

Subfertility: causes, treatment and outcome

G. David Adamson MD

Clinical Professor

Fertility Physicians of Northern California, Stanford University School of Medicine, Stanford, CA, USA

Valerie L. Baker* MD

Fertility Physicians of Northern California, 540 University Avenue, Suite 200, Palo Alto, CA 94301, USA

Common causes of subfertility include ovulatory disorders, tubal disease, peritoneal adhesions, endometriosis, uterine abnormalities, abnormalities of sperm and advancing female age. Infertility is unexplained after thorough evaluation in about 5–10% of cases. Significant caveats must be attached to the interpretation of available data regarding infertility treatments. Successful ovulation induction in anovulatory women is possible for nearly all women except in cases of ovarian failure. Surgery is an option for some patients with tubal damage, adhesions, endometriosis and uterine abnormalities. Male factor infertility may be amenable to treatment of a specific cause, but is often empirical with the use of intra-uterine insemination (IUI) or in vitro fertilization (IVF). Egg donation is currently the most effective treatment available for age-related infertility when other treatments have not been successful. Couples with unexplained infertility may be effectively treated with ovulation induction plus IUI or IVF.

Key words: infertility; in vitro fertilization (IVF); ovulation; oligo-ovulation; gonadotrophins; endometriosis; adhesions; tubal surgery; congenital uterine abnormality; myoma; male factor infertility; intra-uterine insemination (IUI); oocyte donation; unexplained infertility.

CAUSES OF SUBFERTILITY

Several key events are necessary for conception to occur. A mature egg must be released from the ovary. The egg must be picked up by a fallopian tube and then fertilized by sperm in that tube. The embryo must be transported to the uterus by the fallopian tubes. Finally the embryo must implant into the uterine lining and develop. Infertility results when a problem develops in one or more of the steps in the process. Numerous conditions can cause infertility, but many effective treatments are available to increase the chances for conception in infertile patients.¹

Ovulation factor infertility

Infrequent or absent ovulation accounts for approximately 20% of all infertility cases.² Regular menstrual cycles strongly suggest that a woman is ovulating. Cycle lengths

* Corresponding author. Tel.: +1-650-322-1900; Fax: +1-650-322-1730.

E-mail address: vbaker@fpnc.com (V. L. Baker).

of roughly 22–35 days are usually ovulatory, especially if accompanied by premenstrual symptoms such as bloating and breast tenderness. If a woman has menses more or less often, she is probably not ovulating or is ovulating infrequently. Amenorrhoea is suggestive of ovulatory dysfunction except in patients with uterine disease such as Asherman's syndrome or a congenital uterine abnormality.

It is important to determine the cause of anovulation (absent ovulation) or oligo-ovulation (infrequent ovulation) before embarking on a treatment plan. The most common cause of anovulation or oligo-ovulation is polycystic ovarian syndrome (PCOS), the aetiology in about 70% of cases.³ Other common causes are hypothalamic dysfunction, hyperprolactinaemia, age-related ovulation dysfunction and premature ovarian failure. Congenital adrenal hyperplasia is a relatively rare cause of oligo-ovulation. Extremes of weight (such as that associated with anorexia or with morbid obesity) may also lead to anovulation by producing hypothalamic dysfunction. In patients with a body mass index (BMI) of less than 20, low gonadotrophin releasing hormone secretion leads to low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion and thus low ovarian oestradiol secretion. At the other extreme of weight, women with a BMI greater than 27 have an increased risk of oligo-ovulation.⁴ Clinical distinction between these aetiologies may be made on the basis of history, physical findings and selected laboratory testing, as has been recently reviewed.⁵

Tubal factor infertility

Open and functional fallopian tubes are necessary for conception. Tubal and/or adhesive factors account for about 35% of all infertility cases.² Infertility may result from complete blockage of the distal end of the fallopian tube (hydrosalpinx) as a sequela of sexually transmitted disease, surgical intervention for management of ectopic pregnancy or other intra-abdominal condition, non-gynaecological abdominal-pelvic infection (uncommonly) or, rarely, as a congenital anomaly. Proximal obstruction may result from salpingitis isthmica nodosa or other inflammatory conditions, or it may be idiopathic. Partial obstruction may result in an altered immunochemical and hormonal environment and abnormal tubal peristalsis and function. Peritubal adhesions can impair tubal mobility and oocyte pickup and/or sperm transport.^{6,7} Very badly damaged obstructed tubes may fill with fluid, creating hydrosalpinges, and lower *in vitro* fertilization (IVF) success rates unless salpingectomy or partial salpingectomy is performed.^{8,9}

