blocked. The procedure may also be considered a treatment as the fluid can flush out the tubes and remove any blockages.
Salpingolysis	The removal of adhesions around the outside of the tube (nearest the uterus).
Fimbriolysis	The removal of adhesions from the fimbrial end of the tube (nearest the ovary).
Salpingostomy (or Neosalpingostomy)	Forming a new opening in the tube that is completely blocked at its outer fimbrial end.
Salpingectomy	The removal of one or both of a woman's fallopian tubes
Tubal anastomosis	Rejoining a tube after cutting out a blocked part.
Tubal canalization	Pushing a wire through a blockage.

[20] Fluoroscopy is an imaging technique that using a continuous x-ray and a fluorescent screen which allows the surgeon to see what is going on inside the body in real time.

[21] A hysteroscope is a very thin telescope (about 3-5mm in diameter) that is inserted through the vagina and cervix.

The evidence

Although mainly used to diagnose problems in the uterus or fallopian tubes a hysterosalpingography can also be used to "flush" the tubes in a procedure known as tubal flushing. Tubal flushing with an oil-soluble contrast material (or dye) seems to increase the chances of pregnancy and live birth by approximately three-times when compared to no intervention. The increase is especially noticeable among women with endometriosis who have normal patent fallopian tubes, where the chance of pregnancy is increased by almost seven-times and the chance of live birth is increased by just over five-times (Johnson *et al.,* 2007). Further research is required, but tubal flushing with oil-soluble material could prove to be a simple, less invasive and a less costly alternative to IVF where the women has normal unblocked fallopian tubes (Johnson *et al.,* 2007).

A recent Cochrane review published in July 2008 concluded there was not sufficient evidence to determine the effectiveness of fallopian tube surgery to overcome infertility caused by tubal disease (Pandian *et al.,* 2008). Most of the evidence on the effectiveness of tubal surgery was published around 20 years ago, before IVF became available. Evidence from a cohort study indicated that 29% of women who underwent surgery became pregnant within three years compared to 12% of women who did not have surgery (Wu, 1988). Live birth rates of 27%, 47% and 53% within one, two and three and a half years were reported in a case series study of women with proximal tubal damage who underwent tubal anastomosis (Paton, 1987).

A Cochrane review found that surgically removing blocked or damaged fallopian tubes before IVF treatment can increase pregnancy rates (Johnson *et al.,* 2004). Surgery to remove affected fallopian tubes before IVF treatment approximately doubles the chances of having a live birth compared to no treatment before IVF (Johnson *et al.,* 2004). Clinical guidelines recommend that for women with proximal tubal obstruction[22], selective salpingography plus tubal catheterisation, or hysteroscopic cannulation may be treatment options as they all improve the chance of pregnancy (NCC WCH, 2004).

The woman's age, the number of children desired, co-existing infertility factors, risks for ectopic and multiple pregnancy and treatment costs are among the main factors to consider before deciding on tubal surgery and IVF (ASRM, 2008). Despite being expensive and invasive, IVF is the preferred choice over tubal surgery for older women with declining reproductive potential and significant tubal damage (ASRM, 2008b; Pandian *et al.,* 2008).

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[22] The proximal end of the fallopian tube is nearest the uterus.

6.3 Uterine surgery

Surgery may be required to treat uterine abnormalities such as **uterine fibroids, intrauterine adhesions** and **septate uterus.**

6.3.1 Uterine fibroids

Uterine fibroids (also known as myomas) are the most common benign (non-cancerous) tumour found in women. Fibroids are benign swellings of the muscle wall of the uterus. The reported incidence of fibroids in women of reproductive age varies widely from 5.4% to 77% depending on the method of diagnosis (Lethaby and Vollenhoven, 2005). Most women (50-80%) with fibroids have no symptoms. Symptoms that may occur include heavy and prolonged periods, pelvic and period pains, or pressure symptoms (Buttram and Reiter, 1981). Around 27% of women with fibroids may be infertile and 3% may have recurrent pregnancy loss (Buttram and Reiter, 1981). The cause of fibroids is unclear. The risk of fibroids is increased in women who have never been pregnant and women who are obese (Lethaby and Vollenhoven, 2005), and the incidence increases towards the end of a woman's reproductive years (Griffiths *et al.,* 2006). Many women with relatively large fibroids conceive without any intervention. However, there is an increased risk of miscarriage, pain, premature and or a complicated labour and haemorrhage after giving birth (RCR & RCOG, 2000).

Uterine fibroids can be removed surgically by performing a myomectomy, which involves carefully removing the fibroids while leaving the womb in place. This procedure can be done by laparotomy (surgery through an incision made in the abdominal wall) or by laparoscopy (a thin, telescope-like viewing instrument is inserted through an incision in the abdomen to look for abnormalities inside the uterus), or hysteroscope[23]. The aim of the surgery is to restore normal uterine structure, return normal menstrual function and enhance fertility (Taylor and Gomel, 2008).

Uterine artery embolization (UAE) or uterine fibroid embolization (UFE) is a new minimally invasive procedure that involves placing a small catheter into an artery in the groin and directing it to the blood supply of the fibroids. Small particles are injected through the catheter. These particles block the arteries that provide blood to the fibroids, thus causing them to shrink. A contrast material can also be injected through the catheter to allow pictures of the blood vessels to be obtained by x-ray. The procedure can be conducted under general anaesthetic or conscious sedation, epidural, or spinal anaesthesia (Gupta *et al.,* 2006).

[23] A hysteroscope is a very thin telescope (about 3-5mm in diameter) that is inserted through the vagina and cervix.

The evidence

The main surgical approach for treating uterine fibroids whilst leaving the uterus in place is **myomectomy**. There is currently not enough evidence to recommend which method of myomectomy is better in terms of fertility outcome (Griffiths *et al.,* 2006). A Cochrane review (Griffiths *et al.,* 2006) investigating the effectiveness of myomectomy via laparotomy, laparoscopy or hysteroscopy identified only one relevant RCT (Seracchiolo *et al.,* 2000). This RCT compared the efficacy of laparotomic myomectomy with laparoscopic myomectomy. No difference was found in fertility outcomes such as pregnancy rates (55.9% after laparotomy versus 53.6% after laparoscopy) or abortion rates (12.1% after laparotomy versus 20% after laparoscopy). Although the average operating time is slightly longer for laparoscopy (100 minutes compared to 89 minutes for laparotomy) the average hospital stay for patients undergoing laparoscopy was significantly shorter (76 hours compared to 143 hours for laparotomy) (Seracchiolo *et al.,* 2000). Other reported benefits of laparoscopy were less febrile illness[24], less blood loss and less post-operative pain compared with laparotomy (Seracchiolo *et al.,* 2000). Women should be aware of the risks of myomectomy to her future fertility. There is a small risk of excessive haemorrhage during surgery that might necessitate an emergency hysterectomy (RCR & RCOG, 2000; Griffiths *et al.,* 2006). Adhesions or scarring left inside the pelvis after myomectomy can decrease the chance of becoming pregnant and increase the chance of uterine rupture in future pregnancies (although uterine rupture during pregnancy is a rare event) (RCR & RCOG, 2000). Microsurgical techniques used during surgery and adhesion-reducing agents used after surgery can reduce the formation of adhesions (RCR & RCOG, 2000).

Results from two large cohort studies (the FIBROID and HOPEFUL studies) show that the majority of women treated with **utrine artery embolization (UAE)** or uterine fibroid embolization (UFE) have a significant reduction in symptoms, return to a normal quality of life within six months of the operation and treatment is effective for 3-5 years (Goodwin *et al.,* 2008; Hirst *et al.,* 2008). However these studies reported that between 14% and 23% of patients required an additional procedure for symptoms by three to seven years after the operation. Although UAE is less invasive than myomectomy and has been shown to be as safe and as effective at reducing symptoms as myomectomy, there remains some uncertainty on the effects of UAE on women who become pregnant after the procedure. A recent RCT comparing myomectomy to UAE reported significantly more pregnancies (33% vs. 17%), deliveries (19% vs. 5%) and fewer abortions (6% vs. 9%) among women treated with myomectomy compared to UAE (Mara *et al.,* 2008). UAE may also increase the risk of miscarriage, pre-term delivery and postpartum bleeding[25] (Agdi & Tulandi, 2008). For women who wish to retain their fertility

[24] An illness of sudden onset accompanied by fever.

[25] Postpartum bleeding of up to 500ml is normal in women in first 24 hours after giving birth. Uterine discharge of blood, tissue and mucus from vagina may continue for several days and gradually decrease in amount during the weeks following childbirth.

and are unwilling to have a hysterectomy under any circumstance, myomectomy currently remains the best treatment option for uterine fibroids (Hirst *et al.,* 2008; SOGC, 2005; RCR & RCOG, 2000).

6.3.2 Intrauterine adhesions

Intrauterine adhesions, also known as Asherman's syndrome, are quite rare, with the prevalence rate in the general population estimated to be 1.5% (Al-Inany, 2001). Asherman's syndrome mainly occurs when trauma to the endometrial lining triggers the normal wound-healing process, which causes the damaged areas to fuse together. Treatment involves surgery to cut away scar tissue and afterwards oestrogen supplements may be prescribed to stimulate uterine healing or subsequent surgery to cut away newly formed adhesions (Ashermans Syndrome website, 2008).

The evidence

Hysteroscopic surgery is the main procedure for diagnosis and treatment of intrauterine adhesions (Yu *et al.,* 2008). The pregnancy rates range from 22% to 45%, and live births range from 28% to 32% in women who have received treatment for intrauterine adhesions (Berman, 2008). Surgical treatment is usually followed by hormonal treatment to help the endometrium to re-grow and new anti-adhesive barriers may also prevent recurrence of intrauterine adhesions (Kodaman & Arici, 2007). Women who become pregnant after being treated for intrauterine adhesions should be monitored closely as there is a high risk of complications such as spontaneous abortion, pre-term delivery, intrauterine growth restriction, placenta accreta or praevia[26], or even uterine rupture (Yu *et al.,* 2008).

6.3.3 Septate uterus

Septate uterus is a congenital abnormality where the uterus is divided by a wall of tissue (or septum). Although a uterine anomaly such as septate uterus is not an infertility factor in itself, it seems to have an impact in delayed natural conception and poor pregnancy outcomes (Grimbizis *et al.,* 2001). Septate uterus is the most common congenital anomaly among infertile women (Saravelos *et al.,* 2008). Four out of five women (79%) with untreated septate uteri will have a miscarriage and around one in 10 (9%) will have a pre-term delivery (Homer *et al.,* 2000). A recent critical review of studies suggested that the prevalence of congenital uterine anomalies is approximately 6.7% in the general population, 7.3% in the infertile population and 16.7% among women who have recurrently miscarried (Saravelos *et al.,* 2008). A surgical procedure known as hysteroscopic metroplasty can be used to treat septate uterus. A hysteroscope is a very thin telescope-like tube that can be inserted into the uterus through the vagina and cervix. Metroplasty refers to surgical reconstruction of the uterus.

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[26] Placenta accreta is a condition where the placenta is implanted too deeply and does not separate easily at delivery. Placenta praevia is when the placenta implants itself unusually low in the uterus, next to or covering the cervix.

The evidence

The largest study published to date of 61 women with uterine septa and otherwise unexplained infertility, reported that 41% conceived within 14 months of having a hysteroscopic metroplasty, and approximately 30% had a live birth, with two thirds delivered by caesarean section (Pabuccu and Gomel, 2004). A review of retrospective studies suggested that pregnancy rates after hysteroscopic metroplasty improved to approximately 80% and miscarriage rates were only around 15% (Homer *et al.,* 2000). For women who do become pregnant after hysteroscopic metroplasty close monitoring is advisable, even when no complications were experienced at surgery, as rupture of the uterus remains a risk during pregnancy (Homer *et al.,* 2000).

6.4 Surgery for endometriosis

Endometriosis has in the past been treated medically with ovulation suppression agents. Although this approach is effective at relieving pain, the evidence indicates it is not effective at improving fertility, and can cause adverse effects such as weight gain, hot flushes and bone loss (Hughes *et al.,* 2007). There is no evidence to support the use of medical treatment in women with endometriosis who wish to conceive (Hughes *et al.,* 2007) and therefore it should not be offered (NCC WCH, 2004). Surgery aims to remove or destroy all visible endometrial growths by cutting them away or by using a heat source or laser to burn the growths. The two surgical methods are (i) ablative surgery, which aims to destroy the growths where they are found using electrical heat or laser; and (ii) excisional surgery, which aims to cut out and remove all endometriosis growth.

The evidence

A Cochrane review that combined the results of two RCTs reported that laparoscopic surgery in the treatment of minimal and mild endometriosis improved fertility (Jacobson *et al.,* 2002). The pregnancy rate of women with mild endometriosis was found to be 81% after laser laparoscopy and 84% after laparotomy, compared with 54% with medical treatment (Paulson *et al.,* 1991). Evidence from cohort studies also suggest that surgery in the treatment of moderate and severe endometriosis improves fertility with similar or slightly higher pregnancy rate after laparoscopy (54-66%) compared with laparotomy (36-45%) (NCC WCH, 2004). A recent review of the best available evidence estimated that the absolute increased chance of conceiving after surgery for endometriosis-associated infertility is between 10 and 25% (Vercellini *et al.,* 2009). Post-operative treatment with hormones does not improve pregnancy rates after surgery and therefore is not recommended (NCC WCH, 2004).

