# Management of infertility: an overview

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## Introduction

Healthy sperms, eggs, fallopian tubes, uterine milieu and receptive endometrium constitute the essentials for conception. Failure in one or more of these leads to infertility which is defined as failure to achieve a pregnancy within 12 months of regular coitus. The incidence of infertility is around 8-10% (Lass 1999). Semen abnormalities (35%), tubal and pelvic pathology (35%), ovulatory (15%) and unexplained infertility (10%) dominate the list of causes of infertility.

## Management of infertility

Systemic disease should be excluded in both partners and it is important to commence investigations and treatment early because of declining ovulation with age.

Evaluation of **male infertility**: Relevant questions are a history of mumps, torsion or haematoma of testis, inguinal or scrotal surgery and gonadotoxins such as chemotherapy, radiation and exogenous androgenic steroids. Physical examination comprises size, consistency and undescended testes, absence of vas and varicocele.

Semen analyses (SA) is performed after 3 days abstinence and examined within 2 hours. Normal parameters constitute a volume of between 2.0 and 5.0 ml., concentration of >20 million per ml., motility of 50% and normal morphology >20%. White blood cells or bacteria indicate infection and require culture.

If SA is abnormal, serum assay for FSH and LH (necessary to produce sperm and testosterone respectively), testosterone and prolactin are performed along with chromosome analysis in severe oligo- or azoospermia.

The commonest cause of male infertility is primary testicular failure with small testes and high FSH, the aetiology of which remains unclear.

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Secondary causes are related to pituitary deficiencies, thermal injury (cryptorchidism), chemical (occupation), hypoxia (torsion and haematoma), absence of vas deferens, viral (mumps), genetic factors and auto-immunity. Unlike primary testicular failure, pituitary defect is amenable to replacement therapy, cryptorchidism by early treatment, chemical toxins by avoidance of exposure and hypoxia by prompt treatment of torsion and haematoma but currently the last three may require special sperm retrieval techniques. With counts of >1 million and reasonable motility and morphology, IVF with ICSI (intra-cellular sperm injection) should give good results.

## Female infertility

In the history it is important to inquire whether infertility is primary or secondary, age, duration of infertility, coital frequency and regularity of menstrual cycles. Important features in examination are BMI, hirsutism, uterine size and pelvic mass.

The causes of female infertility are abnormalities in ovulation, patency and function of fallopian tubes and endometrial receptivity.

Investigations comprise early follicular phase blood assay for FSH, LH, ultra-sound of pelvis (preferably transvaginal), hysteroscopy and laparoscopy if necessary.

Ovulation problems could be due to polycystic ovarian disease (PCOD) which will need weight reduction if BMI is >30 and clomiphene to induce ovulation. Endo-crinological (hypothalamic/pituitary dysfunction, hypo or hyperthyroidism and hyperprolactinaemia) causes which will require appropriate treatment while the only option for premature ovarian failure and chromosomal oocyte dysfunction is ovum or embryo donation.

Intra-uterine adhesions (Asherman's syndrome), uterine septa and submucus fibroids require hysteroscopic excision.

Hydrosalpinges and ART: The 'flushing' effect and embryo-toxins of fluid released from hydrosalpinges may hinder implantation. Management is by laparoscopic excision or occlusion of the tubes.

In cases of tubal damage or obstruction, micro-surgical repair with reconstruction and refashioning of damaged fallopian tubes at laparoscopy or laparotomy should be attempted in suitable cases.

Receptivity of endometrium:  In practice endometrial thickness with the triple sign is taken as a reflection of endometrial receptivity. Although this indicates a suitable time for transfer of the embryo, it does not say anything about the architecture, chemical, endocrine or immunological status necessary for implantation.

**Unexplained infertility** – The diagnosis of unexplained infertility is made by exclusion where there is no discernible abnormality in both male and female (Some cases of unexplained infertility may be due to sperm-zona dysfunction responsible for fertilisation failure – Schatten 1999). Management is by follicular tracking by trans-vaginal ultrasound to synchronise coitus with natural or induced ovulation so as to enhance fertilisation. If no response after 3-6 months or earlier if the age of female is >35 years, proceed to IUI-H.