Endometriosis and peritoneal factor infertility

Peritoneal factor infertility refers to abnormalities involving the peritoneum, such as endometriosis and associated abnormalities of the peritoneum. Endometriosis is found more commonly in women with infertility compared with women of normal fertility. Women with endometriosis may have an earlier onset of diminished ovarian reserve. Immunological and genetic factors are also likely to be important in the pathogenesis and pathophysiology of endometriosis.^{10,11} While there has been much debate it is likely that even minimal endometriosis can reduce a woman's fertility.^{12,13} In cases of extensive endometriosis, tubal function may be compromised by adhesions. Whether adhesions are the result of endometriosis or of other inflammatory conditions, most clinicians believe fertility is compromised in their presence and that adhesiolysis appears to be beneficial in women with infertility.¹⁴

Uterine factor infertility

Abnormalities may be present in the cavity of the uterus where the embryo needs to implant and develop. These include intrauterine adhesions, polyps, fibroids, or an abnormally shaped uterine cavity. Problems within the uterus could theoretically interfere with implantation of the early embryo or increase the incidence of miscarriage. The hysterosalpingogram (HSG) is often used as an initial screen of the uterus cavity. The saline hysteroogram (SHG) is a pelvic ultrasound done while injecting saline (salt water) through the cervix to outline the uterine cavity. Unlike the HSG, it allows visualization of both the wall and the cavity of the uterus, a difference that may be helpful in assessing the position of fibroids and determining whether or not they are resectable through the hysteroscope. As a screen for abnormalities in the uterus, the SHG is a more sensitive and more specific screening test compared with the HSG, using findings at hysteroscopy as the gold standard.^{15,16}

An inadequate progesterone effect on the uterine lining is called a luteal phase deficiency. Luteal phase defects may be due to either deficient progesterone production or the inability of the uterine lining to respond to oestrogen in the proliferative phase and/or progesterone in the luteal phase. It is debatable how often a luteal phase defect can explain either infertility or recurrent miscarriage, if it explains these problems at all.¹⁷ Studies that have attempted to determine whether luteal phase deficiency is a cause of infertility have not included control groups of fertile women. Furthermore, normal fertile women who have regular menstrual cycles may have luteal phase abnormalities in nearly one-third of their cycles.¹⁸ Many infertility specialists no longer routinely do an endometrial biopsy at this time because the information has not usually been helpful in improving live birth rates.

Conditions within the cervix can contribute to infertility, but they are rarely the sole cause. Risk factors for cervical abnormalities may include cone biopsy and diethylstilboestrol (DES) exposure. Chronic infections may, in some cases, contribute to poor cervical mucus. In order to determine if there is a problem with the cervix, a postcoital test (PCT) may be performed. An ovulation predictor kit may help determine the proper day for the PCT, because improper timing is a major reason for an abnormal result. Many physicians are not currently recommending the PCT because its value in guiding infertility treatment is not clear.

Male factor infertility

A male factor is the sole cause for infertility in about 20% of couples and contributes to infertility in a further 30–40%.¹⁹ Appropriate evaluation of the male is important and should not be overlooked. Although a cause for decreased sperm quality may be determined in some cases, subfertility is currently idiopathic for many men.

Azoospermia may be classified as obstructive (such as with congenital absence of the vas deferens, ductal obstruction, or vasectomy) or non-obstructive. Most cases of non-obstructive azoospermia are due to primary testicular failure. Endocrine abnormalities, such as hyperprolactinaemia, which secondarily affect spermatogenesis, are less common. Genetic disorders associated with azoospermia or severe oligospermia include Klinefelter's syndrome (47, XXY) and microdeletions of the Y-chromosome. Congenital absence of the vas deferens is associated with cystic fibrosis mutations.

Oligospermia may result from hormonal problems, retrograde ejaculation, varicocele, or a primary testicular problem with sperm production.²⁰ Genitourinary

infection may interfere with sperm function. Environmental factors such as medications, drugs, alcohol, tobacco abuse and radiation may impair sperm production and function. Deficiency of trace elements such as zinc, folate and selenium may impair sperm function.²¹ Antiserum antibodies may impair fertility in couples with unexplained infertility.²² In many cases, no treatable cause of poor sperm quality can be found.

A recent review of the effects of male age on semen quality and fertility concluded that increasing age is associated with a decline in semen volume, sperm motility and sperm morphology, but not with sperm concentration.²³ There is probably some decline in male fertility with age, particularly over the age of 50, but results are confounded by female partner age. There is no age at which men cannot father a pregnancy. Fertility is thus much more related to the age of the female partner.