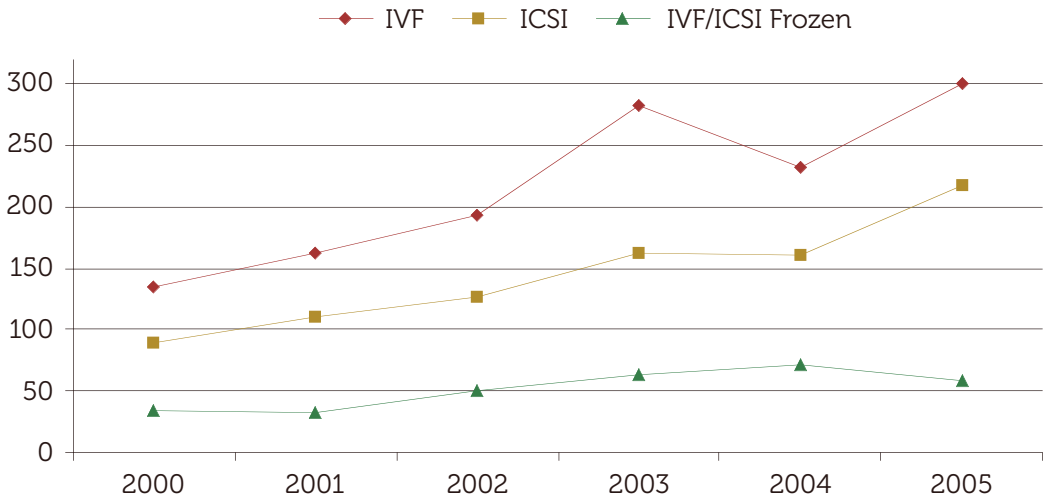
A recent Cochrane review examined the available evidence on the most effective technique for treating ovarian endometrioma[27]; either surgical excision of the cyst or surgical ablation of the cyst by draining the contents and destroying the cyst wall with electrical heat or laser (Hart *et al.,* 2008). The evidence suggests that surgical excision results in more favourable outcomes than surgical ablation for spontaneous pregnancy in women who were previously subfertile with an endometrioma. For women who may undergo fertility treatment following the surgery, there is currently insufficient evidence to determine the best surgical technique with regard to achieving pregnancy (Hart *et al.,* 2008). A recent review of the best available evidence concluded that the use of surgery before, after, or as an alternative to IVF needs clarification (Vercellini *et al.,* 2009).

[27] Endometrioma is a type of cyst formed when endometrial tissue grows in the ovaries.

Seven: Assisted Reproductive Technology

The most recent data shows that in Ireland in 2005 there were 301 babies delivered following IVF using fresh embryos, 217 deliveries following ICSI using fresh embryos and 59 deliveries following either ICSI or IVF using frozen embryos (Nyboe Andersen *et al.,* 2009). The number of deliveries following IVF and ICSI with fresh embryos and IVF and ICSI with frozen embryos has generally been increasing in Ireland (Figure 2).

Figure 2 Number of deliveries following ART in Ireland



Source: Andersen *et al.,* 2006-2008; Nyboe Andersen *et al.,* 2009

7.1 Intrauterine insemination (IUI)

Intrauterine insemination is the process of inserting sperm into the woman's uterus. This is done using a fine plastic tube that is passed through the cervix and into the uterus. The procedure is timed to coincide with the release of an egg or eggs (ovulation) in a natural or a stimulated cycle. Ultrasound and hormonal analysis are used to monitor progress throughout the treatment. If successful, fertilization takes place in the uterus. This technique requires that the woman have normal fallopian tubes and a uterus. IUI is particularly useful where women have deficient cervical mucus, ovulatory dysfunction, or endometriosis; or there is male factor infertility[28] or unexplained infertility (Duran *et al.,* 2002). It is often used before resorting to

[28] For example, low semen volume, poor sperm parameters (volume, density, motility, viability and normal morphology), or defects of sperm-cervical mucus interaction.

more complex and invasive ART such as IVF, with or without ICSI (Duran *et al.,* 2002). The majority of pregnancies occur during the first six cycles, and the number of attempts should not exceed nine cycles (ESHRE, 2008).

IUI may involve timed insemination of sperm into the uterus during a natural cycle, or insemination following ovarian stimulation using, for example, anti-oestrogens or gonadotrophins (NHS WCH, 2004). When the ovaries are stimulated, more eggs are released, which increases the chance of conception. However, this also increases the risk of multiple pregnancies (Cantineau & Cohlen, 2007).

Correct timing of insemination is vital for the success of the IUI as spermatozoa and oocytes have only a limited period of time to survive (Janssen *et al.,* 2008). Generally one insemination (single) is conducted per cycle, although two inseminations (double) may be conducted as this is thought to increase the chance of conception (Cantineau *et al.,* 2003).

While the IUI technique places sperm directly into the uterus, fallopian tube perfusion is a technique that places sperm into the woman's fallopian tube and therefore closer to the eggs. Fallopian tube perfusion involves a pressure injection of sperm suspension that ensures the sperm flush right through the fallopian tube (Cantineau *et al.,* 2004).

An alternative method of insemination is intracervical insemination (ICI). This involves injecting semen high into the cervix. Unlike IUI where the semen has to be prepared or washed, raw or unwashed semen can be used in ICI (Besselink *et al.,* 2008).

The evidence

IUI effectiveness

The most recent data from the European Society of Human Reproduction and Embryology (ESHRE) shown that in 2005 in Ireland 1,194 cycles of IUI with husband semen were performed in women aged under 40. This resulted in 110 pregnancies giving a pregnancy rate of 9.2% per procedure (Nyboe Andersen *et al.,* 2009). The corresponding figures in women aged 40+ are far lower, 199 cycles were performed which resulted in 11 pregnancies giving a pregnancy rate per procedure of 5.5%.

IUI with donor semen is far less commonly conducted in Ireland [See section 7.5, table 21]. It is recommended that couples with mild male factor fertility problems, unexplained fertility problems or minimal to mild endometriosis should be offered up to six cycles of IUI as this increases the chance of a pregnancy (NHS, 2007; NCC WCH, 2004).

Table 5 Intrauterine insemination with husband semen in 2005

		Cycles N	Pregnancies N (%)	Singleton N (%)	Twin N (%)	Triplet N (%)
Women aged under 40	Ireland	1,194	110 (9.2)	94 (85.5)	8 (7.3)	0 (0.0)
	Europe	120,613	15,154 (12.6)	11,787 (87.9)	1,470 (11.0)	156 (1.1)
Women aged 40+	Ireland	199	11 (5.5)	10 (90.9)	0 (0.0)	0 (0.0)
	Europe	8,295	617 (7.4)	574 (94.4)	30 (4.9)	4 (0.7)

Note: Europe - Data was available from 21 European countries.
Source: Nyboe Andersen et al. (2009)

The success of IUI depends on several factors such as the cause of infertility, ages of partners, sperm quality and duration of infertility (Rowell & Braude, 2003) and variations in the procedure such as including ovarian stimulation. Using different implantation techniques may also influence the outcome. The evidence of effectiveness is summarised below.

IUI vs. timed intercourse

IUI is often used for couples with male factor subfertility (Bensdorp *et al.,* 2007). It can be used with or without ovarian stimulation. A recent Cochrane review investigating the effectiveness of IUI for male subfertility found a lack of good quality evidence from RCTs comparing IUI with timed intercourse. Therefore, no firm conclusions can currently be made regarding the effectiveness of IUI versus timed intercourse, in either natural or ovarian stimulated cycles, as more evidence is required (Bensdorp *et al.,* 2007).

Stimulated IUI vs. IUI only

A Cochrane review investigating IUI for male subfertility found no significant difference in live birth rate or pregnancy rate per couple for women treated with IUI with and without ovarian stimulation (Bensdorp *et al.,* 2007). When IUI is used to manage male factor fertility problems, ovarian stimulation should be avoided as it is no more clinically effective than un-stimulated IUI, and it is associated with a risk of a multiple pregnancy (NCC WCH, 2004). A Cochrane review investigating IUI for unexplained infertility concluded that the pregnancy and live birth rates following IUI with ovarian stimulation were just over double the rates following IUI without ovarian stimulation (Verhulst *et al.,* 2006). However, guidance from NICE recommends that ovarian stimulation should not be offered along with IUI for treating couples with unexplained fertility problems due to the risk of multiple pregnancies (NCC WCH, 2004). More evidence is required to determine the size of the multiple pregnancy risk with IUI with ovarian stimulation (Verhulst *et al.,* 2006). However, recent data (see table 5 above) indicates

that that IUI with mild ovarian stimulation is a relatively effective and safe treatment option with twin rates across Europe of around 11% (Nyboe Andersen *et al.,* 2009).

Type of ovarian stimulation protocols with IUI

A recent Cochrane review investigated which ovarian stimulation protocol maximised the chance of becoming pregnant while minimising the risk of multiple pregnancies and OHSS (Cantineau & Cohlen, 2007). The review reported that the combined results of seven RCTs showed ovarian stimulation with gonadotrophins significantly improved the pregnancy rate per couple when compared with ovarian stimulation with anti-oestrogens (clomifene citrate), however no difference in live birth rate was found, although only one study reported this outcome (Cantineau & Cohlen, 2007). The rates of multiple pregnancies, miscarriages and OHSS were similar in IUI with gonadotrophin and IUI with anti-oestrogen stimulation (Cantineau & Cohlen, 2007). The evidence indicates that GnRH-agonists are expensive and increase the number of multiple births without increasing the chance of pregnancy. Therefore, GnRH-agonists should not be used along with IUI. More evidence on the effectiveness of GnRH-antagonists with IUI is required before any recommendations can be made regarding their use. Current data is unclear as to whether aromatase inhibitors, such as letrozole, are more effective than anti-oestrogens (clomifene citrate). However, cost should be considered, as letrozole is ten times more expensive than clomifene citrate (Kompas (2001), cited in Cantineau & Cohlen, 2007).

Single vs. double IUI insemination

The National Institute of Clinical Excellence recommended in their 2004 guidelines on fertility that single rather than double IUI should be offered (NCC WCH, 2004). This recommendation was based on evidence from a Cochrane review including three small RCTs that suggested no difference in outcome between single and double insemination (Cantineau *et al.,* 2003). The Cochrane review has since been updated with additional evidence, in particular, evidence from a RCT involving 1270 patients (Liu *et al.,* 2006). This RCT found that double IUI increased the pregnancy rate significantly in patients with male factor infertility although in patients with unexplained infertility single IUI was as efficient as double IUI. However, further research is still required to inform clinical practice (Cantineau *et al.,* 2003).

Timing of IUI

Performing IUI at the correct time is crucial to the success of this treatment. Ideally IUI should be performed around the moment of ovulation. There are various methods that can be used, such as measuring the levels of lutenizing hormone (LH) in urine or blood, administering human chorionic gonadotrophin (hCG), ultrasound or basal body temperature charts (Janssen *et al.,* 2008). A Cochrane review is currently being conducted to evaluate the effectiveness of different timing methods in both natural and stimulated cycles with IUI (Janssen *et al.,* 2008).

IUI vs. fallopian tube sperm perfusion

The Cochrane review comparing the effectiveness of IUI with fallopian tube sperm perfusion found convincing evidence that fallopian tube sperm perfusion resulted in almost three times higher pregnancy rates in couples with unexplained infertility. However, for couples with other non-tubal infertility the evidence is unclear on whether IUI or fallopian tube sperm perfusion is more effective (Cantineau *et al.,* 2004). Therefore when IUI is used to manage unexplained fertility problems, fallopian tube sperm perfusion should be offered over the standard insemination technique (NCC WCH, 2004).

IUI vs. ICI

A Cochrane review recently identified four relevant RCTs investigating the effectiveness of IUI compared with ICI using donor sperm (Besselink *et al.,* 2008). The review concluded that although ICI is less invasive, it is not as effective as IUI regarding pregnancy outcomes. The live birth rate per women after IUI treatment was almost double that of ICI, based on the findings of three studies. The pregnancy rate per woman after all treatment cycles was just over three times higher after IUI treatment compared with ICI treatment (Besselink *et al.,* 2008). However, the cost and risk from infection with IUI is likely to be higher than ICI, due to the sperm requiring preparation in the laboratory before insemination, and the use of an intrauterine catheter during the insemination process (Besselink *et al.,* 2008).

7.2 In vitro fertilisation

In vitro fertilisation (IVF) means fertilisation outside of the body. IVF involves taking medication to stimulate the ovaries to produce more eggs than usual. When these eggs have formed, a small operation is needed to retrieve them. The eggs are mixed with the sperm in a laboratory dish and incubated for two to three days. The aim is for the sperm to fertilise the eggs to form embryos. One or two of these embryos are then placed inside the woman's uterus using a fine plastic tube passed through the cervix. Any other embryos that have formed in the dish can be frozen (cryopreserved) for future use by the couple who produced them. This avoids having to repeat the ovulation stimulation and harvesting procedure, which can be risky and uncomfortable. If frozen embryos remain after the couple have completed their treatment the options available in Ireland are to donate them to another couple or to store them indefinitely (Medical Council, 2004). IVF is a useful treatment in women with damaged fallopian tubes, unexplained infertility, endometriosis and male infertility. It may also be used after several failed attempts with ovulation induction or IUI. IVF may be offered as a first-line treatment in women of older maternal age, irrespective of the cause of infertility (ESHRE, 2008). When severe sperm abnormalities are present, alternative treatment to IVF, such as ICSI, should be considered.