Intra-uterine insemination – husband (IUI-H) by-passes the sometimes 'noxious' effect of sperm antibodies in the cervical mucus and facilitates the passage of sperm into the fallopian tube. This is continued for 6 months or shorter if the age of female is >35 years. DI (donor insemination) for IUI is discussed below.

In the final analysis, while many were treated success-fully, those with significant ovarian, tubal or sperm dysfunction, including prolonged and unexplained infertility had little hope of fecundity and will need IVF. IVF is not entirely complication-free. Moreover, IVF does not cure the infertility; it temporarily bridges the infertility gap. It is important to make the couple aware of these and frequent visits, multiple injections and most important the cost of IVF.

### In vitro fertilisation (IVF)

The main indications for IVF are severely damaged fallopian tubes, oligo-astheno-terato-zoospermia) and unexplained infertility.

**Response to stimulation:** Prior to embarking on IVF it is prudent to assess how the ovaries are going to respond. AMH (Anti-Mullerian Hormone) is an excellent but expensive tool while previous response, age, FSH, antral follicular count (AFC) and ovarian volume have reasonable predictive value.

### IVF protocol

Currently, IVF technique involves initial down-regu-lation of the pituitary with gonadotrophic releasing hormone (GnRh) agonists or antagonists. Once the pituitary is suppressed the ovaries are stimulated with follicle stimulating hormone (FSH) to produce multiple follicles. Follicular response is monitored by ultra-sound and oestrogen assay. An artificial luteinising hormone (LH) surge is triggered by the administration of human chorionic gonado-tropin (HCG) and 36 hours later the eggs are harvested by transvaginal, ultrasound-directed aspiration. The eggs are fertilised in vitro (IVF) with or without intra-cytoplasmic sperm injection (ICSI), followed by embryo transfer at the pro-nucleate stage on day 2-3 or blastocyst stage on day 5 or 6. Induction protocols using GnRH analogues often led to a luteal phase defect and required progesterone support administered, usually as vaginal suppo-sitories, to support the pregnancy till 12-16 weeks.

### Pituitary suppression

Oral contraceptives enable the timing of IVF cycle to be regulated. Pre-treatment with GnRH agonists prevents premature surge of LH which results in premature ovulation and cancellation of the cycle. However, the initial 'flare' effect of GnRH agonists is not desirable in most women. GnRH antagonists, a later innovation in the genre of pituitary suppres-sants, avoid a flare-effect by immediate down regulation and also minimise the risk of OHSS. Both GnRH agonists and antagonists provide better control and smoother and more reliable follicle stimulation with more eggs and more importantly more pregnancies (Tarlatzis and Bili 2001). GnRH antagonists prevent ovarian cyst formation with less need for luteal support and with less medication but the pregnancy rates are similar for both (Tarlatzis and Kolibianakis 2007).

### Ovulation induction

Ovarian hyper-stimulation syndrome (OHSS) and multiple pregnancies are avoided by tailoring the dose of FSH according to age, PCO (polycystic ovaries), serum AMH and FSH level, past history, ovarian volume, antral follicle count and body mass index (BMI).

### Triggering an artificial LH surge

An LH surge is triggered with 5-10,000 units of HCG (human chorionic gonadotrophin). Recent studies indicate that in cycles suppressed with GnRh anta-gonist triggering by GnRh agonist is effective and minimises OHSS and luteal phase defect.

## Ovum pickup

Compared to the more invasive, less accurate and cumbersome laparoscopic aspiration of eggs, transvaginal ultrasound-guided aspiration of follicles provides easier, accurate and more efficient harvesting of eggs (Wickland and Hamberger 1985).

## Sperms

The husband's sperms are obtained on the day of ovum pickup. Frozen specimens are thawed where the husband cannot produce a sample on demand or be present, where sperms were procured by special sperm retrieval techniques or stored pre-chemo or radiotherapy.

## Fertilisation

In cases of severe oligo-astheno-terato-zoospermia spontaneous IVF is poor. Early attempts to facilitate fertilisation with partial zona dissection (PZD) and sub-zonal injection (SUZI).

Were only marginally successful. The technique of intra-cytoplasmic sperm injection (ICSI) involves injecting a single sperm, even a non-motile one, directly into the ooplasm (Palermo, Joris, Devroey and Van Steirteghem 1992). ICSI has revolutionised fertilization and improved fertilisation rates resulting in more good quality embryos (Palermo et al 2001).