Infertility associated with advancing female age

Definitions and evidence of reproductive ageing

An age-related decline in female fertility begins many years prior to the onset of menopause, despite continued regular, ovulatory cycles. Ovarian reserve is a term often used to describe a woman's reproductive potential with respect to ovarian follicle number and oocyte quality. The drop in fertility associated with diminished ovarian reserve is due to depletion of eggs and to a decline in average egg quality.

Although there is no strict definition of what may be considered advanced reproductive age, a decline in fertility, on average, begins for women in their late twenties or early thirties, becoming more pronounced after the age of 35.²⁴ A study of the effect of female age on fertility found that the percentage of non-contracepting women who ultimately remained childless rose steadily according to their age at marriage: 6% at age 20–24, 9% at 25–29, 15% at 30–34, 30% at 35–39, and 64% at 40–44.²⁵ Similarly, a sharp decline in pregnancy rate with advancing female age is noted with donor insemination recipients (which control for fertility of the male partner and coital frequency) and with advanced infertility therapies such as IVF.^{26,27} Once an older woman becomes pregnant she also has a markedly increased risk of spontaneous abortion.²⁸ According to the 1999 report of *Assisted Reproductive Technology Success Rates*, the percentage of clinical pregnancies that failed to result in a live birth rose according to the woman's age in non-donor cycles. The miscarriage rate was approximately 15% for patients under the age of 35 and it began to increase among women in their mid-to-late thirties. The miscarriage rate was 29% at age 40 and 43% at age 42.²⁷

Preclinical pregnancy loss may be a major explanation for the decrease in fertility associated with age. Holman²⁹ studied women in rural Bangladesh because these women were sexually active but did not use contraception. He monitored 1561 menstrual cycles with ultrasensitive pregnancy assays. He found that age had minimal effect on the rate of conception. However, there was a significant increase in the probability of pregnancy loss with increasing female age, from 0.55 for a 20-year old to 0.96 by age 40. He concluded that the age-related decline in fertility is related to early pregnancy loss, which typically goes undetected clinically, rather than to failure to conceive.

Physiology of reproductive ageing

The age of menopause is variable and is associated with ultimate depletion of the ovarian follicle pool.³⁰ Subtle changes in circulating peptides occur, including increased

early follicular serum concentrations of FSH and a decrease in inhibin B.³¹ These changes precede overt changes in menstrual regularity and ovarian steroid secretion. Risk factors for early loss of ovarian reserve include smoking, family history of premature ovarian failure, significant ovarian pathology due to severe endometriosis and/or pelvic adhesive disease and previous ovarian surgery.

The age-associated decline in female fertility and increased risk of spontaneous abortion are probably attributable to abnormalities in the oocyte that appear to be more common in older women. The meiotic spindle in older women is frequently abnormal, both with respect to chromosome alignment and microtubule matrix composition.³² Higher rates of single chromatid abnormalities in oocytes, as well as aneuploidy in pre-implantation embryos and ongoing pregnancies are observed in older reproductive age women.^{33,34} This increase in the rate of aneuploidy is probably the major factor explaining the age-related increased rates of spontaneous abortion and decreased live birth rates that occur in women of advanced reproductive age. Other changes in the oocyte that have been noted with ageing include increased mitochondrial DNA deletion, increased chromosomal degeneration (dissociation of chromatids), increased apoptosis and decreased rate of in vitro maturation.³⁵⁻³⁷

Uterine pathology such as fibroids and endometrial polyps increases with advancing age and may affect fertility in individual cases; however, there is little evidence that uterine factors have a significant impact on age-related infertility.³⁸ Age appears to have no significant effect on morphological or histological response to steroid stimulation and most studies have found no age-related decline in delivery rates associated with oocyte donation in the absence of uterine pathology after adequate exogenous hormone stimulation.^{39,40}

Recommendations regarding counselling and evaluation

Because of this marked effect of age on success rate, it is common for older couples to begin treatment sooner and, in some cases to consider more aggressive treatment than younger couples. The infertility work-up for women of advanced age should be done expeditiously. All causes of infertility should be investigated, including an assessment of ovarian reserve. Although it may take longer than 1 year for a normal older woman to conceive, it is reasonable to pursue an infertility evaluation after only 6 months of attempting pregnancy. The consequences of undiagnosed infertility factors can be even more detrimental to women who have a limited timeframe for achieving a successful pregnancy.