Table 6 The procedures involved in IVF

[1]	**Ovarian stimulation**	Pituitary down-regulation Superovulation
[2]	**Egg retrieval**	Type of pain relief provided Follicle flushing
[3]	**Fertilisation/Insemination**	Day 2-3 (cleavage) or Day 5-6 (blastocyte) Pre-treatment with antibiotics Assisted hatching
[4]	**Embryo replacement**	Pre-transfer irrigation Type of provider Type of media used (hyaluronic acid) Ultrasound guided embryo transfer Number of embryos transferred Transfer of fresh or frozen embryos Type of catheter used Endometrial thickness Bed rest or no bed rest Acupuncture
[5]	**Luteal support**	Some form of luteal support is necessary in IVF to help implantation of the embryo

A summary of the overall effectiveness of IVF is first provided in this section. Following this, evidence on more specific techniques within each of the five main stages of IVF treatment is summarised. Only a brief summary of evidence is provided for ovarian stimulation techniques, as the evidence for this is mostly summarised in section 5.2. Table 6 above lists the techniques of IVF where evidence is provided in this review.

7.2.1 Overall effectiveness of IVF

The most recent data collected by the European Society of Human Reproduction and Embryology (ESHRE) shows that 1,429 treatment cycles of IVF were carried out in Ireland in 2005. In 2005 data was collected from six of the seven clinics in Ireland offering IVF. The most recent data from the ESHRE are presented in Tables 7- 21 and figures 3 and 4.

Table 7 IVF trends in Ireland (using fresh embryos)

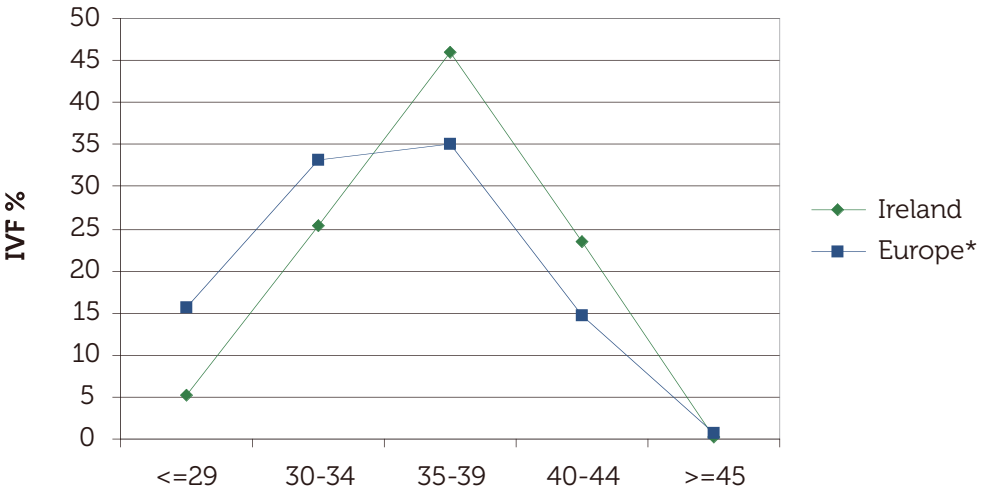
	2000	2001	2002	2003	2004	2005
Cycles	782	917	952	1,078	1,267	1,429
Aspirations	725	812	845	1,058	1,079	1,186
Transfers	682	756	796	982	979	1,099
Clinical Pregnancies	166	203	250	341	298	349
Deliveries	135	162	193	282	233	301
Clinics in Ireland (Clinics reporting to ESHRE)	5 (3)	5 (3)	5 (5)	5 (4)	7 (6)	7 (6)

Source: Andersen et al. (2004-2008); Nyboe Andersen *et al.,* 2009

In general the use of IVF in Ireland has been increasing with 301 babies delivered in 2005 following IVF treatment. The figures in table 7 will be slightly lower than the true figures, as not all clinics in Ireland reported data to the ESHRE register each year.

The age of women treated with IVF in Ireland is slightly older when compared with the average age distribution in Europe (Figure 3). A similar comparative age distribution is seen for women in Ireland treated with ICSI (Figure 4, page 76). The effect of age on IVF outcome is summarised in section 7.8.

Figure 3 Age distribution of women treated with IVF in 2005



* Europe figures are the average from 27 European countries (Source: Nyboe Andersen *et al.,* 2009).

The percentage of pregnancies per IVF transfer in Ireland using fresh embryos (31.8%) is very similar to the European average (30.3%), although these figures are lower when compared with data from the United States (42%) (Table 8). The percentage of pregnancies per transfer of frozen embryos following IVF and ICSI treatments in Ireland is slightly lower (22.5%). This figure is slightly higher when compared with the European average (19.1%), although lower than that of the USA (35.1%) (Table 9).

Table 8 Pregnancies and deliveries with IVF in 2005 (using fresh embryos)

	Percentage of pregnancie			Percentage of deliveries		
	Per cycle	Per aspiration	Per transfer	Per cycle	Per aspiration	Per transfer
Ireland	24.4	29.4	31.8	21.1	25.4	27.4
Europe	NA	26.9	30.3	NA	NA	NA
USA	?	?	42.0	?	?	34.3

Note: NA=Not Available; Europe - Data was available from up to 30 European countries, Nyboe Andersen et al. (2009); USA – Data from CDC MMWR Surveillance Summaries for 2005 (Wright *et al.,* 2008)

Table 9 Pregnancies and deliveries in 2005 (IVF & ICSI using frozen embryos)

	Percentage of pregnancie		Percentage of deliveries	
	Per thawing	Per transfer	Per cycle	Per aspiration
Ireland	17.9	22.5	11.3	14.1
Europe	19.0	19.6	NA	NA
USA	NA	35.1	NA	28.0

Note: NA=Not Available; Europe - Data was available from up to 27 European countries, Nyboe Andersen et al. (2009); USA – Data from CDC MMWR Surveillance Summaries for 2004 - (maybe updated soon) (Wright *et al.,* 2007)

A Cochrane review of four RCT reported that for couples with unexplained infertility IVF might result in more pregnancies than other options for unexplained infertility, but this is still uncertain (Pandian *et al.,* 2005). The review concludes that until more evidence is available, IVF may not be the preferred first treatment choice for these couples, and less invasive options may be more appropriate.

7.2.2 [1] Ovarian stimulation

Pituitary down-regulation & Superovulation

See section 5.2 for medicines used for pituitary down-regulation and superovulation.

Table 10 Aspects of ovarian stimulation considered in this review

Aspects of procedure	Summary of evidence
Natural or stimulated cycles for fresh embryo replacement	Natural or unstimulated cycles results in lower pregnancy rates and therefore are not usually recommended.
Mild ovarian stimulation protocols	Evidence in favour of mild ovarian stimulation IVF is growing, although further studies are required to determine its effectiveness compared to conventional IVF.
Natural or stimulated cycles for frozen embryo replacement	Evidence currently insufficient regarding the use of natural or stimulated cycle to prepare the endometrium.

Natural or unstimulated cycles in IVF result in lower pregnancy rates per cycle of treatment compared to stimulated cycles with clomifene citrate and gonadotrophins. Therefore natural cycle in IVF are not usually recommended unless in rare circumstances where gonadotrophin use is inadvisable for the patient (NCC WCH, 2004).

Mild stimulation involves administering a lower dose of fertility drugs for a shorter time period compared with conventional IVF. As only one embryo is transferred, the likelihood of a multiple pregnancy is substantially lower, although fewer eggs may be available for collection. There is growing evidence in favour of mild ovarian stimulation. A recent review has shown that concerns around reducing the number of oocytes retrieved are unjustified (Verberg *et al.,* 2009) and when compared with standard IVF treatment (stimulation with GnRH agonist long-protocol and transfer of two embryos), IVF with mild ovarian stimulation (GnRH antagonist co treatment combined with single embryo transfer) resulted in similar cumulative live birth rates (Heijnen *et al.,* 2007). Further evidence is required to determine the effectiveness of mild ovarian stimulation IVF compared with conventional IVF treatment.

When replacing frozen embryos, a natural cycle or artificial cycle to prepare the endometrium can be used. A recent Cochrane review including seven RCTs with 1120 women concluded that there is not enough evidence to support one menstrual cycle regimen over another. However, if an artificial cycle using oestrogen and progesterone preparations is used, the evidence supports the addition of a GnRH-agonist (Ghobara & Vanderkerchove, 2008).

7.2.3 [2] Egg retrieval

Table 11 Aspects of egg retrieval considered in this review

Aspects of procedure	Summary of evidence
Ultrasound guidance transvaginal aspiration	Transvaginal aspiration with ultrasound guidance is the current standard procedure for retrieving eggs from the ovaries.
Type of pain relief	Pain relief available includes conscious sedation, and local, epidural or general anaesthesia. There is not sufficient evidence to support any one method over another. No difference in pregnancy rates with the different pain relief methods.
Follicule flushing	May be beneficial when only a few follicles are available, but does not appear to increase number of eggs retrieved or pregnancy rates when 3+ follicles have developed.

Ultrasound guided transvaginal aspiration

To improve the effectiveness of IVF, hormones are used to stimulate the production of more than one follicle in a process known as superovulation. Ultrasound and monitoring hormone levels are conducted to determine when the women's eggs have reached the correct maturity. Egg retrieval used to be conducted via a laparoscope. However, around 20 years ago evidence indicated that follicle aspiration guided by transvaginal ultrasound was as, or more effective and had many advantages over the laparoscopic method such as being less invasive and carrying fewer associated complications or side effects (Tanbo *et al.,* 1988). This is now the current standard procedure for retrieving eggs from the ovaries. The transvaginal aspiration procedure involves passing a needle through the top of the vagina into the ovary and follicles. The follicles are fluid filled sacs that contain oocytes. The fluid in the follicles is drawn up (or aspirated) through the needle and the eggs detach from the follicle wall and are sucked out of the ovary. Between five and 20 eggs may be removed from both ovaries during the procedure, which normally takes around 15 to 30 minutes. The needle is guided by ultrasound so the health professional can position the needle correctly. The procedure is painful, and has been likened to the intense pain sometimes experienced around menstruation (Stener-Victorin, 2005). Pain relief is normally provided during the egg retrieval procedure.

Pain relief

The various types of pain relief available include conscious sedation, and local, epidural or general anaesthesia. Conscious sedation[29] does not require an anaesthetist, causes relatively few complications and is well tolerated. It is the most commonly used method of pain relief during transvaginal oocyte retrieval (Trout, 1998). A survey of assisted conception clinics in the UK found 84% of the clinics used conscious sedation and 16% used general anaesthesia (Elkington *et al.,* 2003). It is recognised that any drug which depresses the central nervous system has the potential to impair respiration and or circulation, therefore safe practice guidelines of administering sedative drugs should be followed (AOMRC, 2001). The Academy of Medical Royal Colleges (2001) has suggested that safe sedation techniques are developed for specific specialities including assisted conception units. Guidelines have been developed in the UK by the Royal College of Nursing and the British Fertility Society to optimise patient safety during sedation in assisted conception units (RCN, 2004; BFS, 2003). A Cochrane review investigating the most effective method of pain relief for oocyte retrieval did not identify sufficient evidence to support any one method over another (Kwan et al. 2005). The effect of pain relief methods is known to be influenced by the patient's expectation and feeling of being safe and comfortable with the chosen method (Stener-Victorin, 2005). Other factors that may influence the pain experienced during oocyte retrieval are body mass index (BMI), the duration of oocyte retrieval and the number of follicles punctured, follicular flushing and the size of the aspiration needle used (Ng *et al.,* 1999). The egg retrieval procedure may need to be carried out more than once before a pregnancy or live birth is achieved. It has been reported that the first egg retrieval procedure is the most painful (Gohar et al. 1993).

Many of the drugs used for pain relief have been detected in the follicular fluid soon after being administered. There has been concern of negative effects of such drugs on reproductive outcome due to the potential toxic effects on oocyte maturation and fertilisation. However, evidence from the Cochrane review (Kwan et al. 2005) and from the Agency for Healthcare Research and Quality (Myers et al. 2008) found no difference in pregnancy rates when comparing the different pain relief methods. The incidence of post-operative nausea and vomiting was similar in all groups being compared (Kwan et al. 2005).

Follicle flushing

Follicle flushing may be used during the egg retrieval procedure to increase the number of eggs retrieved. This involves flushing the follicle with a small amount of solution to improve the aspiration of eggs from the follicle. Although follicle flushing may be beneficial when there are only a few follicles available, it should not be offered to women who have developed three

[29] Conscious sedation is a technique using medication to depress the central nervous system so that treatment can be carried out, but verbal contact with the patient is maintained throughout the sedation.

or more follicles as evidence shows no increase in the number of eggs retrieved or pregnancy rates (NCC WCH, 2004). Follicle flushing increases the procedure duration and the associated pain, and therefore the amount of pain relief required. A Cochrane review (Wongtra-ngan *et al.,* 2004) is currently being conducted on the impact of follicle flushing on pregnancy and live births.

