Patient selection for assisted reproductive technology treatments

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Assisted reproductive technology refers to procedures in which the oocyte is handled or manipulated in vitro before replacement, either as an oocyte or an embryo. Because of rapid advances in this area, infertile couples may seek direct referral for assisted reproductive treatments, instead of trying simpler measures such as ovulation induction and intrauterine insemination. It is important to establish whether these conventional infertility treatments are appropriate, as such treatments are generally safer, less stressful, and more affordable. On the other hand, subjecting infertile couples to unnecessary delay by offering inappropriate treatments—for example, ovulation induction for tubal infertility or intrauterine insemination for severe male-factor infertility—would reduce the overall chance of success because of the age-related decline in female fecundity. The choice of infertility treatments thus depends on a balance of factors: the chance of pregnancy without treatment; the chance with simpler and safer, but less successful, infertility treatments; or the chance with the more complex and costly, but more effective, assisted reproductive treatments. The factors that should be taken into consideration include the age of the woman, the duration of infertility, the causes of infertility, the availability and cost of alternative treatments, and—most importantly—the acceptability.

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Introduction

Infertility is defined as the failure by a couple of reproductive age to conceive after 12 months or more of regular coitus without using contraception. This definition is based on epidemiological studies, which have shown that 80% of couples in the general population normally conceive by that stage.[1] It is estimated that 15% of couples living in developed countries are infertile.[2] There has been no major change in prevalence, but there has been an increase in demand for treatment during the past decade because of the perception that effective assisted reproductive technology (ART) treatments are now available. Table 1 summarises the ART procedures that are most commonly practised throughout the world.

Although ART was initially developed for patients with tubal infertility, it is currently used for almost all kinds of infertility problem, because its success rates are expected to be higher than those of conventional treatments. However, ART treatment also has disadvantages. It involves greater expense, and potentially serious complications such as ovarian hyperstimulation syndrome and multiple pregnancies can occur. There are also fears that drugs that induce ovulation may increase the risk of ovarian cancer. Infertility treatment should therefore be individualised to avoid subjecting couples to unnecessary risks due to overtreatment, such as the unnecessary use of ART treatments, or to inappropriate delay because of undertreatment.

Table 2 summarises common infertility treatments and their indications. It should be emphasised that the choice of treatment is also influenced by other factors such as the age of the woman and the duration of infertility. The age of the female partner is one of the most important factors determining spontaneous fertility. It is also a major factor in determining the success of any form of infertility treatment. Using the database established in 1991 by the Human Fertilisation and Embryology Authority, Templeton et al[3] analysed 36 961 in vitro fertilisation (IVF) cycles that

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Table 1. Common assisted reproductive technology procedures