Preconceptual counselling should include a discussion of the increased risks of aneuploidy, spontaneous abortion and obstetric complications (such as delivery by Caesarean section and gestational diabetes) associated with increasing maternal age.⁴¹ The rate of all clinically significant cytogenetic abnormalities in live births rises from about 1/500 for women under the age of 30, to 1/270 at 30, 1/80 at 35, 1/60 at 40 and 1/20 at 45.⁴² The preconceptual medical evaluation should include screening for significant medical disorders such as hypertension and diabetes, which are more frequent in women of older reproductive age. In women over 40, it is advisable to order a mammogram prior to pregnancy attempt.

Unexplained infertility

In approximately 5–10% of couples seeking pregnancy, all of the above tests are normal, and in a much higher percentage of couples only minor abnormalities are found.

These couples are often said to have unexplained infertility. Couples with unexplained infertility may have problems with egg quality that have not been detected with any of the available tests. In other cases, couples with unexplained infertility may have a problem with the ability of the sperm to fertilize the egg, undiagnosed tubal dysfunction or implantation failure. Ongoing studies are trying to elucidate a genetic basis for unexplained infertility in some couples.

EVIDENCE-BASED TREATMENT

Pitfalls in analysis of studies of infertility treatment

The provision of cost-effective infertility treatment that is evidence-based is far more complex than it initially appears. First, it is very difficult to know how effective different treatments are because well-designed studies to measure treatment outcome are uncommonly performed. Second, even when treatment outcome is known, it is often difficult to know whether any given patient is typical of those for whom the outcome is known, and therefore could be expected to have a similar outcome. Third, there are two patients in every infertile couple, markedly increasing the complexity of diagnosis and treatment. Fourth, costs of treatment are very variable in different practice settings and locations around the country. Fifth, the couple's objectives, values and ethics may limit the type of treatment acceptable to them. Sixth, there are different options, some of which result in a child of varying biological connectedness to the infertile couple, each having different value to the couple. Seventh, infertility can be a life crisis placing emotional stress on couples, resulting in difficult decision-making. Finally, the prognosis and couple's objectives can change with the passage of time.

Determining the effectiveness of treatment is difficult because so few really well designed and analysed studies have been performed in reproductive medicine. This problem is confounded by the rapid pace of innovations and utilization of new technologies. Even studies that attempt to answer clinical questions scientifically can suffer from non-representative sampling, poor selection of research subjects, improper allocation of treatment, improper stratification of confounding variables, use of inappropriate controls, bias of subjects or evaluators or non-objective assessment of outcome. Other flaws include inadequate sample size, failure to collect data on variables influencing the interpretation of results, poor response rates in surveys, subjects lost to follow-up, extensive missing data and quality control problems. If a study has not been designed and conducted in such a manner that the investigator's hypothesis can be tested by the selected methodological approach, then no amount of statistical revision or other manipulation will suffice to correct this basic flaw.

When evaluating the literature to determine cost-effective treatment, clinicians need to use logic and common sense to distinguish between promising advances and self-promotion and to have some understanding of basic statistics. They also need to be able to evaluate expressions of probability because even experienced clinicians frequently misunderstand *P*-values.

Although there are certainly problems with the interpretation of available data, it still can be useful to attempt to compare treatment success in order to make clinical decisions. Some approximations of commonly performed treatment success rates are given in Tables 1–3, below.

Table 1. Pregnancy rates following treatment for tubal factor infertility.

| Treatment | Pregnancy rate (%) |
|---|--------------------|
| Salpingolysis/ovariolysis | 25–62 |
| Fimbrioplasty | 60–70 |
| Fimbrioplasty (post-infectious) | 27 |
| Salpingostomy (tubal reconstruction) | 21–39 |
| Tubal anastomosis | 52–82 |
| Tubal anastomosis (uterotubal junction obstruction) | 50–69 |
| Tubal cannulation | 25–35 |
| Salpingostomy (for ectopic pregnancy) | 38–80 |
| Methotrexate (for ectopic pregnancy) | 50–55 |
| Fulguration of endometrial implants | 40–75 |
| Repeat tuboplasties | 6–20 |
| IVF (per cycle) | 15–25 |

Source: Adapted from Silverberg & Hill (1991).⁵⁰

Table 2. Pregnancy rates following treatment of endometriosis-associated infertility.

| Treatment | Stage/monthly fecundity (%) | | |
|----------------------|-----------------------------|----------|--------|
| | Minimal/mild | Moderate | Severe |
| Expectant | 3 | 3 | 0 |
| Medical ^a | 3 | 4 | 2 |
| Surgical | 5 | 5 | 3 |

Source: Adapted from Adamson (2001).²⁷

^a After discontinuation of ovarian suppression medications.