7.2.4 [3] Fertilisation / Insemination

Table 12 Aspects of fertilisation/insemination considered in this review

Aspects of procedure	Summary of evidence
Cleavage (day 2-3) or blastocyst (day 5-6) embryo transfer	Standard practice is to transfer cleavage stage embryos. Blastocyst embryo transfer currently does not improve pregnancy rates.
Type of culture medium used	Insufficient evidence on the effect on IVF outcomes. Culture media containing hyaluronic acid may improve pregnancy rates.
Pre-treatment with antibiotics	Do not affect clinical pregnancy rates.
Assisted hatching	Does not improve pregnancy rates, although it may be useful in women with previous failed IVF treatment.

Cleavage stage or blastocyst stage embryo transfer

Standard practice in IVF involves transferring embryos into the woman's uterus when they reach the cleavage stage (two to three days after fertilisation). Previous guidelines reported that transferring embryos on day 2-3 and days 5-6 appeared to be equally effective in term of increased pregnancy and live birth rates per cycle started (NCC WCH, 2004). Current evidence suggests there is now a significant difference between transferring embryos at the cleavage stage or blastocyst stage (Blake *et al.,* 2007). A recent Cochrane review reported that more women have a pregnancy and baby with transfer of blastocyst stage embryos than with standard (cleavage stage embryo transfer) IVF (Blake *et al.,* 2007). Significantly more live births were reported per couple with blastocyst stage transfer (36.0%) compared with cleavage stage transfer (29.4%). Clinical pregnancy rates per couple were also significantly higher in blastocyst stage transfer (40%) compared with cleavage stage transfer (36%). No differences in multiple pregnancy rates or miscarriage rates were reported. More embryos were frozen with cleavage stage transfers, and failure to transfer any embryos was higher among the blastocyst stage transfer group. Freezing embryos allows couples an additional opportunity to achieve a pregnancy. Therefore although blastocyst stage transfers have a higher implantation rate, this should be considered with the higher failure to transfer rate and the fewer embryos frozen.

As cleavage stage transfer allows for additional attempts using stored frozen embryos, the cumulative pregnancy rates were estimated to be similar in cleavage (38%) and blastocyst (39%) stage transfers (Van der Auwera et at, 2002). The techniques used to freeze cleavage and blastocyst stage embryos are different and if improvements can be made in the blastocyst freezing technique, then the cumulative success rate of blastocyst stage transfer would increase (Blake *et al.,* 2007).

Type of culture media

The culture media (or surrounding liquid that the embryo develops in in the laboratory) is very important for embryo growth. The two main types of culture media are monoculture systems and sequential systems. Monoculture systems are a single formulation designed to support the embryo from zygote to blastocyst stage (Lane & Gardner, 2007). An embryo at cleavage stage and blastocyst stage grows best in different in vitro environments. By using different culture media (sequential or stage specific media) the optimal media for the embryo throughout its development is provided. The use of sequential media has lead to improvements in blastocyst development, and higher implantation and pregnancy rates after both cleavage stage and blastocyte stage (Blake *et al.,* 2007; Lane & Gardner, 2007). Culture media can contain a variety of components, such as glucose, amino acids, ammonium, and macromolecules such as albumin or hyaluronan (or hyaluronic acid) (Lane & Gardner, 2007). Improved pregnancy rates have been reported when media containing hyaluronic acid are used compared to standard media containing recombinant albumin; in some RCTs this difference is significant (Friedler *et al.,* 2007; Urman *et al.,* 2008). A Cochrane review is currently being conducted to investigate whether inclusion of hyaluronic acid in embryo transfer media affects live birth rates compared to media without it (Blake *et al.,* 2008).

It should be noted that the type of culture media is only one factor that can influence the development of the embryos in vitro. Factors such as carbon dioxide and oxygen levels, and the number of incubator chambers may also influence embryo development (Lane & Gardner, 2007), although these are not discussed in this review.

Pre-treatment with antibiotics

A RCT of 350 women reported that administering antibiotics to women before embryo transfer significantly reduced bacterial contamination of the catheter by approximately 20% (Brook *et al.,* 2006). No difference was found in clinical pregnancy rates between the women who had the antibiotic (36%) and the women who didn't (35%). However, pregnancy rates are significantly affected by the presence or absence of bacterial contamination and the degree and type of contamination, therefore practitioners should try to minimise the risk of contamination to improve the chances of pregnancy (Brook *et al.,* 2006).

Assisted hatching

Assisted hatching is sometimes used with IVF. Assisted hatching involves disrupting the zona pellucida either by thinning it (using chemicals or laser), making a hole (using chemicals, laser or cutting it), or completely removing it (using chemicals). The zona pellucida is the gel-like coat that surrounds the oocyte. During fertilisation, the zona pellucida prevents more than one sperm penetrating the oocyte and encloses the early embryo until it becomes a blastocyst. The blastocyst then has to escape from the zona pellucida before it can implant in the uterus. The zona pellucida appears to become more dense the longer the time spent in vitro, and it is thicker in older women (Kilani *et al.,* 2006) and smokers (Shiloh *et al.,* 2004). A thicker zona pellucida is associated with lower implantation rates in the uterus (Das *et al.,* 2006). A Cochrane review found that the results from seven RCTs showed assisted hatching had no effect on live birth rates. Data from 16 robust studies indicates that assisted hatching significantly increases clinical pregnancy rates by 20%. However, the chances of having a multiple pregnancy are significantly increased (by 67%) with assisted hatching compared to the controls. In practice, this raises concerns about the use of assisted hatching and the number of embryos transferred with this method (Das *et al.,* 2006).

7.2.5 [3] Embryo transfer

Embryo transfer is an important stage of the IVF treatment. It is estimated that up to 85% of replaced embryos fail to implant, despite apparently normal embryos being selected (Sallam *et al.,* 2002). Failure of IVF at this stage may be due to poor embryo quality, lack of receptiveness of the uterus, or the techniques used in the embryo transfer process (Brown *et al.,* 2007). The table overleaf lists the aspects considered in this review, with a brief summary of the evidence. Further description of the evidence is provided following the table.

Table 13 Aspects of embryo transfer considered in this review

Aspects of procedure	Summary of evidence
Pre-transfer irrigation	Neither improves or adversely affects pregnancy rate.
Practitioner performing embryo transfer	No difference in pregnancy rate
Ultrasound guided embryo transfer	40% improvement in pregnancy & live birth rates with ultrasound guided embryo transfer compared with 'clinical touch' methods.
Number of embryos transferred	Single embryo transfer plus subsequent frozen embryo transfer can be as effective as double embryo transfer in carefully selected patients.
Transfer of fresh or frozen embryos	Pregnancy rates following frozen embryo transfer have always been found to be lower than following fresh embryo transfers.
Cryopreservation of embryos	Embryo cryopreservation procedures and success rates of frozen-thawed embryo transfer vary widely.
Cryopreservation of oocytes	No successful live births from oocyte freezing are believed to have occurred in Ireland. Live birth rate per thawed oocyte is around 2%.
Type of embryo transfer catheter used	Choice of embryo transfer catheter does appear to influence pregnancy outcomes.
Endometrial thickness	Pregnancy rate increases as the thickness of the endometrial lining increases.
Bed rest or no bed rest	Bed rest of more than 20 minutes following embryo transfer does not improve outcome of IVF
Acupuncture	Acupuncture given on the day of embryo transfer appears to increase the live birth rate with IVF treatment.

Pre-transfer irrigation

Evidence shows that flushing the endometrium before the embryo is transferred does not improve the pregnancy or live birth rate (Myers *et al.,* 2008). A randomised trial of 240 women found that direct flushing of culture media into the uterine cavity neither improves nor adversely affects the pregnancy rate (Berkkanoglu *et al.,* 2006).

Practitioner performing embryo transfer
One randomised study reported no difference in clinical pregnancy rates after ultrasound-guided embryo transfer by a trained midwife (31%) and a gynaecologist (29%) (Bjuresten *et al.,* 2003). Similarly, an observational study investigating the ongoing pregnancy rates achieved by six physicians performing 977 embryo transfers reported that the practitioner performing the embryo transfer does not appear to affect the pregnancy rate (van Weering *et al.,* 2005).

Ultrasound guided embryo transfer
A transcervical catheter is used to replace embryos between days 2-5 of development. In the past the 'clinical touch' method was used to guide the placement of the transfer catheter. However, this method relies on the clinician's skill and judgement to correctly position the catheter. Ultrasound guidance is now commonly used to guide embryo transfer as there is convincing evidence that it results in substantial improvements in pregnancy and live birth rates compared to 'clinical touch' methods (NHS WCH, 2004; Myres *et al.,* 2008). A Cochrane review reported that pregnancy and live birth rates are improved by 40% when using ultrasound guided embryo transfer compared with 'clinical touch' methods (Brown *et al.,* 2007). Although there was no distinction in the Cochrance review between fresh and frozen replacement cycles, one RCT reported that ultrasound-guided transfer resulted in a clinical pregnancy rate of 34.4% compared to 19.8% with embryo transfers using clinical touch (Coroleu *et al.,* 2002).

Number of embryos transferred
Approximately one in 80 women will have a multiple birth following natural conception (Braude *et al.,* 2006). In Ireland, one in four (25.1%) deliveries following IVF or ICSI are multiple (Nyboe Andersen *et al.,* 2009). This compares to just over one in five (21.8%) of deliveries across Europe being multiple births. Multiple births are associated with increased morbidity and mortality of the babies and increased risk of complications during pregnancy [See section 7.9.1].

The European Society of Human Reproduction and Embryology (ESHRE) advocates single embryo transfer in selected groups of patients as the only means of lowering the rate of twin pregnancies (ESHRE, 2008). In Europe, single embryo transfer occurs in around 20% of all IVF and ICSI cycles. However in Ireland only 8.7% of the embryos transferred are single (Nyboe Andersen *et al.,* 2009) [See table 14]. To maximise the chances of achieving pregnancy from elective single embryo transfer (eSET), guidelines from the British Fertility Association and Association of Clinical Embryologists state that private fertility clinics should review the costs of frozen embryo replacement cycles to ensure patients are offered the most cost effective option (Cutting *et al.,* 2008). Patients who are at high risk of multiple pregnancies should be actively selected for eSET. Factors that influence the chance of multiple pregnancy if more

than one embryo is replaced include the age of the woman, the first cycle of treatment, the number of embryos available for transfer, embryo quality and the stage at which the embryo is transferred (Cutting *et al.,* 2008).

A Cochrane review examining the effectiveness of single versus double embryo transfer found that the live birth rate and pregnancy rates following single embryo transfer are lower than those following double embryo transfer in a single fresh IVF cycle, as are the chances of multiple pregnancy (Pandian *et al.,* 2004). One of the RCTs included in the Cochrane review randomised 327 women to receive double embryo transfer and 307 women to receive a single embryo transfer, followed (if there was no live birth) by the transfer of one frozen and thawed embryo (Thurin *et al.,* 2004). This trial found that transferring a single embryo, and if necessary one frozen-and-thawed embryo, resulted in a pregnancy rate (47.9%) and live birth rate (38.8%) that was not substantially lower than that with double embryo transfer (52.6% and 42.9% respectively). Only one of the 128 (0.8%) women in the single embryo transfer group had a multiple birth (twins), while significantly more women (47 of the 142, 33.1%) in the double embryo transfer group had multiple births (46 twins, 1 triplets).

The first study to evaluate the overall cost-effectiveness of an eSET policy in everyday clinical practice reported that implementing an eSET policy along with an effective embryo freezing programme, results in a better outcome and lower treatment cost for women under the age of 40 having IVF and/or ISCI (Veleva *et al.,* 2009). In practice, a broad policy of eSET will minimise multiple pregnancy rates, but will also lower pregnancy rates per fresh IVF cycle. Therefore, eSET should be conducted for selected women who have a higher risk of twins. This would include younger women (under 35 years), in their first or second cycles of IVF, who use fresh non-donor eggs or embryos, and who have a number of good quality embryos for future use. As eSET is a relatively new concept, patient education and a positive attitude among the treatment team are required to maximise acceptance of an eSET strategy (Cutting *et al.,* 2008). Acceptance of eSET in Ireland is likely to be more sensitive to success rates as all fertility treatments are self-funded. Increasing use of eSET reduces the health risks to mother and babies, but increases the number of treatment cycles (fresh and frozen) that are required by couples to achieve an equivalent birth rate (Thurin *et al.,* 2004). Currently, eSET is part of embryo transfer policy (by legislation and/or guideline/voluntary agreement) in five EU countries, and most European countries now have a two-embryo transfer policy in place (ESHRE, 2008).