In azoospermia, special sperm retrieval techniques of epididymal sperm aspiration (MESA), percutaneous epidymal sperm aspiration (PESA), testicular sperm aspiration (TESA) or extraction (TESE) are employed along with ICSI.

## Embryo culture

Good culture systems incorporating improved incu-bating chambers, environment control and extended culture with sequential appropriately-constituted media, tailored for cleavage up to blastocyst-stage has optimised embryo quality (Gardner and Lane 2001).

## Embryo transfer

Successful transfer requires ultrasound guided atrau-matic correct placement of the embryo (Schoolcraft 2001).

Choosing optimal embryos for transfer – quality embryos can be chosen by zygote scoring or blastocyst transfer (Scott and Smith 1998; Gardener et al 1998) and if indicated, pre-implantation genetic diagnosis (PGD). Blastocyst transfer is physiological, screens some chromosomally abnormal and poor quality embryos. This is recommended if there are >4 embryos

on day 3. With fresh single blastocyst transfer birth rate has remained high, and multiple birth rate has been reduced to <10%, less than half the Australian national average and with two-thirds of the miscarriage rate (Jansen 2006).

Gamete intra-fallopian transfer (GIFT), where sperm plus eggs and zygote intra-fallopian transfer (ZIFT), where embryos are transferred at laparoscopy into the fallopian tubes, are variations of IVF. Though initially more successful than IVF, the improved technology of IVF now produces equal or better results without resorting to invasive laparoscopy. Hence the pre-ference today of IVF over GIFT and ZIFT.

## Implantation

Apart from transferring quality embryos implantation can be enhanced by improving endometrial milieu. Endometrial receptivity is governed by adequate blood supply, appropriate architecture, nutrients for sustenance of the pre-embryo, immunological and chromosomal factors and complex signals and dialogue between the embryo and endometrium to facilitate apposition, adhesion and invasion, the essential triad for successful implantation. Although endometrial thickness is reassuring, accurate bio-markers for assessment of endometrial receptivity have been elusive to date.

Assisted hatching – Assisted hatching by partial zona dissection enhances the release of the blastocyst from within the zona. It could be performed at the 6-8 cell or blastocyst-stage by chemical or laser technique (Cohen et al 1990). Assisted hatching increases the implantation and pregnancy rates in previous implantation failures but has no place for first IVF attempts, while its role in advanced age, 'thick zona' and frozen-thawed embryos remain uncertain (Velga and Boiso 2001).

Immunological influences in implantation-failure are not totally unexpected given the immunologically and genetically unrelated embryo and host endo-metrial tissue. However, the role of intravenous immuno-globin for repeat implantation failure remains controversial.

Anti-thrombogenic therapy with aspirin and heparin is helpful in abnormal implantation, placentation and early embryonic vascular compromise with (Damario and Rosenwaks 2001).

## Luteal support

With GnRh agonists and HCG protocol, luteal support with progestagen is necessary. However, the use of GnRh antagonists with GnRh agonist as

triggering agent reduces OHSS and the need for luteal support (Fauser et al 2002).

### Cryo-storage of sperms, eggs and embryos

Vitrification enables eggs and embryos to be frozen with minimal damage.

Freezing has many uses in ART enabling the storage of eggs, embryos, immature oocytes and more recently ovarian tissue whenever pregnancy needs to be deferred for social reasons and prior to chemo or radiotherapy and finally to preserve donor embryos. An additional bonus of saving embryos derived from eggs obtained at an early age is the reduced incidence of aneuploidy.

Clinical indications for storing sperms are problems of masturbation 'on demand', following sperm retrieval for ICSI, prior to chemo- or radio-therapy, pre-vasectomy and for sperm donation.

### Complications of IVF

The main complications are ovarian hyper-stimulation syndrome (OHSS) a potentially life-threatening condition), multiple pregnancies (leading to extreme prematurity with neonatal deaths and prolonged neonatal care), ovarian and vascular trauma, security concerns, carcinogenic effects of ART medications (now disproved) and psychological sequelae for the couple.

### Third-party participation in ART
### Donation of genetic material

Where one or other (or rarely both) partners lack their own genetic potential, the only current option is donation of sperm, ova or embryo.