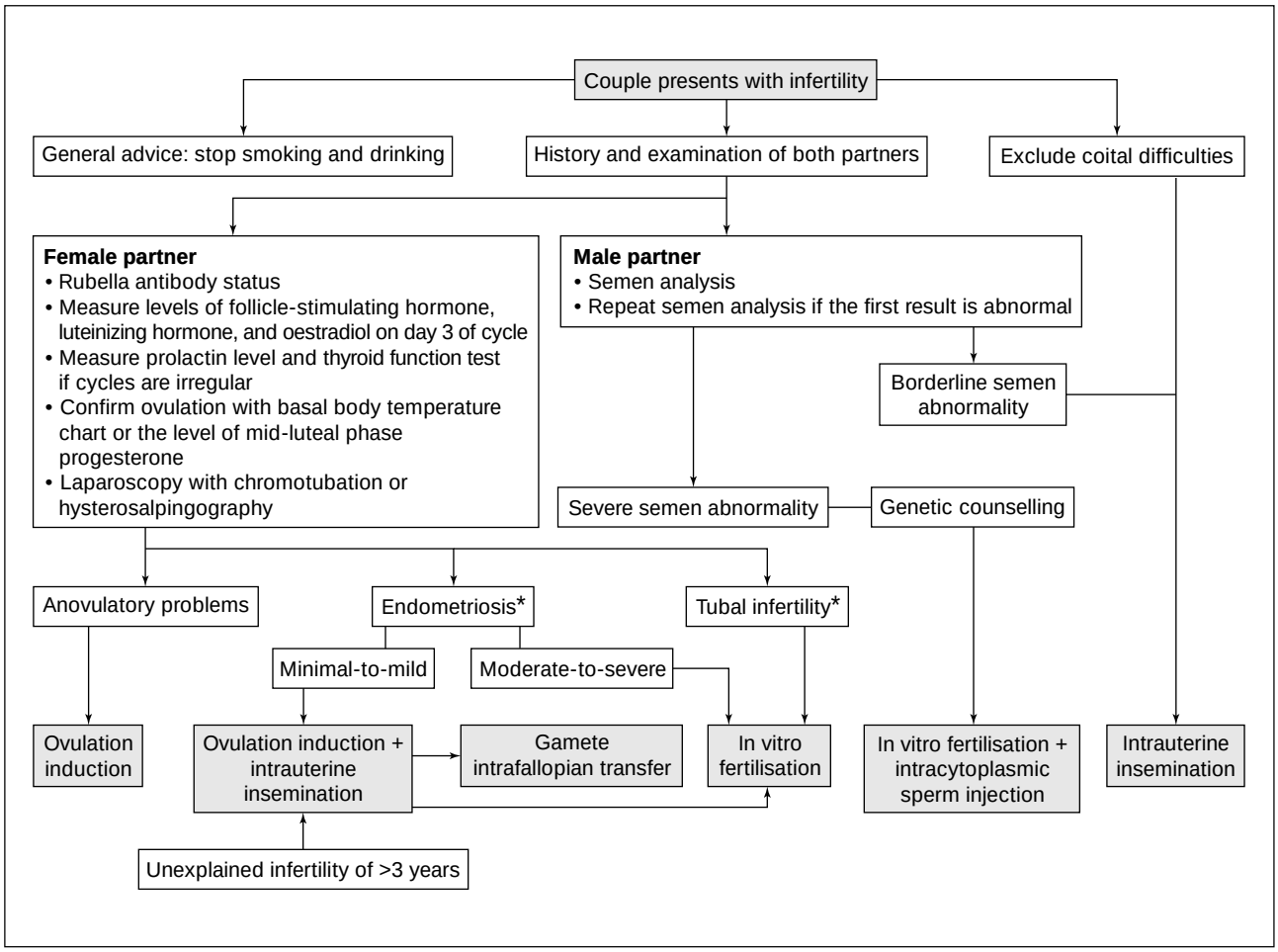
Type of assisted reproductive technology	Procedure
In vitro fertilisation	A four-stage procedure, which includes controlled ovarian hyperstimulation, oocyte retrieval under transvaginal ultrasound guidance, fertilisation with sperm in vitro, and embryo replacement into the uterus
Gamete intrafallopian transfer	Similar to in vitro fertilisation, except that the oocytes and sperm are injected into the fallopian tube under laparoscopic guidance and fertilisation take places within the body
Intracytoplasmic sperm injection	A single sperm is injected directly into the oocyte to facilitate fertilisation; at least a few viable sperm must be present in the ejaculate, epididymis, or testis
Microsurgical epididymal sperm aspiration	For treatment of obstructive azoospermia when no sperm are found in the ejaculate; sperm are directly recovered from the epididymis through needle aspiration
Testicular sperm extraction	For treatment of obstructive or non-obstructive azoospermia when no sperm are found in the ejaculate or the epididymis; sperm are directly recovered from the testis through open biopsy
Frozen embryos	Excess embryos (more than the numbers required for transfer) can be frozen and stored in liquid nitrogen for future use

Table 2. Common infertility treatments and their indications

Infertility treatment	Indications
Ovulation induction alone	Anovulation
Intrauterine insemination alone	Coital problems, immunological factors, cervical factors, borderline male factors
Ovulation induction and intrauterine insemination	Unexplained infertility, minimal-to-mild endometriosis, borderline male factors
Gamete intrafallopian transfer	Unexplained infertility, minimal-to-mild endometriosis
In vitro fertilisation	Tubal infertility, moderate-to-severe endometriosis, male-factor infertility, failure of other treatments
Intracytoplasmic sperm injection	Severe male-factor infertility, previous fertilisation failure
Oocyte donation	Primary or secondary ovarian failure, familial genetic disorders, repeated ART failure

were performed in the United Kingdom. They found a marked decline in pregnancy rates in women older than 35 years, and no pregnancies were recorded for women older than 45 years except in the oocyte donation programme. It seems that although young patients in their 20s may have the option to use safer but only moderately effective treatments, by their late 30s, treatment should be more aggressive. On the other hand, aggressive infertility treatments should be discouraged in women in their 40s because of poor success rates. The duration of infertility is another major factor determining the likelihood of spontaneous pregnancy in untreated infertile couples.[4] As most infertility is not absolute but includes some degree of subfertility, many couples have a background chance of conceiving naturally. The longer the duration of infertility, however, the less likely is that probability. This predictive value is of particular importance to couples with unexplained infertility.