Using large national datasets, the HFEA concluded that offering eSET to around half of IVF patients will lead to a twin rate of less than 10%. This is currently considered to be an acceptable balance between reducing the twin rate whilst maintaining the woman's chances of conceiving (Braude *et al.,* 2006). Belgium has adopted a strategy to reduce multiple births which has not significantly affected pregnancy rates, but has significantly reduced the twin

rate (which now stands at approximately 7%) (Braude *et al.,* 2006). The Belgian strategy, which was implemented along with a reimbursement policy where up to six cycles in a lifetime are reimbursed for all assisted reproduction-related laboratory activities, is shown in the box below:

Women aged less than 35	
1st attempt	Single embryo transfer
2nd attempt	Single embryo transfer if 1 or more top embryos are available Transfer 2 embryos if no top embryo is available
3rd to 6th attempt	Maximum of 2 embryos transferred
Women aged 35 to 39	
1st or 2nd attempt	Maximum of 2 embryos transferred
3rd to 6th attempt	Maximum of 3 embryos transferred
Women aged 39 to 42	
1st to 6th attempt	No limit for number of embryos transferred

Source: Ombelet et al. (2005)

Table 14 Embryos transferred after IVF and ICSI in 2005

	Ireland		Europe*	
	Number	%	Number	%
All transfers	1,859	100	236,480	100
1 embryo	161	8.7	47,348	20.0
2 embryos	1,477	79.5	132,683	56.1
3 embryos	218	11.7	50,841	21.5
4+ embryos	3	0.2	5,436	2.3

Source: Nyboe Andersen et al. (2009). *Data was available from up to 30 European countries, but data incomplete for three countries.

Table 15 Deliveries after IVF and ICSI in 2005

	Ireland		Europe*	
	Number	%	Number	%
All deliveries	518	100	47,966	100
Singleton	388	74.9	37,487	78.2
Twin	128	24.7	10,067	21.0
Triplet	2	0.4	396	0.8

Source: Nyboe Andersen et al. (2009). *Data was available from up to 27 European countries

Transfer of fresh or frozen embryos

The most recent data available from European registers of ART show that in 2005 in Ireland, 524 frozen embryos were thawed, of which 418 were transferred resulting in 94 clinical pregnancies and 59 deliveries (Nyboe Andersen *et al.,* 2009). The pregnancy rate per transfer was therefore 22.5% and the delivery rate per transfer was 14.1%. Pregnancy rates following frozen embryo transfer have always been found to be less than when following fresh embryo transfers.

The neonatal outcomes of 1,267 children born after frozen embryo replacement and 17,857 born after fresh IVF or ISCI treatment on the Danish national controlled cohort study were examined by Pinborg et al. (2008). The multiple pregnancy rates were found to be significantly higher with IVF using fresh embryos (27.3%) compared with IVF using frozen embryos (14.2%). Pregnancy duration was significantly longer for women with frozen embryo replacement and the average birth weight was about 200g more compared with fresh embryo replacement. Similar occurrences of congenital malformations were seen in frozen (7.1%) and fresh (8.8%) embryo replacement offspring.

Cryopreservation methods

The two main ways of freezing human embryos and eggs are (1) the conventional 'slow-freeze' method and (2) the faster 'vitrification' method.

Successful freezing and thawing of embryos and oocytes depends on the avoidance of ice crystals forming. The slow-freeze method involves freezing at a slow controlled rate in the presence of a special liquid known as a cryoprotectant (a form of anti-freeze) to reduce damage to the embryo or oocyte during freezing and thawing.

Vitrification is a newer alternative to the conventional 'slow-freeze' method. It involves a rapid freezing process in which a high concentration of cryoprotectant is used so that ice crystals do not have a chance to form. This method is far quicker and does not require expensive

equipment. However, there is some concern that the high concentrations of cryoprotective solutions used may affect the survival of the oocyte or embryo (Cao et al. 2008; Loutradi *et al.,* 2008).

Current evidence suggests the vitrification method has more favourable outcomes compared to the conventional "slow-freeze" method. A systematic review and meta-analysis of four studies reported that the post-thaw survival rate of cleavage stage embryos was significantly higher (over 15-times) after vitrification compared with slow freezing. The survival rate of blastocyst stage embryos was also just over double following vitrification compared with slow freezing (Loutradi *et al.,* 2008). One RCT reported a higher implantation and pregnancy rate per transfer (14.9% and 35%) with vitrified embryos compared with the conventional slow freezing method (4.2% and 17.4%) (Rama Raju *et al.,* 2005). However, further good quality RCTs are required to confirm this finding.

The duration of frozen embryo storage does not appear to affect the post-thaw survival or pregnancy outcome in IVF patients (Riggs *et al.,* 2008). Due to the lack of regulation in Ireland regarding the disposal of unwanted embryos, frozen embryos have to be stored indefinitely, as they cannot be destroyed. In other countries, such as the UK, frozen embryos are allowed to perish with the consent of both partners. In the UK the maximum storage time for embryos is five years, although this may be extended in certain circumstances (HFEA, 2008).

Embryo cryopreservation

Embryo cryopreservation procedures and success rates of frozen-thawed embryo transfer vary widely. A British Fertility Society survey found wide variation among British IVF clinics regarding the timing of embryo freezing. Most clinics (93%) freeze the majority of embryos on day 2 (in the early cleavage stage), although some clinics freeze embryos from day 1, the pronucleate stage (78%) to day 5-7, the blastocyst stage (33%) (Lewis *et al.,* 2006). The chances of pronuclear stage embryos surviving the freeze-thaw process are around 70%, and pregnancy rates per transfer are around 17-31% (Granne *et al.,* 2008). The wide variation in cryopreservation and thawing practices may benefit from guidelines on standard practice (Lewis *et al.,* 2006).

Oocyte cryopreservation

To-date, it is believed that no successful live births from oocyte freezing have occurred in Ireland. A meta-analysis investigating the efficiency of oocyte freezing found that IVF success rates with slow-frozen oocytes are significantly lower when compared with IVF using fresh oocytes (Oktay *et al.,* 2006). The live birth rate per oocyte injected using ICSI was 3.4% with slow-frozen oocytes and 6.6% with fresh oocytes. The live birth rate per embryo transfer was 32.4% with slow-frozen oocytes and 60.4% with fresh oocytes (Oktay *et al.,* 2006). The analysis also reported that the live birth rates per thawed oocyte were 1.9% for slow frozen oocytes and 2.0% for oocytes frozen using vitrification.

A recent RCT reported that oocyte survival rate was significantly lower (61.0%) in the slow-freezing groups compared with the vitrification group (91.8%) (Cao *et al.,* 2008). Indeed, several reports have shown vitrification of oocytes results in relatively high survival and pregnancy rates (Cao *et al.,* 2008). A recent analysis of 200 infants conceived following oocyte vitrification cycles found the mean birth weight and incidence of congenital abnormalities were comparable to those of infants conceived naturally (Chian *et al.,* 2008).

Table 16 Fresh and frozen embryo transfers in Ireland and Europe in 2005

	Fresh embryos		Frozen embryos	
	Ireland	Europe (N=30 countries)	Ireland	Europe (N=27 countries)
Transfers	1,099	96,729	418	70,151
Clinical pregnancies	349	29,302	94	13,719
Deliveries	301	19,132*	59	8,540#
Pregnancies per transfer	31.8%	30.3%	22.5%	19.6%
Deliveries per transfer	27.4%	na	14.1%	na

Source: Nyboe Andersen et al. (2009); na = data not available; *Data was available from 29 European countries; # Data was available from 25 countries.

Table 17 Deliveries after IVF and ICSI in 2005 (frozen embryos)

	Ireland		Europe*	
	Number	%	Number	%
All deliveries	59	100	8,540	100
Singleton	53	89.8	7,303	85.6
Twin	6	10.2	1,191	13.9
Triplet	0	0.0	38	0.4

*Data from 24 European countries

Type of embryo catheter used

Several types of embryo transfer catheter are available. The catheters vary, for example, in length, quality, malleability and degree of stiffness. Some recent studies have suggested that the type of embryo transfer catheter is an important factor in the success of an IVF programme. A systematic review and meta-analysis by (Abou-Setta *et al.,* 2005) which included ten RCTs, reported that pregnancy rates are significantly higher when a soft embryo transfer catheter is used compared to a firm embryo transfer catheter. However, passing a soft catheter through the cervical canal can be difficult or even impossible, and it is associated with more traumatic events. A Cochrane review is currently being conducted to investigate whether the type of embryo transfer catheter used is associated with pregnancy outcomes (Abou-Setta *et al.,* 2009).

Endometrial thickness

The evidence seems to indicate that replacement of embryos into a uterine cavity with an endometrium of less than 5mm thickness is unlikely to result in a pregnancy and is therefore not recommended (NCC WCH, 2004). However, possibly the largest study conducted investigating the effect of endometrial thickness on pregnancy rate recently concluded that cancellation of embryo transfer based on a thin endometrial lining is unwarranted (Al-Ghamdi *et al.,* 2008). This cohort study analysed 2,464 IVF cycles and showed the pregnancy rate increased from 29.4% among patients with an endometrial lining 6 mm or less, to 44.4% among patients with a lining of 17mm or more. Successful pregnancies have occurred from cycles with endometrial lining of less than 4 mm thick (Sundstrom *et al.,* 1998). There is also evidence that pregnancy rates are not reduced with very thick endometrial linings (Al-Ghamdi *et al.,* 2008; Yoeli *et al.,* 2004; Dietterich *et al.,* 2002).

Bed rest or no bed rest

There is good evidence to indicate that bed rest of more than 20 minutes following embryo transfer does not improve the outcome of IVF treatment (NCC WCH, 2004). More recent studies, including a RCT comparing pregnancy rates among women who had 30 minutes of bed rest, or who were discharged immediately following embryo transfer, also found no improvement (Purcell *et al.,* 2007).

Acupuncture

A Cochrane review including 13 RCTs with a total of 2,209 participants reported that acupuncture given on the day of embryo transfer appears to increase the live birth rate with IVF treatment (35% compared with 22% in the control group) (Cheong *et al.,* 2008). However, this finding may be due to a placebo effect. A recent RCT reported that placebo acupuncture[30]

[30] The needles used in placebo acupuncture are blunt and do not penetrate the skin, they appear shorter when pushed against the skin and also give the patient a pricking penetration sensation similar to the needles used in real acupuncture.

was associated with significantly higher overall pregnancy rate (55.1%) when compared with real acupuncture (43.8%) (So, *et al.,* 2009). It could be that the placebo acupuncture needles still obtain a response and therefore may not be a suitable control to use.

The evidence in the Cochrane review found that having acupuncture around the time of oocyte retrieval or repeating acupuncture two to three days after embryo transfer did not improve pregnancy outcomes (Cheong *et al.,* 2008). Acupuncture is relatively painless and causes few side effects, however it may potentially be harmful if used during early pregnancy. Some evidence suggests an increase in miscarriage rates when used during early pregnancy. Therefore acupuncture should only be offered at the time of embryo transfer until further good quality evidence is available to determine the possible association between acupuncture received around the time of embryo transfer and miscarriage (Cheong *et al.,* 2008).

7.2.6 [5] Luteal phase support

Table 18 Aspects of luteal phase support considered in this review

Aspects of procedure	Summary of evidence
Type of luteal phase support	hCG results in higher pregnancy rates, but is associated with a significant risk of OHSS. Therefore progesterone is the preferred choice for use in luteal phase support. Combined hCG and progesterone does not appear to significantly improve pregnancy outcome.
Administration of luteal phase support	Vaginal administration of progesterone is usually the first choice for luteal phase support due to its effectiveness and patient acceptance.
Timing of luteal phase support	Luteal phase support should be started within three days after oocyte retrieval.
Adding oestrogen to progesterone luteal phase support	Evidence currently unclear regarding the benefit of adding oestrogen to progesterone in luteal phase support.

Type of luteal phase support

The luteal phase of the cycle is the time between ovulation and the establishment of pregnancy or the onset of menses. The use of GnRH-agonists or GnRH-antagonists for pituitary down-regulation during ART disturbs the production of the hormone progesterone during the luteal phase. Progesterone stimulates the endometrium and prepares it for implantation, and reduces uterine contractions, which increases the chance of successful implantation.

Luteal phase support refers to the hormone supplementation given during the luteal phase to improve implantation rates. Supplementation with progesterone itself, or human chorionic gonadotrophin (hCG) (which stimulates progesterone production) has been shown to improve implantation rates (Daya & Gunby, 2004).

A Cochrane review found that luteal phase support with hCG more than doubled the chances of pregnancy in cycles that used GnRH-analogues for pituitary down-regulation, and significantly reduced the miscarriage rate. However, the risk of OHSS was increased by 20 times when compared with no treatment (Daya & Gunby, 2004). Progesterone therefore, is the safer and preferred option for luteal phase support in ART cycles. When progesterone is used for luteal phase support the chance of a clinical pregnancy increases by 34% compared with no treatment. The miscarriage rate is unaffected, and the risk of OHSS is less than half that of luteal support using hCG (Daya & Gunby, 2004). The addition of hCG to progesterone did not significantly increase pregnancy or live birth rate (Myres *et al.,* 2008).