Table 3. Pregnancy rates following treatment for unexplained infertility.

| Treatment | Monthly fecundity (%) |
|------------------------|-----------------------|
| No treatment | 3 |
| IUI | 4 |
| Clomiphene | 6 |
| Clomiphene plus IUI | 7 |
| Gonadotrophin | 8 |
| Gonadotrophin plus IUI | 18 |
| IVF | 23 |
| GIFT | 26 |

Source: Guzick et al. (1998).⁸¹ Abbreviations used: IUI, intra-uterine insemination; IVF, in vitro fertilization; GIFT, gamete intrafallopian transfer.

Effectiveness of ovulation induction in anovulatory women

Although women with oligomenorrhoea may occasionally ovulate, clomiphene citrate has clearly been shown to increase the chance of conception compared with placebo in these women.⁴³ The development of a single mature follicle is the goal for anovulatory women, whereas the development of multiple follicles (controlled ovarian hyperstimulation) is the goal for ovulatory women who have infertility for reasons other than lack of ovulation. Clomiphene is most effective in women with normal FSH levels and sufficient endogenous oestrogen and is much less effective in women with elevated FSH levels or hypothalamic amenorrhoea.⁵ In anovulatory women with PCOS, clomiphene is expected to induce ovulation in approximately 80% of oligo-ovulatory or anovulatory women.⁴⁴ Monthly pregnancy rate depends on the presence or absence of other infertility factors and may range from <5% to 20%. Twins occur in 10% or fewer of pregnancies and triplets occur with a frequency of less than 1%. In women who fail to ovulate on clomiphene alone, metformin plus clomiphene may achieve ovulation, particularly if women are obese or have evidence of insulin resistance.^{45,46}

Gonadotrophin therapy will lead to ovulation in most women with PCOS and in patients with hypothalamic amenorrhoea.⁴⁷ Multiple pregnancy occurs with a frequency of approximately 25% for twins, 5% for triplets and 2% for quadruplets. Although twins are usually dizygotic, the rate of monozygotic twinning is also increased. Severe ovarian hyperstimulation syndrome occurs in approximately 1% of patients, with moderate ovarian hyperstimulation occurring in 5–7%. The majority of pregnancies occur within 3–4 cycles of treatment.

For women with PCOS, ongoing pregnancy rates with laparoscopic ovarian drilling after 6–12 months are similar to those for 3–6 cycles of ovulatory induction with gonadotrophins.⁴⁸ Multiple pregnancy rates are lower with ovarian drilling. However, ovarian drilling carries a risk of adhesive disease and its impact on long-term ovarian reserve has not been adequately studied.

For women with hyperprolactinaemia, the dopamine agonist bromocriptine leads to ovulation in approximately 80%.⁵ Cabergoline, a long-acting dopamine agonist, is at least as effective as bromocriptine and appears to be better tolerated.⁴⁹

Effectiveness of tubal surgery

A large number of factors affect pelvic surgery results. It is possible that only the best results are reported (Table 1).^{14,50} In addition, most reproductive surgical studies lack control groups and the choice of procedure and surgical technique is variable and unrandomized. It is also clear from reviewing the literature that although much attention has been given to objective scoring systems, great variability still exists regarding the consistency of description of surgical findings, operations and results. It is, therefore, very difficult to compare various studies and even more difficult to compare results to one's own experience. Surgeons must recognize their own limitations when evaluating the results to be expected in their own patients.

The fallopian tube is a complex structure, not a simple conduit. Therefore, numerous surgical factors can affect outcome. The most important may be the degree of damage to the lining of the tube before surgery and the post-operative reformation of adhesions. Severe underlying intratubal pathology, such as intratubal adhesions, may be impossible to repair. In addition, the patient may have tubal epithelial pathology, for example salpingitis isthmica nodosa or fibrosis. Fallopian tubes may also re-occlude.

Poor surgical technique can result in failure to remove disease, re-appose tissue or prevent surgical trauma. Extensive periadnexal adhesions carry a very poor prognosis and progressive inflammatory disease such as tuberculosis carries an essentially hopeless prognosis. Although some tubal problems are correctable by surgery, women with severely damaged tubes are so unlikely to become pregnant that IVF offers the best hope for a successful pregnancy.