Even in normal couples with proven fertility, the average monthly conception rate is only 20% to 25%. The peak rate is 33% in the first month of trying, falling rapidly to approximately 5% each month thereafter.[5] The expectation of any infertility treatment must be judged against this finding. Infertility treatment should be offered when the chance of conceiving naturally is unacceptably low (<1% to 2% per cycle or 20% to 30% after 2 years).[6] Simple treatments such as ovulation induction and intrauterine insemination (IUI) are suitable only in certain situations (Table 2) and will be expected to achieve a pregnancy rate of approximately 10% per cycle. Assisted reproductive techniques are suitable for almost all kinds of infertility problems, but treatment with even the most advanced ART is expected to achieve only a 25% to 30% success rate per cycle. Treatment may need to be repeated several times before success is achieved. As a constant rise in the cumulative pregnancy rates during the six initial



* Surgical treatment of endometriosis and tubal infertility is not shown

Fig. The investigation and management of the infertile couple

cycles has been demonstrated,[7] in general it is worth pursuing treatment for up to six cycles. Before an infertile couple is recruited into an IVF programme, they should be warned that both the cumulative pregnancy and live-birth rates decline with the age of the woman. Tan et al[8] have reported that the cumulative pregnancy and live-birth rates after five IVF cycles were 54% and 45%, respectively, at age <35 years, 38.7% and 28.9% at 35 to 39 years, and 20.2% and 14.4% at age ≥40 years.[8] The stress, time away from work, cost, and complications of the treatment should also be emphasised. Alternatives such as adoption or childlessness should be discussed. Patient acceptability is very important, but it is often neglected during the infertility evaluation.

Infertility evaluation

The Figure summarises the investigation and management of an infertile couple. The cornerstone of any infertility evaluation relies on the assessment of coital difficulties, cervical or immunological factors, ovulation, tuboperitoneal pathology, and semen quality.

Assessment of coital, cervical, or immunological problems

Coital difficulties should be recognised if a detailed sexual history is obtained. Cervical or immunological factors need to be considered when results from post-coital tests are repeatedly negative. Further investigations to detect antibodies against components of sperm are then necessary. The use of systemic corticosteriods to treat men who have anti-sperm antibodies is not recommended, as the evidence of benefit is conflicting and there are potentially serious side effects such as aseptic hip necrosis.[9] Treatment using IUI with or without ovarian stimulation can bypass the problem of sperm progression through cervical mucus. However, ART should be considered after repeated failure of IUI treatments.

Assessment of ovulation

A detailed menstrual, medical, and drug history should be obtained. Women with normal regular menstrual cycles of 28 to 30 days are usually ovulating. Simple assessments such as a biphasic pattern of the basal body temperature chart or an appropriate rise of the

midluteal serum progesterone concentration provide presumptive evidence of ovulation.

In patients with suspected anovulation, the following tests should be performed: measurement of the levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, and testosterone (all samples having been taken at early follicular phase before day 5 of the cycle), as well as the prolactin level and the thyroid function test. After excluding any secondary medical or endocrine causes, anovulatory problems are usually categorised under four conditions.[10]

Hyperprolactinaemic anovulation
Patients with hypergonadotrophic anovulation may present with galactorrhoea. If a serum prolactin concentration confirms hyperprolactinaemia, investigations to exclude a pituitary adenoma and hypothyroidism are performed. These tests comprise computerised tomography or magnetic resonance imaging of the pituitary gland and the thyroid function test. Taking a detailed drug history is also important, because the use of some commonly prescribed drugs such as phenothiazine, haloperidol, metoclopramide, cimetidine, and methyldopa is associated with hyperprolactinaemia. The first-line treatment is the use of dopamine agonists such as bromocriptine. These drugs can be combined with anti-oestrogens, if ovulation does not occur despite normalised prolactin concentrations.[11]

Hypogonadotrophic anovulation
The causes of hypogonadotrophic hypogonadism are often functional and transient. Anovulation may be stress-induced or related to weight loss or excessive exercise. An organic cause should be excluded, however, particularly if there are neurological symptoms. The evidence for hypogonadotrophic hypogonadism is a low level of FSH, LH, and oestrogen, and the absence of withdrawal bleeding after a progesterone challenge test. The primary aim of treatment should be to correct the underlying cause. It has been shown that spontaneous ovulation will return in underweight women after correction of their nutritional deficiency.[12] Anti-oestrogens are not effective in this condition, owing to the non-functioning hypothalamic-pituitary-ovarian axis. Ovulation induction should be achieved by using either a pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophins in a specialist infertility centre, in which the woman is intensively monitoring during ovulation induction.