Administration of luteal phase support

Progesterone can be administered via daily intramuscular injections, vaginal pessaries, vaginal tablets or gel. Progesterone becomes less efficient when taken orally, and is associated with side effects such as drowsiness, hot flushes, nausea and fluid retention (Pritts & Atwood, 2002). Further research is required to determine the usefulness of this route of administrating the hormone (Fatemi *et al.,* 2007). There is no detectable difference between oral progesterone and the various formulations of vaginal progesterone; both result in lower pregnancy and live birth rates compared to intramuscular progesterone (Myres *et al.,* 2008). A meta-analysis including five RCTs found clinical pregnancy rates and live birth rates to be significantly higher when intramuscular progesterone was used, compared with vaginal progesterone (Pritts & Atwood, 2002). However, vaginal administration of progesterone often remains the first choice due to greater patient acceptance and fewer side effects (Fatemi *et al.,* 2007).

Timing of luteal phase support

Further evidence is required to determine the best time to start luteal phase support. Available evidence indicates that luteal phase support should be started within three days after oocyte retrieval (Fatemi *et al.,* 2007).

Adding oestrogen to progesterone luteal phase support

The benefit of adding estradiol[31] to progesterone in luteal phase support is currently unclear. Results from some RCTs indicate that the addition of oestrogen significantly improves pregnancy and live birth rates in IVF cycles that use GnRH-agonists for pituitary down-regulation (Myres *et al.,* 2008). However, a systematic review and meta-analysis of ten RCTs found no benefit on pregnancy rates with the addition of estradiol to progesterone in luteal phase support (Gelbaya *et al.,* 2008).

[31] Estradiol is the most potent natural oestrogenic hormone secreted by the ovaries.

The current trend towards single embryo transfer may lead to the use of milder ovarian stimulation protocols, which would reduce or even remove the luteal phase defect currently seen with some ART (Fatemi *et al.,* 2007).

7.3 Gamete intrafallopian transfer (GIFT) & Zygote Intrafallopian Transfer (ZIFT)

A gamete is an egg or a sperm. The Gamete Intrafallopian Transfer (GIFT) technique involves collecting eggs and sperm in the same way as for IVF. The eggs and sperm are then mixed together in a dish and immediately transferred to the fallopian tubes. This is done laparoscopically through a small incision in the abdomen, or by a catheter passed through the cervix. This allows the sperm to "naturally" fertilise the egg inside the woman's fallopian tube or uterus. The woman's fallopian tubes need to be healthy in order for GIFT to be successful, and to avoid extra-uterine pregnancy. GIFT may be used as a treatment in cases of unexplained fertility, although IVF treatment has now replaced the need for GIFT. Zygote Intrafallopian Transfer (ZIFT) is a similar procedure to GIFT, although the newly fertilised egg (or zygote) is returned to the women's fallopian tubes instead of a mixture of eggs and sperm.

The evidence

IVF has almost completely replaced GIFT and ZIFT and they are now rarely carried out. The pregnancy rates following GIFT are similar or slightly higher than IVF treatment (NCC WCH, 2004). However, the extra inconvenience and discomfort of the required laparoscopy and general anaesthetic with GIFT and ZIFT does not make the slightly increased pregnancy rates worthwhile (Brinsden, 2007).

Similar to IVF, the risk of multiple pregnancies is also increased with GIFT when compared with a natural conception, as more than one egg may be transferred to the fallopian tubes. The chances of having an ectopic pregnancy with ZIFT are double that following IVF treatment (Habana & Palter, 2001). GIFT and ZIFT procedures are now rarely used, due to the effectiveness and benefits of other available ARTs. GIFT may be favoured over IVF for religious reasons, however, as it allows fertilization to occur naturally within the fallopian tubes.

7.4 Intracytoplasmic sperm injection (ICSI)

The substance inside an egg is called the cytoplasm, and intracytoplasmic sperm injection involves injecting a single sperm directly into the cytoplasm of an egg. This procedure is carried out using a micro-injection needle to inject a single sperm into an egg which is being held in place by gentle suction using another micro-tool (Fishel, 2006). The egg containing the sperm is then placed into the uterus in the same way as with IVF. ICSI is a useful technique for couples that have been unsuccessful with IVF, or where the quality or number of sperm is too low for normal IVF to be successful.

The evidence

Three RCTs comparing ICSI to IVF found no significant differences in pregnancy outcomes (Myers *et al.,* 2008). In standard IVF, a complete failure of fertilization occurs in up to 30% of cases (Palermo *et al.,* 2009). ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF (NCC WCH, 2004). Approximately 98% of all patients should achieve fertilisation and the transfer of at least one embryo with ICSI treatment (Fishel, 2006). Clinical pregnancy is expected in approximately 30% of patients having embryo transfer (Nyboe Andersen *et al.,* 2009). The most recent Irish data shows that in 2005 there were 760 transfers of embryos fertilised using ICSI. This resulted in 259 clinical pregnancies (34.1% pregnancies per transfer) and 217 deliveries (28.6% deliveries per transfer) (Nyboe Andersen *et al.,* 2009).

Table 19 Pregnancies and deliveries with ICSI in 2005

	Percentage of pregnancies			Percentage of deliveries		
	Per cycle	Per aspiration	Per transfer	Per cycle	Per aspiration	Per transfer
Ireland	28.7	32.0	34.1	24.1	26.8	28.6
Europe	NA	28.5	30.9	NA	NA	NA

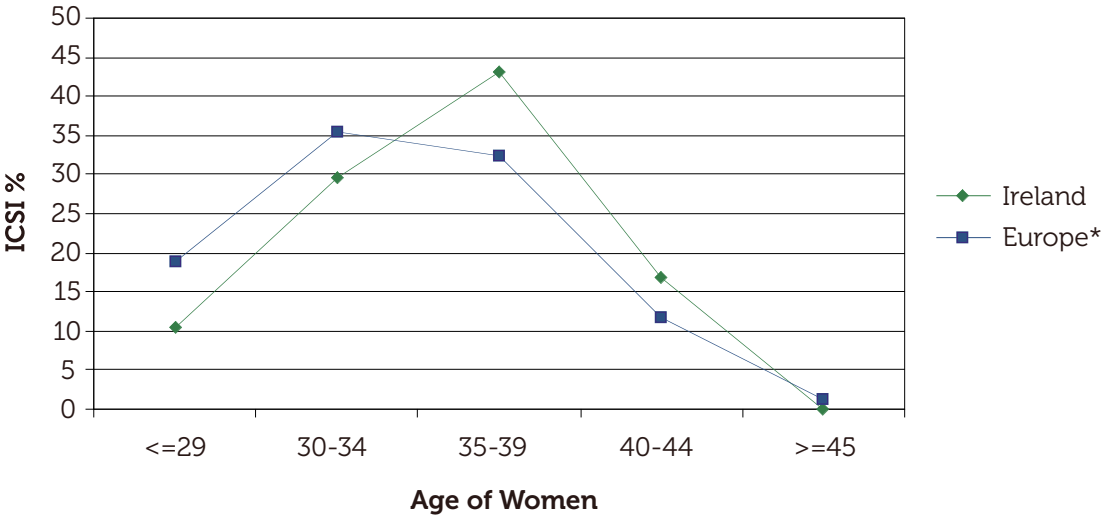
Note: NA=Not Available; Europe - Data was available from up to 30 European countries, Nyboe Andersen et al. (2009);

In couples considering ICSI, genetic counselling is indicated due to the higher incidence of genetic abnormalities in men with severe male infertility (ESHRE Capri Workshop Group, 2007). Chromosomal abnormalities have been detected in 2.1%-8.9% of men attending infertility clinics, compared with 1% in the general male population (NHS WCH, 2004).

Mild ovarian stimulation is recommended in ICSI cycles, as fewer oocytes are required. Compared to superovulation, mild ovarian stimulation is less complex, less time consuming and less costly, and is associated with fewer side effects (ESHRE Capri Workshop Group, 2007).

The age of women treated with ICSI in Ireland is slightly older when compared with the average age distribution in Europe. A similar comparative age distribution is seen for women in Ireland treated with IVF (Figure 3, page 51). The effect of age on IVF outcome is summarised in section 7.8.

Figure 4: Age distribution of women treated with ICSI in 2005



*Europe figures are the average from 27 European countries (Source: Nyboe Andersen *et al.,* 2009).

7.5 Donor insemination (sperm or egg donation)

When there is a problem with the male partner's sperm, sperm from a donor can be used. However, with the availability of ICSI there has been a reduction in the use of donor sperm. Donor insemination is still a useful procedure, for example when the male partner is likely to pass on an inheritable genetic condition or an infection such as HIV (NCC WCH, 2004). Donor sperm may be used in IUI, ICSI or IVF treatment. Donors are tested for various infections such as HIV and hepatitis B and C. Donor sperm is usually cryopreserved as tests for infections are repeated on donors after six months to prevent transmission of disease (Besselink *et al.,* 2008). As there are no adequate facilities in Ireland for screening donors, the donor sperm used in Ireland is obtained from outside the country. Most of the donor

sperm used in Ireland is obtained from Denmark or England. Danish law states that the donor identity cannot be revealed to the recipient couple or the child, and the donor is not allowed to receive information on the recipient couple or the child. A child conceived using donor sperm from England (donated before 1st April 2005), who has been told of his/her origins, can obtain some non-identifiable information about the donor from a central registry in England. Children conceived using sperm donated in England after 1st April 2005 can obtain identifying information about the donor once they reach the age of 18 (HFEA, 2006).

Using donated eggs is far less common than using donated sperm. There is a shortage of donated eggs throughout Europe. One clinic in Ireland has now established an egg donor programme working in partnership with a fertility clinic in the Ukraine.

The evidence

In Ireland, the pregnancy rate per IUI procedure was higher with donor sperm (44.1%), compared to IUI with husband sperm (9.2%) in women aged under 40 (See table 5 and section 7.1). Only 11 IUI procedures with donor sperm were carried out in women aged 40+ in 2005, with three resulting in pregnancy (27.3%).

Table 20 Pregnancies and deliveries after egg donation in 2005

	Donation	Transfers	Pregnancies N (%)	Deliveries	Pregnancies per transfer (%)	Deliveries per transfer (%)
Ireland	6	6	2	2	33.3%	33.3%
Europe	11,491	10,920	4,576	NA	41.9%	NA

Source: Nyboe Andersen et al. (2009); NA: Data not available; 'Europe' data was available from 23 European countries.

The most recent data from ESHRE shows that after egg donation there were two deliveries resulting from six donated embryos in Ireland in 2005 (Nyboe Andersen *et al.,* 2009).
Data available from 23 European countries showed that in 2005 there were 4,576 clinical pregnancies that resulted from the transfer of 10,920 donated eggs. Therefore the clinical pregnancy rate per transfer was 41.9%. This is slightly higher than the average pregnancy per transfer of 30.3% with IVF using fresh embryos in Europe in 2005 (Nyboe Andersen *et al.,* 2009). The reason for this is that donor eggs must be obtained from women who are 35 years or younger (HFEA, 2007/8). A recent retrospective cohort study investigated the reproductive performance of pregnancies among egg donors (when their own eggs are fertilised and re-implanted) and egg donor recipients (when eggs from a donor are fertilised and implanted

into a recipient) (Zegers-Hochschild *et al.,* 2009). The study found that similar chances of pregnancy with eggs re-implanted in the women who donated them and in women who receive donated eggs. As well as having similar embryo implantation rates, the egg donors and their recipients had similar gestational age at delivery, weight of newborn and perinatal mortality.

Table 21 Intrauterine insemination with donor semen in 2005

		Cycles N	Pregnancies N (%)	Singleton N (%)	Twin N (%)	Triplet N (%)
Women aged under 40	Ireland	68	30 (44.1)	25 (83.3)	2 (6.7)	0 (0.0)
	Europe	18,515	3,498 (18.9)	2,876 (88.0)	353 (10.8)	39 (1.2)
Women aged 40+	Ireland	11	3 (27.3)	3 (100.0)	0 (0.0)	0 (0.0)
	Europe	2,053	189 (9.2)	173 (93.5)	12 (6.5)	0 (0.0)

Source: Nyboe Andersen et al. (2009); 'Europe' data was available from 19 European countries

7.6 Preimplantation Genetic Diagnosis and Screening

Preimplantation Genetic Diagnosis (PGD) involves removing some cells from an embryo (a process known as a biopsy) and examining the genetic material in the laboratory. PGD falls into two categories – High risk PGD (referred to as PGD) and low risk PGD (which is referred to as PGS or Preimplantation Genetic Screening) (Thornhill et al. 2005). PGD aims to prevent the birth of affected children in fertile couples with a high risk of transmitting genetic disorders, for example cystic fibrosis, sickle cell anaemia and Huntington's Disease. PGS aims to improve pregnancy rates in subfertile couples undergoing IVF/ICSI treatment, for example women of advanced maternal age, couples with repeated IVF failure or repeated miscarriages (Thornhill et al. 2005).

The evidence

The effectiveness of PGS is currently unclear. PGS appears to significantly reduce the incidence of spontaneous abortions (Harper *et al.,* 2008). However, one RCT has shown no benefit of PGS in subfertile women under the age of 35 undergoing IVF treatment (Mastenbroek *et al.,* 2007). PGD and PGS are labour intensive, time consuming and invasive to the embryo. However the risk of miscarriage is reduced and pregnancies with viable but abnormal embryos may be avoided (Harper *et al.,* 2008). Further good quality studies are required to determine the usefulness of PGS, and the group of patients likely to benefit most.

