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Medications used in assisted reproduction

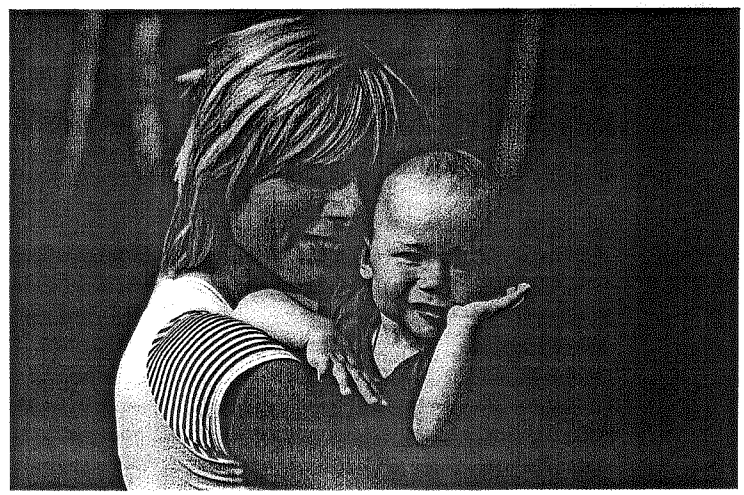
By Dr Luke Bereznicki and Professor Gregory Peterson

Learning objectives:

After reading this article, pharmacists should be able to:

- Discuss the role of the superovulation process in assisted reproduction.
- Discuss the use of gonadotrophins and gonadotrophin releasing hormone in assisted reproduction.
- Briefly discuss the risk of adverse effects associated with medications used in assisted reproduction.

Competencies addressed: 3.1.2, 4.2.1, 4.2.2



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Introduction

Normal fertility has been defined as achieving a pregnancy within two years by regular unprotected intercourse. However, many regard infertility as the failure to conceive after one year of unprotected intercourse. Approximately 10% of couples experience difficulty conceiving a child. *In vitro* fertilisation (IVF) is now a widely accepted treatment for unexplained infertility; the live-birth rate per treatment cycle ranges from 13% to 28%.[1] It has been 30 years since the first child conceived after IVF was born in the United Kingdom in 1978.[2] The first birth following IVF treatment in Australia occurred in 1980. Currently more than 45,000 IVF treatment cycles take place each year in this country.[3] In 2006, there were 10.5 assisted reproduction technology (ART) cycles per 1,000 women of reproductive age (15 to 44 years), which resulted in over 8,400 live births.[3] In most developed countries, ART represents 1% or more births. In Australia ART represents almost 3% of total births.[3,4] Most costs associated with IVF are reimbursed via Medicare (including up to 80% of out of pocket expenses). The number of attempts at IVF is unlimited, and treatment is open to women over the age of 40 years, for whom IVF is likely to be less effective than for younger women. This article will briefly discuss the medications used in assisted reproduction.

Assisted reproduction technology

There are a number of procedures and techniques encompassed by the terms assisted conception or ART. These include IVF, intracytoplasmic sperm injection (ICSI) and gamete intrafallopian transfer (GIFT), all of which are covered by Medicare. The IVF process involves ovarian stimulation (or superovulation), egg retrieval, fertilisation, embryo culture, and the transfer of embryos to the uterus.[5] Fertilisation of eggs can occur by culturing sperm and eggs in the laboratory or by ICSI, in which a single sperm is injected into an egg. ICSI, the most common ART procedure in Australia, has been shown to be more effective than IVF at increasing the rate of pregnancy in couples with severe male-factor infertility.[5] GIFT involves the placement of eggs and sperm in the fallopian tubes for *in vivo* fertilisation. The use of GIFT has declined since its introduction in Australia in 1985, and only accounts for a small number of ART treatment cycles.[3]

Gonadotrophins

The purpose of the superovulation process in IVF or ICSI is to achieve multifollicular development, as opposed to its role in anovulatory infertility, which is to induce the formation and ovulation of a single dominant follicle.[6] This generally requires injected preparations containing follicle-stimulating hormone (FSH), an anterior pituitary hormone. FSH was originally obtained from the urine of postmenopausal females, and purified to remove contaminants such as various proteins and luteinising hormone (LH).[7] Subsequently, purified urinary and recombinant preparations were developed. Recombinant

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products have the advantage of improved purity and batch-to-batch consistency compared to urinary products. Recombinant FSH is available as follitropin-α and follitropin-β, both of which are listed in Section 100 of the Pharmaceutical Benefits Scheme when used for IVF/GIFT treatment subsidised by Medicare.