Tubal re-anastomosis is, in general, a surgical procedure that is associated with much better outcome than repair of tubes damaged by infection or severe endometriosis. However, shortened fallopian tubes following re-anastomosis have a poor prognosis, as do disturbances in tubo-ovarian spatial relationships.^{51,52}

Effectiveness of tubal surgery is compromised by subsequent ectopic pregnancies, which can occur 5–50% of the time, and post-operative pelvic inflammatory disease.^{53,54} Other factors reducing live birth rate include male factor infertility, the presence of bilateral as opposed to unilateral disease, the presence of bipolar as opposed to unipolar disease and the presence of uterine pathology that is not surgically correctable such as adenomyosis or DES exposure.⁵³ Although reversal of tubal ligation leads to lower cumulative clinical pregnancy rates for women of advanced reproductive age, this option may be considered for infertile women up to the age of 42.⁵⁵

The presence of hydrosalpinges can reduce the success of IVF, particularly if they become filled with fluid and sonographically visible during the cycle.^{8,56} For this reason, removal of very badly damaged tubes should be considered before an IVF cycle.⁹ There are some data to suggest that separation of the damaged tube from its connection to the uterus can be an effective alternative to salpingectomy. This procedure can be considered if salpingectomy might compromise the ovarian blood supply.

Effectiveness of endometriosis treatment

Although surgical treatment of endometriosis is discussed in detail in Chapter 7, several comments are worth noting here. With endometriosis, a number of factors can complicate the effectiveness of treatment (Table 2).⁵⁷ These include the woman's age, duration of infertility and additional infertility factors. The combination of different treatments over time also confounds the issue. It appears that laparoscopic treatment in skilled hands is as effective as laparotomy and that ectopic pregnancy rate and spontaneous abortion rates are not different from the infertile population generally.^{58,59}

Overall, with minimal and mild endometriosis, laparoscopic surgery may improve live birth rates, although prospective data are limited and not all studies confirm this finding.^{60,61} The short-term increase in monthly fecundity with surgical treatment of minimal or mild endometriosis is probably lower than the monthly fecundity expected with treatments for unexplained infertility such as controlled ovarian hyperstimulation (COH) and intra-uterine insemination (IUI) or assisted reproductive technology. Although medical suppression is effective for management of pain associated with endometriosis it is not indicated as a treatment for infertility.^{59,62,63} Expectant management is reasonable in young patients with a short duration of infertility. Moderate and severe endometriosis should be treated surgically at the time of diagnosis. Expectant management is inappropriate. There are insufficient data to recommend medical suppression pre-operatively and no data show benefit post-operatively.

Effectiveness of treatments for uterine factors

Surgical treatment of the uterus

There are no good trials to actually determine whether or not myomectomy is beneficial with respect to infertility. Myomectomy may improve the success of IVF if the myoma is distorting the uterine cavity.⁶⁴ Many clinicians perform myomectomies for documented uterine cavity distortion whether or not IVF is being considered. A potential complication of myomectomy is post-operative adhesions or the subsequent need for Caesarean section. Polypectomy may reduce the rate of miscarriage in couples undergoing IVF.⁶⁵ Most uterine anomalies do not require surgical treatment of the uterus.⁶⁶ A septate uterus should generally be treated hysteroscopically at the time of diagnosis, especially in a couple with recurrent miscarriage.⁶⁷

Adenomyosis and DES exposure may affect the live birth rate of various infertility treatments, but are not surgically correctable.^{68,69}

Non-surgical treatments for other uterine abnormalities

Treatment for luteal phase defect may consist of administering progesterone or ovulation drugs. Given that it is unclear if luteal phase defect is in fact a true cause of infertility (except in cases of severe uterine abnormalities such as that associated with radiation), it is unlikely that treatment for luteal phase defect is truly effective in improving live birth rates. Cervical problems are generally treated with antibiotics, hormones, or by IUI. It is difficult to assess the cost-effectiveness of these types of treatments given that cervical factors are rarely the sole cause of infertility.

Effectiveness of treatments for male factor infertility

Male factor infertility may be amenable to treatment of a specific cause if one is identified. If a varicocele is palpable, repair may be considered as a treatment option when semen analyses are abnormal and the female is either normal or has a correctable problem.²⁰ When a specific cause cannot be identified, male factor infertility is treated by IUI or IVF. IUI leads to a higher pregnancy rate than timed intercourse in couples with male factor subfertility, with a non-significant trend toward a higher pregnancy rate with COH/IUI compared with IUI alone.⁷⁰ At least 1 million total motile sperm should be available for IUI. Fewer sperm than this will result in lower pregnancy rates. IVF is the treatment of choice for couples with severe male factor infertility. ICSI results in pregnancy rates equivalent to those in women with no male factor infertility. However, ICSI may not necessarily increase live birth rates compared with conventional insemination of eggs at IVF if the degree of male factor infertility is mild. Donor sperm are used much less frequently since ICSI has evolved to treat almost all male factor infertility. Pregnancy rate can be approximately doubled by using ovarian stimulation and IUI for couples using donor sperm with pregnancy rates of 15–20% for gonadotrophins and IUI.^{71,72} Treatments for male factor infertility are discussed in detail in Chapter 3.