The European Society of Human Reproduction and Embryology (ESHRE) has collected data on PGD since 1997. The most recent data (for 2005) (published by Goossens et al. (2008) was collected from 39 centres worldwide. This data shows that 3,488 cycles were performed for PGD and PGS and a total of 42,778 oocytes were collected. Seventy percent of the oocytes were fertilised, and 99% of the embryos were successfully biopsied, of these 94% gave a diagnostic result, of which only 35.7% were transferable. The average pregnancy rate was 19% per oocyte retrieved and 26% per embryo transferred. The overall delivery rate was 16% per oocyte retrieved, and 22% per embryo transferred. There were 650 clinical pregnancies following PGD or PGS in Europe in 2005, 27% of which were multiple pregnancies. Data was collected on 550 deliveries in Europe in 2005. Data on the babies born following PGD or PGS are being collected by the ESHRE.

Currently PGD and PGS are not availble in Ireland (CAHR, 2005). Elsewhere they are relatively unregulated. However, the use of these treatments is rapidly increasing. Almost 6000 cycles were performed for PGD and PGS in 2006 (ESHRE PGD Consortium, 2008), compared with 3,488 reported in 2005 (Goossens *et al.,* 2008). The ESHRE have developed consensus-based guidance on the best way to practice PGD and PGS based on clinical experience and data (Thornhill *et al.,* 2005). The next annual report of PGD/PGS data hopes to report the percentages of centres conforming to these guidelines.

7.7 In Vitro Maturation (IVM)

In vitro maturation (IVM) involves taking immature eggs from un-stimulated, or minimally stimulated ovaries and maturing them in the laboratory (in vitro) for one to two days. When the eggs have matured they are fertilised using ICSI and transferred to the womb a few days later. IVM eliminates the risk of OHSS as it does not require ovarian stimulation. IVM is particularly useful for women with PCOS, as these women have a significant risk of OHSS. Other benefits of IVM are that it is less expensive and has a shorter treatment regimen than IVF.

The evidence

The use of IVM is increasing. In 2005, IVM was reported in eight European countries. A total of 247 aspirations were reported, which resulted in 23 pregnancies (a pregnancy rate of 9% per aspiration) (Nyboe Andersen *et al.,* 2009). The evidence on the effectiveness of IVM is limited. A recent Cochrane review found no relevant RCTs to assess the effectiveness of IVM compared with other conventional ART (Siristatidis *et al.,* 2009). Evidence from an observational study reported a clinical pregnancy rate of 21.5% (Cha *et al.,* 2005), which is slightly lower than the average clinical pregnancy rates reported with IVF in Ireland (31.8%) and in Europe (30.3%), although it is similar to the clinical pregnancy rates reported with frozen embryo transfers in

Ireland (22.5%) and Europe (19.6%). A case control study comparing 107 IVM cycles with 107 IVF cycles reported a non-significant difference in live birth rates per retrieval with IVM (15.9%) and IVF (26.2%) (Child *et al.,* 2002).

Good quality evidence from RCTs is required to assess the usefulness of IVM compared with IVF or ICSI for women with PCOS. Until then, it may be more appropriate to continue to offer conventional ART to sub-fertile women with PCOS (Siristatidis *et al.,* 2009).

7.8 Factors affecting outcome of ART

Female age

The optimal female age range for successful IVF treatment is 23 to 39 years (NCC WCH, 2004). The chances of a live birth per IVF treatment cycle are:-

Table 22 Chances of live birth with female age

Women aged	Chances of a live birth per treatment cycle
23-35	20%
36-38	15%
39	10%
40+	6%

Source: (NCC WCH, 2004).

Evidence shows no significant difference in ectopic pregnancy rates following IVF in women aged over 35 compared with younger women, although an increase in miscarriages among women aged over 34, 35 and 40 years has been reported in several studies (NCC WCH, 2004).

Number of treatment cycles

Evidence indicates that the chance of a live birth following IVF is consistent for the first three cycles of treatment, but that the effectiveness after three cycles is less certain (NCC WCH, 2004). Evidence from a recent analysis of over 200 IVF cycles reported that successful outcome decreased with each additional treatment cycle, with the most noticeable decline in clinical pregnancy rates occurring after the third cycle (Martin-Johnston *et al.,* 2009).

Pregnancy history

Evidence from observational studies published in the 1990s indicated that IVF is more successful in women who have previously been pregnant and/or who have had a live birth (NCC WCH, 2004).

Alcohol
There is a lack of evidence on the influence of alcohol on IVF outcome. One observational study of 221 couples with female infertility found that maternal and paternal alcohol consumption of more than one unit (12g) per day up to one year before an IVF or GIFT attempt was associated with a significant decrease in the success rates (Klonoff-Cohen *et al.,* 2003).

Smoking
There is convincing evidence that smoking has a negative influence on IVF outcome (Klonoff-Cohen, 2005). In both active and passive smokers, the membrane covering the oocyte (known as the zona pellucida) is thicker, compared to that of non-smokers. This makes it harder for sperm to penetrate the oocyte and therefore fertilisation more difficult.

Caffeine
Only one study (Klonoff-Cohen *et al.,* 2002) has investigated the effect of caffeine consumption of men and women on IVF success rates. This study reported that caffeine intake was not related to oocyte retrieval, fertilisation, embryo transfer or pregnancy. However women who consumed over 50mg per day of caffeine (about half a mug of instant coffee) were found to be a greater risk for not achieving a live birth with IVF or GIFT. The study also reported that women consuming more than 50mg per day of caffeine significantly decreased the length of pregnancy by up to 3.8 weeks, compared to women who consumed 0-2mg of caffeine per day. Due to the lack of published studies, there is currently inadequate evidence regarding the effect of caffeine on IVF outcome. Current advice for pregnant women in Ireland is to limit caffeine consumption to 200mg per day (about 2.5 cups instant coffee, or 2 cups brewed coffee, or 4 cups of tea) (SafeFood website, 2009).

Weight
A review of 2660 couples undergoing IVF or ICSI treatments found that obese women (with BMI over 30kg/m^2) had an increased risk of early pregnancy loss (occurring before 6 weeks gestation) and a lower live birth rate (Fedorcsák *et al.,* 2004). Increased BMI was associated with an impaired response to ovarian stimulation for IVF and ICSI, with increased FSH requirement, longer stimulation, increased risk of insufficient follicle development and fewer oocytes aspirated (Fedorcsák *et al.,* 2004). Underweight (BMI less than 18.5kg/m^2) was not found to have a negative effect on IVF or ICSI outcome (Fedorcsák *et al.,* 2004). Women should ideally have a BMI between 19 and 30kg/m^2 before commencing assisted reproduction, as a BMI outside this range is likely to reduce the success of assisted reproductive treatments (NCC WCH, 2004).

Stress (anxiety/depression)
The results of a recent cohort study that included 783 women found anxiety and depression had no influence on cancellation and pregnancy rates of a first IVF or ICSI treatment (Lintsen *et al.,* 2009). The evidence on the negative impact of stress on IVF outcome is suggested, although inconclusive, due to the many different ways of measuring stress (Klonoff-Cohen, 2005).

7.9 Risks and adverse effects associated with ART

No medical treatment, including infertility treatment is completely risk-free. Most women however go through IVF and other ART without serious problems (Kennedy, 2005). A description of the main risk factors is provided below.

7.9.1 Multiple pregnancies

A multiple pregnancy can result from any treatment that uses drugs to stimulate egg production, or when more than one embryo is replaced during IVF, ICSI or egg donation (Kennedy, 2005). The likelihood of a twin pregnancy is around 10% following treatment with clomifene citrate treatment (Kennedy, 2005). In Ireland, about 1 in 4 (25.1%) pregnancies from IVF or ICSI result in a multiple birth (Nyobe Andersen *et al.,* 2009). Irish data indicates that approximately 3% of live births after natural conception are multiple (Dept Health & Children & ESRI, 2008).

A multiple pregnancy may initially seem attractive to couples that have tried for a long time to get pregnant. However, they are associated with a significant increase in mortality and morbidity of both the mother and babies. The maternal risks associated with multiple pregnancy include increased risk of miscarriage, pregnancy induced high blood pressure, anaemia, pre-eclampsia (3 times higher with twins and 9 times higher with triplets)[32], gestational diabetes (approximately 2-3 times higher with multiple births), increased chance of hospitalisation before the birth, caesarean section and post-partum haemorrage[33] (RCOG, 2007b; Braude, 2006; Fauser *et al.,* 2005). Data from observational studies suggest that women who have had a pre-term delivery (delivery before 37 weeks) approximately double their risk of coronary heart disease, and women who have had a very low birthweight baby (less than 2.5kg) have 7-11 times the risk of death from cardiovascular causes compared to women who delivered babies weighing 3.5kg or more (Sattar & Greer, 2002).

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[32] A condition during pregnancy that has symptoms of high blood pressure, fluid retention and protein in the urine. The condition may be mild or serious.

[33] Excessive bleeding after birth.

In relation to children, half of twin babies and 90% of triplets are born prematurely with low birth weight. When compared with singleton births, twins are five times more likely to die within the first week of life (triplets are nine times as likely), and twins are four times as likely to have cerebral palsy (triplets are 18 times as likely) (Braude *et al.,* 2006).

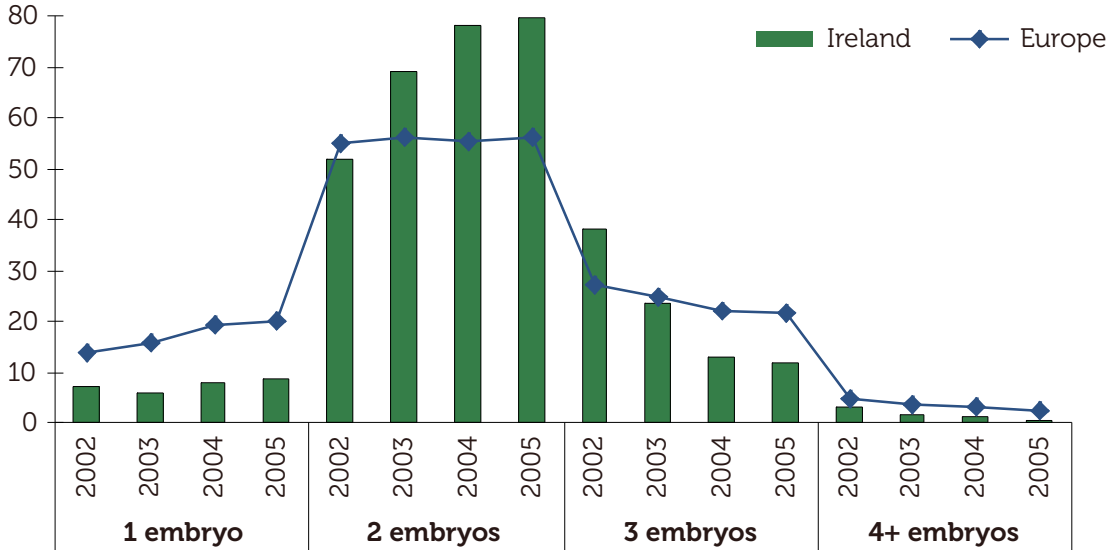
The numbers of live multiple births in Ireland increased by 27% from 1,463 in 1999 to 1,859 in 2005 (Dept Health & Children & ESRI, 2008). An effective way to reduce the risk of multiple pregnancies is to limit the number of embryos transferred at one time during IVF. Around one in four women will have a multiple birth following IVF with the transfer of two embryos (ESHRE, 2008). Most twins following ART are dizgotic (non-identical twins) as more than one egg is fertilised or more than one embryo is transferred to the woman. Non-identical (monozygotic) twins, occur when one egg is fertilised and splits in two creating twins who have the same genes as each other. Although less common, the risk of identical twins is also increased by approximately two to five times following ART (Braude *et al.,* 2006). Therefore a woman may become pregnant with twins when only one embryo is transferred.

Many countries across Europe are now implementing eSET (elective single embryo transfer), the transfer of one embryo at a time into a women's womb, thereby reducing the number of multiple births. Single embryo transfer is now imposed in Belgium, as already mentioned, and is currently being proposed in Nordic countries, and more countries are adopting guidelines or legislation to decrease the number of embryos transferred (ASRM, 2007). Data from Ireland in 2005 shows that when considering IVF and ICSI together, the percentage of single embryo transfers was 8.7%, dual embryo transfers 79.5%, triple embryo transfers 11.7%, and four or more embryo transfers 0.2% (Nyboe Andersen *et al.,* 2009). In Ireland, the percentages of single and double embryo transfers have been increasing and the transfer of three of four-plus embryos have been decreasing (see Figure 5). When compared with average percentages across Europe, Ireland generally has a lower percentage of single embryo transfers, although a higher percentage of double embryo transfers. Elective SET appears a straightforward solution to reduce multiple births from IVF, but there are various barriers to its implementation in Ireland:

- The need for fertility clinics to maintain acceptable pregnancy rates for women with different prospects of success.
- Requiring additional thawed single embryo transfer due to failed previous attempt(s) is more costly to the patient, more time consuming (may require more time off work), and requires more visits to the fertility clinic with more invasive treatment, medical consultations and medication.
- Requiring additional thawed single embryo transfer due to failed previous attempt(s) increases the emotional stress for the couple and the discomfort experienced by the woman.