Hypergonadotrophic anovulation
Hypergonadotrophic anovulation implies ovarian resistance or failure and is diagnosed when plasma concentrations of FSH are higher than 20 IU/L from repeated measurements. If the patient is younger than 40 years, this condition should be further investigated and treated as a premature menopause. The only effective practical treatment for hypergonadotrophic anovulation is oocyte donation.

Normogonadotrophic anovulation
Patients with normogonadotrophic anovulation have normal FSH concentrations, but LH concentrations may be elevated. They are not hypo-oestrogenic and will bleed in response to a progesterone withdrawal test. The majority of these women have polycystic ovaries.[13] This condition should be suspected if the woman is obese and hirsute, or if there is hyperandrogenaemia or an elevated LH to FSH ratio.[13] Polycystic ovaries can be diagnosed using ultrasonography.

Apart from weight loss in obese normogonadotrophic anovulation patients,[14] the first-line treatment is the use of anti-oestrogens such as colmifene (clomiphene) citrate. The starting dose of clomifene is 50 mg/d for 5 days, from day 2 to day 6 of each cycle. The dosage can be increased in monthly increments up to 200 mg/d. Early referral to specialist infertility centres should be considered if patients are still anovulatory at the maximum dosage (clomifene resistance) or if there is failure to conceive after 12 cycles of successful treatment with confirmation of ovulation (clomifene failure). The alternatives for patients with clomifene resistance polycystic ovarian disease are either medical induction of ovulation with pulsatile GnRH or gonadotrophins, or surgical treatment with ovarian wedge resection or laparoscopic ovarian drilling. Medical treatments provide a good cumulative pregnancy rate, but they increase the risk of multiple pregnancies and ovarian hyperstimulation.[10] The spontaneous ovulation rate after surgical treatment is reported to be 60% to 80%,[15,16] but the efficacy in terms of pregnancy and the ovarian damage associated with the procedure has yet to be evaluated.[17]

Assessment and treatment of tuboperitoneal disease
Tubal damage and pelvic adhesions may result from pelvic inflammatory disease, or may be secondary to endometriosis or previous lower abdominal or pelvic surgery. There is still debate regarding the appropriate time for testing tubal patency. Early investigation for tuboperitoneal pathology should be undertaken when there is a suspicious history or the presence of symptoms such as dysmenorrhoea or dyspareunia. However, in low-risk patients, the common practice is to delay a test of tubal patency until there have

been up to six to12 ovulatory cycles. This approach has been challenged, however, as pelvic infection or endometriosis can be completely silent. Serological tests for *Chlamydia trachomatis* infection have been suggested as a simple screening method for unsuspected previous infection, which would indicate likely tubal damage.[18] Early laparoscopy is then indicated in seropositive women.[19]

Methods used to assess tubal patency include laparoscopy with chromotubation, or hysterosalpingography. The latter technique may be used as a screening test for tubal patency in low-risk patients. However, laparoscopy with chromotubation should be the preferred method of investigation, particularly when there is a strong suspicion of peritoneal disease. Laparoscopy may also be necessary when there is a hysterosalpingogram showing suspected false-positive results due to tubal spasm or during planning for infertility surgery.

The two choices for the treatment of tubal infertility are tubal surgery or IVF. In general, pregnancy rates after tubal surgery are not as good as those achieved by IVF. The overall 2-year cumulative pregnancy rate after tubal surgery is only 20%,[20] which can now be expected in a single cycle of IVF treatment. Tubal surgery may still be appropriate in carefully selected cases, because different types of tubal surgery have different prognoses. Surgery may be offered in cases of mild pelvic adhesions, proximal tubal obstruction, or mild distal tubal disease, although the eventual chance of pregnancy after 2 years is not much more than 50%.[20] Hence, if a pregnancy has not occurred within 12 months (at most 24 months) of tubal surgery, IVF should be offered.

Owing to the poor prognosis of tubal surgery, IVF should be the first-line treatment for significant pelvic adhesions or moderate-to-severe distal tubal disease.[20] Early referral for IVF is also necessary for women of advanced age or when coexisting problems such as male-factor infertility are present.