Effectiveness of treatments for age-related infertility

COH with IUI has limited efficacy for older women, yielding a delivery rate per cycle of 5% or less (range 1.4–5.2%) for women over 40 with infertility that is unexplained

except by age.^{73–76} This compares with a live birth rate per cycle of 17–22% for women under 35, and 8–10% for women aged 35–40.⁷⁷ Advancing age is associated with reduced ovarian responsiveness to gonadotrophins and the chance of live birth is virtually zero when FSH levels rise above the normal limit, particularly for older women, irrespective of menstrual cyclicity.

The presence of infertility factors such as male factor, tubal disease, endometriosis, or pelvic adhesions would argue for proceeding directly to IVF in women of advanced reproductive age. Pregnancy rates from IVF are higher than with COH/IUI, but do decline significantly with age. Thus, the difference in live birth rate between IVF and COH/IUI becomes smaller for women in their forties. According to the 1999 Society for Assisted Reproductive Technology (SART) report, live birth rates per cycle were 32% in women aged under 35 years, 26% in women aged 35–37, 18% in women aged 38–40, 10% in women aged 41–42 and 5% in women over 42.²⁷ This age-related decline in IVF success is related not only to decreased ovarian responsiveness to gonadotrophins, but more importantly to a marked decline in embryo implantation rates. Implantation rates decline as a function of female age: 18.2% at age 25–29, 16.1% at 30–34, 15.3% at 35–39 and 6.1% at 40–44.⁷⁸ Embryonic aneuploidy is probably a major reason for implantation failure in older women.⁷⁹

Oocyte donation yields the highest live birth rate of any assisted reproductive technology (ART) treatment and is the treatment of choice for age-related infertility that is not successfully addressed by other treatments. Pregnancy rates with oocyte donation are dependent on the age of the donor. Although the incidence of uterine factors such as fibroids may increase with advancing age, no discernable drop in pregnancy rate was noted with increasing age of the recipient in the 1999 SART report (with up to age 46 being included in the report), with a live birth rate per transfer of approximately 40% reported.²⁷ Pregnancy rates with donor oocytes are much higher than those with the usual infertile population because of the improved egg quality.

In women of advanced reproductive age, it is helpful to outline a general plan for the course of therapy when treatment is initiated. If a couple would pursue IVF, a recommendation for this treatment should be considered after a maximum of 3–4 cycles of COH/IUI for women in their late thirties and older. Repeated cycles of COH/IUI may lead to a delay in the initiation of an IVF cycle, a delay that may be particularly detrimental for women in this age group. If infertility factors such as male factor or tubal disease are present in addition to age-related infertility, couples should be encouraged to proceed to IVF without first pursuing COH/IUI.

Effectiveness of treatments for unexplained infertility

Proposed treatments for unexplained infertility include IUI, COH/IUI and the ARTs.⁸⁰ IUI alone appears to have a minimal effect on the likelihood of conception for couples with unexplained infertility.^{80,81} Clomiphene alone appears to lead to a higher chance of pregnancy than no treatment or placebo.⁸² Many clinicians have studied the relationship between endometriosis and unexplained infertility; ovulation stimulation appears to benefit both.^{81,83}

With COH/IUI, a wide range of success has been reported (Table 3).^{72,81} Cycle fecundity with COH/IUI is expected to be lower when the diagnosis is unexplained infertility than when the diagnosis is anovulation. For anovulatory women the treatment is correcting an identified problem, whereas in couples with unexplained infertility it is quite possible that oocyte quality is compromised or sperm dysfunction is present. Cycle fecundity is also expected to be lower if significant male factor infertility

is present than if the semen analysis is normal. Female age is one of the most important predictors of success, as discussed below.

Generally, three to six cycles of ovarian hyperstimulation and IUI are clinically appropriate in couples with unexplained infertility. IUI is more effective than intracervical insemination.⁷² Some controversy exists as to the optimal number of inseminations per cycle. Data would generally support one well-timed IUI when an adequate number of sperm are present.⁸⁴ Should timing of insemination be difficult to determine, then two inseminations 2 days apart may be helpful and may improve pregnancy rates. Two inseminations may be appropriate in gonadotrophin cycles because of the increased cost of the cycle relative to the cost of IUI.