Sperm donation – This is indicated no sperm could be obtained even with special soerm retrieval techniques. With the introduction of intra-cytoplasmic sperm injection (ICSI) in 1990), the need for sperm donation has dropped dramatically.

Ovum donation may be needed for women who are older, oligo or anovulatory, premature menopause, fertilisation failure, recurrent miscarriage, postmeno-pausal or who have genetic defects. Other recipients are women with post radio- or chemo-therapy anovu-lation or those with no ovaries.

Embryo donation: Indications for this comprise the above coupled with severe male infertility.

Pregnancy in the older female: Fertility is markedly compromised several years before the menopause, suggesting that factors other than complete depletion of the follicular store play a role in the loss of oocyte

competency in 'ageing' women (Serhal 2004). The use of higher doses of gonadotrophins coupled with the 'flare-effect' of GnRH agonists and reducing the dose may be helpful. Embryo cryo-preservation while still young provides the most successful option, freezing mature and immature oocytes and ovarian tissue with subsequent *in-vitro* maturation or autologous trans-plantation offer additional avenues (Ng and Ho 2007). The post-menopausal uterus does respond well when supported by steroid therapy and enable embryos to implant efficiently (Antinori et al 1993).

Aneuploidy is present in 50% of early IVF embryos which increases with maternal age. Pre-implantation genetic diagnosis to exclude aneuploid embryos may also be useful.

However, the logical deduction that aneuploidy screening will increase implantation and pregnancy rates and reduce miscarriages has not yet been proven (Staessen et al 2004). Even though it is early days, rejuvenating the 'ageing' cytoplasm with donor cytoplasm containing mRNA, proteins and mito-chondria, one-third of repeat IVF failures, supposedly due to poor embryo development, fell pregnant with this technique (Cohen et al 1997).

Posthumous parenting: The use of stored gametes or embryos after the death of one or other (or rarely both) partners is possible though a concern in ethical and theological circles and a minefield in the court-room.

Surrogacy
The surrogate may or may not contribute her eggs or the sperm, egg or embryo may be from the commissioning couple or donor. Surrogacy may lead to ethical, religious and legal complications (Rothenberg 1988).

### Preservation of reproductive potential

Indications are to defer pregnancies, pre- chemo-or radiotherapy and where premature ovarian failure is anticipated. Eleanora Porcu (2001) quotes a post-thaw survival rate of 57% after cryo-preservation of eggs. In vitro maturation (IVM) of immature oocytes from biopsied or surgically removed ovaries and more recently by transvaginal aspiration of antral follicles is promising (Suikkari and Soderstrom-Antttila 2007). Preservation of male reproductive potential.

Prompt freezing in patients with haematoma and torsion of testes and prior to vasectomy may avoid the need for sperm donation.

### Pre implantation genetic diagnosis (PGD)

In PGD, blastomere biopsy and analysis of single cells by polymerase chain reaction (PCR) and

fluorescent in-situ hybridisation (FISH) is performed (Lavery and Winston 1999).

Fifty per cent of spontaneous early pregnancy losses show chromosomal abnormalities, and more than 90% of chromosomally abnormal pregnancies miscarry (Grace, El-Toukhy and Scriven et al 2006). Indications for PGD are older woman, known chromosomal abnormality, recurrent IVF failure and pregnancy loss.

### Future technologies in reproductive medicine

Transplantation of stored ovarian tissue has been achieved (Donnez et al - 2004) and Mierow et al - 2005) while uterine transplantation, gene therapy, stem cell technology (SCT) and therapeutic cloning are all in the research phase but clinical applications are not too far away.

## Conclusion

In the past quarter of a century, exponential advances in reproductive medicine with improvements in ovulation induction, ultrasonography, culture systems, fertilisation and molecular biology have led to safer and more successful methods with expanded scope to investigate and treat many more types of infertility.

Infertility management has improved and now offers a chance for almost all kinds of infertility including those who lack sperm, eggs or uterus, unexplained infertility, recurrent fertilisation-failure or pregnancy loss or have genetically abnormal conceptions.

Future advances in transplantation technology and stem cell technology will offer avenues for all women to 'have their own uterus' and their own genetic make-up for their progeny.

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