Endometriosis-associated infertility

Endometriosis, even of a minor degree, is associated with marked subfertility.[6] Medical treatment of endometriosis has no proven benefit in infertility.[21,22] On the contrary, the chance of pregnancy is delayed by the duration of medical treatment. Surgical ablation of minimal-to-mild endometriosis has been shown to improve fertility in subfertile women,[23] so this should be considered at the time of a diagnostic laparoscopy. Ovulation induction by using IUI should be offered to patients with minimal-to-mild endometriosis if the duration of infertility is more than 3 years, as studies have shown that ovulation induction with IUI is more effective than either no treatment or IUI alone.[24]

There is no evidence that medical treatment of moderate-to-severe endometriosis either alone or as an adjunct to surgery improves fertility.[21,22] Surgical treatment of moderate-to-severe endometriosis has been shown to improve fertility, but a full explanation of the high surgical risk should be given.[22,25] In vitro fertilisation should also be offered as an alternative to or following unsuccessful surgery.[9]

Semen quality and the treatment of male-factor infertility

Table 3 lists the criteria of the World Health Organization (WHO) for normal semen characteristics.[26] It has been estimated that less than 10% of male-factor infertility is amenable to conventional medical or surgical treatments. Referral for IUI or ART procedures should be considered if there are two abnormal semen samples that have been taken at least 3 months apart.[26]

In patients with borderline semen abnormality, sperm preparation for IUI may correct the abnormality, but a minimum of 10 million motile sperm per whole sample is still required. For a severe semen-factor (sperm concentration <10 million spermatozoa per millilitre; or <20% motility; or <20% normal forms) or when there is history of fertilisation failure, IVF and intracytoplasmic sperm injection (ICSI) should be the primary treatment option.[27] With the

Table 3. World Health Organization criteria for normal semen characteristics[26]

Characteristic	Value
Volume	≥2.0 mL
pH	7.2-8.0
Sperm concentration	≥20 x 10^6 spermatozoa per mL
Motility	≥50% with forward progression, or ≥25% with rapid progression
Morphology	≥30% with normal forms
Vitality	≥75% live, ie excluding dye
White blood cells	<1 x 10^6 /mL
Immunobead test	<20% spermatozoa with adherent particles
Mixed antiglobulin reaction test	<10% spermatozoa with adherent particles

introduction of ICSI, which requires only a single sperm to be injected per oocyte, it is now possible to use epididymal or testicular sperm even when there are no sperm in the ejaculate. Epididymal sperm can be obtained by performing microsurgical epididymal sperm aspiration in men with obstructive azoospermia. Alternatively, testicular sperm can be obtained by using testicular sperm extraction in men with non-obstructive azoospermia. It is thus worthwhile referring affected couples to specialist infertility centres for urological assessment and, if necessary, to perform sperm recovery and ICSI. However, prior to offering any treatment to these couples, particular consideration should be given to the relevant genetic issues. Increasing evidence has suggested a genetic linkage to reproductive failure in 10% to 30% of men with severe oligoasthenoteratospermia.[28] Accordingly, these patients should be counselled about the possibility of transmitting sex chromosomal aberrations or fertility problems to their offspring before they are recruited into the ICSI programmes.[22,29]

Unexplained infertility

In 20% of couples presenting with infertility, a detailed history and examination followed by complete investigation will fail to elicit any clear explanation for the couple's problem. The main factors determining the chance of conceiving naturally are the duration of infertility, the woman's age and the previous pregnancy history.[4,30] As the spontaneous conception rate only starts to significantly decrease after 3 years of trying,[30] conservative management until then could be considered, taking into account the woman's age.[9] There is no evidence of any benefit from clomifene treatment,[31] and assisted conception should wait, except when the female partner is in her late 30s. After more than 3 years of infertility, the chances of natural conception are negligible.[30] Ovulation induction with IUI is a simple and moderately effective treatment,[32] and in general it is worth pursuing for up to six cycles of treatment, before considering ART. The advantage of this approach is that the risks associated with ART are avoided, particularly those relating to oocyte retrieval. Both gamete intrafallopian transfer and IVF are effective ART treatments in couples with unexplained infertility; both methods have similar efficacies.[33] In centres where IVF laboratories are available, however, IVF is the preferred method, because of the additional information it provides on fertilisation, which may be defective for couples with unexplained infertility. Furthermore, performing IVF avoids the anaesthetic and operative risks of laparoscopy.[9]

Conclusion

The main indications for assisted reproductive procedures include tubal disease, endometriosis, male infertility, and prolonged unexplained infertility. Assisted reproductive technology treatments are offered when the chance of conceiving by other means is unacceptably low or the women's age leaves insufficient time for other treatments. The major factor adversely affecting the success of ART is advanced female age, so early referral to specialist infertility centres should be considered, especially for women older than 35 years. On the other hand, aggressive ART treatment should be discouraged in women in their 40s, as the chance of success is often unrealistic except in oocyte donation programmes.

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