General comments regarding the effectiveness of IVF and GIFT

IVF has success rates between 1–40%, with an average of around 25–30% per cycle, the variation depending on many differences among patients, with female age being by far the most important.²⁷ Although older data had suggested that GIFT may have a slightly higher success rate than IVF, most recent data from SART have not confirmed a difference. Furthermore, it is not clear whether the apparent increase in GIFT success rates in the past was real or due to other factors, such as patient selection or variance in the quality of embryology laboratories. GIFT has the disadvantages of not allowing for selection of embryos, higher cost and the need for a surgical procedure. If surplus eggs are used to create embryos for cryopreservation, the couple must then bear the expense of GIFT plus the cost of embryo culture and cryopreservation. A recent meta-analysis of published randomized controlled trials found no difference in implantation and pregnancy rates between women undergoing GIFT and IVF.⁸⁵ For most patients who are candidates for ARTs, even those without male factor infertility or tubal disease, IVF is the treatment of choice.

There is a slight reduction in the success rates of IVF with increasing numbers of cycles.⁸⁶ An increasing duration of fertility also decreases success rates. Previous pregnancy and live birth increases success rates slightly.²⁷ Most diagnostic categories have similar success rates, although some clinicians believe that a small number of patients with multiple pelvic surgeries or history of severe endometriosis have success rates that are about 5% lower, possibly because of a poorer response to ovarian stimulation.^{87–89} Others have suggested the possibility of decreased oocyte quality in endometriosis patients.^{90–92} Some endometriosis patients may benefit from pre-treatment for 2 months with ovarian suppression.⁹³

OBJECTIVES FOR MANAGING INFERTILITY

Overall objectives for managing infertility include making an accurate diagnosis and then utilizing guidelines for medical treatment, surgical treatment, or the use of ART. In addition, overall disease state management should be implemented from the beginning of treatment and conditions under which discontinuation of therapy will occur should be identified. Efforts to help the couple to understand the course of diagnosis and treatment, their options, endpoints in treatment, and eventual resolution of their infertility should be established at the time of initial diagnosis. Cost-effective, evidence-based infertility management depends on an organized plan of diagnosis and treatment from the time of initial presentation.⁹⁴ This includes the use of simpler,

cheaper tests first and the establishment of a correct diagnosis followed by simultaneous treatment of the male and female utilizing effective therapy. Cost-effectiveness increases with shorter duration of therapy and faster referral for unsuccessful couples. Patient satisfaction, which includes involvement in the decision-making process, also improves cost-effectiveness. Finally, resolution of the couple's infertility, either through the birth of their own biological child or through other options, needs to be achieved as quickly and cheaply as possible. Whenever possible, treatment choices should be based on the available evidence regarding their efficacy and risks, as well as on the wishes of the individual couple.

SUMMARY

Common causes of subfertility include ovulatory disorders, tubal disease, adhesions, endometriosis, uterine abnormalities, sperm dysfunction and advancing female age. Infertility is unexplained after thorough evaluation in about 5–10% of cases, while only minor abnormalities are found in many other couples. The provision of cost-effective infertility treatment that is evidence-based is a challenge given the limited number of well-designed trials of infertility treatments, rapid technological advances and variation in couples' objectives, values and ethical beliefs. Although significant caveats must be attached to the interpretation of available data, it is useful to compare the effectiveness of treatment for various causes of infertility. Successful ovulation induction in anovulatory women is possible for nearly all women except in cases of ovarian failure. The effectiveness of tubal surgery is dependent on the degree of damage to the lining of the tube and the extent of pelvic adhesions. Surgical treatment of endometriosis can improve live birth rate for some infertile couples. Male factor infertility may be

Practice points

- since subfertility has many causes, infertility patients require a comprehensive investigation by knowledgeable physicians before initiation of treatment
- all patients should be counselled about the profound impact of a woman's age on her fertility; investigation and treatment should not be delayed, especially in women over the age of 35
- the major treatment modalities for infertility are controlled ovarian stimulation with IUI for ovulation problems and unexplained infertility, surgery for selected patients with pelvic adhesions, endometriosis and myomas and IVF for patients with severe tubal disease, significant male factor, or failure to conceive with standard infertility treatments

Research agenda

- the causes of premature ovarian ageing need to be elucidated
- the impact of endometriosis, myomas and adhesions on fertility should be studied
- tests that predict sperm function need to be developed
- a quantifiable grading system that predicts implantation and development of each embryo is needed

amenable to treatment of a specific cause, but is often empirical with the use of IUI or IVF. Egg donation is currently the most effective treatment available for age-related infertility when other treatments have not been successful. Couples with unexplained infertility may be effectively treated with ovulation induction plus IUI or IVF.

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