- Patients' and clinicians' views on eSET - for example not seeing twin pregnancies as a complication (van Peperstraten *et al.,* 2008), the woman's belief that her chances of becoming pregnant will be reduced with eSET (Newton *et al.,* 2007).
- The lack of guidelines on fertility treatment in Ireland.
- The lack of data collection and reporting of outcome data from fertility clinics in Ireland.

Figure 5 Trends in number of embryos transferred



Source: Andersen *et al.,* 2006-2008; Nyboe Andersen *et al.,* 2009

7.9.2 Ovarian hyperstimulation syndrome (OHSS)

Stimulation of the ovaries is often performed deliberately using fertility drugs in order to obtain more eggs than would arise in a normal cycle. In some women there is an excessive response to the fertility drugs. The over stimulated ovaries enlarge and release chemicals into the blood stream that make blood vessels leak fluid into the body. This fluid leaks into the abdomen, and in severe cases into the space around the heart and lungs (RCOG, 2007a). Careful monitoring during IVF treatment using ovarian ultrasound can determine the size and number of follicles being produced, and allows early signs of OHSS to be detected. If necessary, the ovarian stimulating medication can be reduced in strength or stopped completely. A "coasting" approach may also be used to prevent OHSS developing. This involves continuing with the treatment, but stopping the stimulation for several days, or proceeding with collecting the eggs, but freezing the embryos so they can be used at a later date (as pregnancy is known to aggravate OHSS) (BFS, 2005).

Mild forms of OHSS, which causes mild abdominal bloating, abdominal discomfort and nausea (RCOG, 2007a) can affect up to one in three (33%) women having ovarian stimulation treatment (Delvigne & Rozenberg, 2002). In more severe forms of OHSS more fluid builds up in the abdomen causing more bloating and pain, nausea and vomiting, extreme thirst with a decreased output of urine, and difficulty with breathing can occur due to a build up of fluid in the chest (BFS, 2005). Severe OHSS has been reported to occur in 0.5% to 5% ovarian stimulation treatment cases (Delvigne & Rozenberg, 2002). Women at higher risk of OHSS include those with polycystic ovaries, women aged under 30 years, use of GnRH agonists, using high levels of hCG, and women who have had previous episodes of OHSS (RCOG, 2006). Mild symptoms of OHSS can be treated with paracetamol. Women suffering from more severe symptoms may be admitted to hospital for treatment that may include anti-sickness medication, an intravenous drip to replace lost fluids, and support stockings and heparin injections to prevent a blood clot (RCOG, 2007a). When a woman is receiving fertility drugs to stimulate the ovaries, she should be carefully monitored to detect early signs of OHSS so that treatment can be modified or cancelled if necessary (BFS, 2005).

7.9.3 Ectopic and heterotopic pregnancies

An ectopic or extra-uterine pregnancy is one that develops outside the uterus. The most common site is within a fallopian tube, but the embryo may also implant on an ovary or elsewhere in the abdominal cavity. Around 4% of women who become pregnant after assisted conception will have an ectopic pregnancy (Braude & Rowell, 2003). This is around double the rate of occurrence in naturally conceived pregnancies (BFS, 2005).

A heterotopic pregnancy is a multiple pregnancy with one embryo developing in the uterus and one embryo developing in a fallopian tube. This is an extremely rare occurrence in naturally conceived pregnancies, but may occur in up to 1% of women who have had assisted conception (BFS, 2005).

The main risk factors for ectopic pregnancy are a history of genital infection or tubal damage, and smoking (Fernandez & Gervaise, 2004). Ectopic pregnancies can be treated with the drug methotrexate if the pregnancy is at a very early stage, or surgery is conducted to remove the pregnancy (BFS, 2005).

7.9.4 Ovarian cancer

There is conflicting evidence on whether fertility stimulating drugs cause ovarian cancer (NCC WCH, 2004). It is known that there is an increased risk of ovarian cancer among women who have never had children (Permuth-Wey & Sellers, 2009; Salehi *et al.,* 2008). A meta-analysis of eight case-control studies concluded that infertility, but not the use of fertility drugs, increases

the risk of ovarian cancer (Ness *et al.,* 2002). It remains uncertain whether the increased risk of ovarian cancer among infertile women is caused by the relatively high proportion of nulliparious women in this population, or by the use of infertility treatments (NCC WCH, 2004). Until evidence is available to make firm conclusions on the risk of ovarian cancer, it may be advisable to identify high-risk infertile patients for ovarian cancer, investigate pre-existing cancer prior to fertility treatment, inform patients of potential risks and obtain informed consent, avoid exposure to long periods of ovulation induction before patients are referred for IVF, and monitor women treated with these drugs, especially those who fail to conceive (Zreik *et al.,* 2008). Guidelines in the UK advise that the lowest effective dose and duration of use of ovarian stimulation treatment should be used (NICE, 2004).

7.9.5 Other cancers

The association between treatment with ovulation stimulating drugs and cancer of the breast, endometrium, cervix, thyroid, colorectum or melanoma has not been established (NCC WHC, 2004).

Eight: Other treatment

8.1 NaPro Technology (Natural Procreative Technology)

Natural procreative (NaPro) technology has been available in Ireland since 1998. The treatment is based on a detailed study of events occurring during ovulation and throughout the menstrual cycle, and by informing couples about their fertility and how to monitor their own fertility cycles. Abnormalities of the reproductive cycle are investigated and treatments are provided. For example, ovulation induction or stimulation, medications to enhance cervical mucus production, or hormonal supplementation in the luteal phase (Stanford *et al.,* 2008) may be given. Many of the medications used with NaPro Technology are widely used in other fertility programmes, although the precise timing and monitoring of such treatments are unique to NaPro Techology (FertilityCare, 2009). The aim of NaPro Technology is to allow conception through natural intercourse.

To date, only one cohort study (Stanford *et al.,* 2008) has been published in a peer-reviewed medical journal. One limitation of NaPro Technology is the length of time required for the initial investigation (four months) and the treatment time (which can last up to two years). Almost 45% of the couples had withdrawn from treatment by the first year and 63% by the second (Sanford *et al.,* 2008). Further studies that compare the effectiveness of NaPro Technology with IVF and other ART treatments are required before the usefulness of this treatment approach can be determined.

The cost of NaPro Technology is usually less than most other ART treatments.

Nine: Key findings

Medicines to improve fertility

- Clomifene is an effective first line treatment for women with PCOS.
- Gonadotrophins appear to be more effective than Clomifene, but they are associated with significantly higher multiple pregnancy rates compared to Clomifene.
- GnRH analogues are often used to prevent spontaneous ovulation when gonadotrophins are given to women undergoing IVF.
    - Use of GnRH-agonists during IVF significantly increases clinical pregnancy rates by up to 127%, whilst making no difference to multiple pregnancy rates or spontaneous abortions.
    - Use of GnRH-antagonists during IVF significantly decreases the gonadotrophin requirements and significantly decreases the risk of OHSS compared with the use of GnRH-agonists. Therefore GnRH-antagonists have fewer side-effects compared with GnRH-agonists.

Surgical treatments

- Women with PCOS who have not responded to Clomifene should be offered LOD since it is as effective as gonadotrophin treatment and is not associated with an increased risk of multiple pregnancies.
- The introduction of IVF has led to a reduced requirement for tubal surgery
- Around 3 in 10 women with uterine fibroids may be infertile. Myomectomy is currently the best treatment option for removing uterine fibroids whilst leaving the uterus in place.
- The chances of conceiving after surgery for endometriosis-associated infertility are increased by 10-25%.

Assisted Reproductive Technology

- The success of IUI depends on several factors including the cause and duration of infertility, ages of partners, and sperm quality. Variations in the IUI procedure such as including ovarian stimulation and using different implantation techniques may influence the outcome. In Ireland, the pregnancy rate per IUI procedure in women aged under 40 is 9.2%.
- In Ireland the percentage of pregnancies per IVF transfer of fresh embryos is 31.8% and 22.5% per transfer of frozen embryos. The percentage of deliveries per IVF transfer of fresh embryos is 27.4% and 14.1% per transfer of frozen embryos.
- IVF might result in more pregnancies than other options for couples with unexplained infertility, however, until more evidence is available, IVF may not be the preferred first treatment choice for these couples, as less invasive options may be more appropriate.
- The success of IVF treatment is dependent on many factors. These include patient factors such as age, weight and pregnancy history, and variations in IVF procedure such as the number of embryos transferred and the method of embryo transfer used.

- In Ireland, the percentage of pregnancies per ICSI transfer is 34.1%. The percentage of deliveries per transfer is 28.6%. Couples should be offered genetic counselling with ICSI, due to the higher incidence of genetic abnormalities in men with severe male infertility.
- The average pregnancy rate per transfer of embryos using donated eggs across Europe was 41.9%. This is slightly higher than the European average pregnancy per transfer of 30.3% with IVF using fresh embryos. The reason for this is that donor eggs must be obtained from women who are 35 years or younger.
- The effectiveness of Preimplantation Genetic Screening is currently unclear, although PGS does appear to reduce the incidence of spontaneous abortion. More evidence on the effectiveness of PGS is required.
- The use of IVM is increasing, although the evidence on its effectiveness is currently limited. Observational studies suggest a pregnancy rate of 21.5% per transfer, which is similar to the 22.5% pregnancies reported per IVF transfer of frozen embryos.

Ten: Glossary

Abortion (Spontaneous abortion) is a pregnancy loss during the first 20 weeks of gestation.

Adhesions refer to scar tissue in the abdominal cavity, fallopian tubes, or inside the uterus. Adhesions can interfere with transport of the egg and implantation of the embryo in the uterus.

Anovulation is the absence of ovulation (ovulatory failure)

Assisted Reproductive Technology (ART) includes several procedures used to bring about conception without sexual intercourse. For example IVF, IUI, GIFT and ZIFT.

A **blastocyst** is an embryo that has been developing for 5-6 days since fertilisation.

Chlamydia is a sexually transmitted infection, which can cause serious damage to a woman's reproductive organs.

A **clinical pregnancy** is a pregnancy in which a beating foetal heart beat has been identified.

Cryopreservation is the freezing and storage of gametes, zygotes, or embryos.

An **ectopic pregnancy** is a pregnancy that occurs outside the uterus, usually in a fallopian tube.

Egg retrieval / aspiration is the process used to obtain eggs from the ovarian follicles for use in in vitro fertilisation.

The **embryo** is the organism in the early stages of growth and differentiation from fertilization to the start of the third month of pregnancy. After that time it is known as a foetus.

Embryo transfer refers to the placement of the embryo into the uterus or into the fallopian tube after in vitro fertilisation.

Endometriosis is a chronic condition characterised by the growth of endometrial tissue in areas other than the uterine cavity, most commonly in the pelvic cavity, including the ovaries

Extra-uterine pregnancy is a pregnancy that develops in a site other than the uterus, most commonly in the fallopian tube.

Fallopian tubes are the two tubes through which eggs travel to the uterus once released from the follicle. Sperm normally meet the egg in the fallopian tube, the site at which fertilization usually occurs.

A **follicle** is a fluid-filled sac that contains an immature egg, or oocyte. Follicles are found in the ovaries. Several follicles develop each cycle, and normally only one will ovulate an egg. During ovulation, a mature egg is released from the follicle. The follicles that do not release an egg disintegrate.

A **gamete** is a reproductive cell, the egg in women and sperm in men.

Gonadotrophins are hormones that control reproductive function, follicle stimulating hormone (FSH) and lutenizing hormone (LH).

Hydrosalpinx is a collection of watery fluid within the fallopian tube that occurs due to damage at the far end of the tube near the ovary. Untreated hydrosalpinx, even if just in one tube, can cause infertility and failure to conceive even with IVF.

Hyperprolactinemia is a condition in which too much prolactin is present in the blood of women who are not pregnant. This can lead to irregular or infrequent periods, or complete cessation of periods.

Hysterosalpingography: A special X-ray procedure in which a small amount of fluid is injected into the uterus and fallopian tubes to detect abnormal changes in their size and shape or to determine whether the tubes are blocked.

Infertility is the failure to conceive following frequent unprotected sexual intercourse for one or two years.

Ovarian hyperstimulation syndrome is a complication associated with ovulation induction. Some women have an excessing response to the fertility drugs used to stimulate induction and their ovaries enlarge and release chemicals into the blood stream that make blood vessels leak fluid into the body.

Ovulation is the release of the egg from the ovarian follicle.

Polycystic ovarian syndrome (PCOS) is a condition characterised by irregular or absent menstrual periods, acne, obesity, and excess hair growth. The condition is quite common among infertile women.

Prolactin is the hormone produced by the pituitary gland in the brain.

Sub-fertility refers to any form of reduced fertility that results in a prolonged duration of unwanted lack of conception.

A **zygote** is a fertilised egg, which has not yet divided.

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The physical and psychological burden the infertile couple are willing to go through, and the financial cost the couples are willing to pay if they can afford it, attest to the high ranking of infertility as a perceived burden of disease

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