Follicle stimulating hormone

FSH plays a central role in controlled ovarian stimulation in women treated with IVF; late follicular development is dependent on FSH. The role of FSH in IVF is to obtain large numbers of oocytes for subsequent selection of embryos for intrauterine transfer. Under normal circumstances, the majority of oocytes undergo atresia (i.e. degenerate and do not ovulate). Only follicles able to respond to FSH and gain increased sensitivity to FSH will undertake the final stages of development and then ovulate. The level of FSH is elevated during the late phase of follicular development, which facilitates the continued growth of a small number of follicles. Each follicle has a threshold requirement for FSH, which needs to be surpassed to ensure ongoing development. Normally only one follicle will become responsive to FSH and continue development. FSH levels then fall in response to increasing levels of oestradiol, but the dominant follicle becomes increasingly sensitive to FSH and continues growth. In IVF, the later stages of follicular development are manipulated with exogenous FSH to increase the duration of the 'FSH window,' within which FSH levels are above the threshold required to stimulate follicular development, in order to increase the number of follicles which can undergo advanced development.

Luteinising hormone

The role of luteinising hormone (LH) is to regulate the timing of ovulation. Under normal circumstances, a sudden mid-cycle surge of LH and FSH occurs. The regulation of this surge involves a number of neurotransmitters and sex hormones. The LH surge occurs as a result of persistently elevated oestrogen levels, a small rise in progesterone, increased pituitary sensitivity to gonadotrophin releasing hormone (GnRH), and a rise in GnRH. This surge is required for the final maturation of the oocyte, release of the dominant follicle and formation of the corpus luteum, providing support for the initial stages of pregnancy. LH also plays a role in follicular development, in synergism with FSH.

Human chorionic gonadotrophin (hCG) and LH share structural and biological similarities, and hCG been used to replace endogenous LH during FSH stimulation protocols. Currently, recombinant LH and recombinant hCG are available for IVF.

Gonadotrophin-releasing hormone

The continuous administration of GnRH agonists (goserelin, leuprorelin and nafarelin) results in a short period of gonadotrophic hypersecretion, followed by suppression of further FSH and LH output. This effectively renders the woman temporarily amenorrhoeic with menopausal symptoms. GnRH antagonist (ganirelix and cetrorelix) administration results in a rapid, reversible suppression of gonadotrophin secretion via competitive antagonism of the GnRH receptor. Their administration results in the suppression of LH (~70%) and FSH (~30%) serum levels after approximately six hours.[6] Therefore, GnRH agonists and antagonists result in a reversible state of chemical hypophysectomy (defined as removal of the pituitary gland). This is useful in IVF treatment for a number of reasons; it allows control over the LH surge and untimely or unwanted release of oocytes, to try and recruit a more synchronous cohort of follicles, and to facilitate scheduling of treatment cycles for the convenience of the patient and clinic. In stimulated cycles, early IVF treatment was hampered by premature ovulation. The use of GnRH agonists allowed a higher oocyte yield, fewer cancelled IVF cycles and a higher pregnancy rate.[8]

Gonadotrophins and gonadotrophic-releasing hormone analogues in practice

Treatment of infertility is highly specialised and depends on the cause. Anovulatory infertility and polycystic ovary syndrome are commonly treated with clomiphene and occasionally with metformin or tamoxifen. Gonadotrophins may be used if clomiphene is unsuccessful in this situation. Gonadotrophins are generally used for IVF. There are many superovulation protocols available. One of most commonly applied regimens is the 'long protocol,' where a GnRH agonist is given to down-regulate the release of gonadotrophins to prevent premature ovulation, followed by the administration of exogenous gonadotrophins. A recent meta-analysis found no significant difference in IVF outcome depending on the type of GnRH analogue employed.[9] This result remained the same when the study population, gonadotrophin type used for stimulation, type of agonist and protocol employed, and the type of antagonist used were considered.

The dose of FSH needs to be carefully titrated to achieve the desired effect on the ovaries without adverse effects or over-stimulation.[7] Starting doses of 150 IU per day of FSH seem to be appropriate for most women undergoing treatment for IVF or ICSI as a part of a GnRH agonist or GnRH antagonist protocol.[6] Higher doses may result in an increased oocyte yield, but ongoing pregnancy rates per started cycle and per embryo transfer may not increase.[10-12] There are a number of disadvantages to over-ambitious ovarian stimulation. These include the risk of ovarian hyperstimulation syndrome, expense, inconvenience and adverse effects for the patient.[13] An alternative approach involves the use of GnRH antagonists and the supplementation of endogenous gonadotrophins with lower doses of FSH. This approach results in fewer oocytes being obtained, but the same rate of pregnancy per cycle.[14] It is uncertain whether recombinant FSH is superior to urinary

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FSH in IVF treatment. In practice, the choice is based on a range of other factors, including cost, purity, batch variance, adverse effects and long-term risks.[15] There also appears to be little difference between the two commercially available recombinant FSH products.[16]

The role of exogenous LH during ovarian hyperstimulation for IVF is less clear. There is some evidence that LH plays an important role in normal follicular development, and also evidence that excessive LH suppression with GnRH agonists is detrimental to the outcome of IVF.[17] Some recent studies suggest that there might be a role for LH supplementation in some women undergoing IVF (e.g. women with hypopituitarism). One study using GnRH agonists found that LH levels that are too low or too high on stimulation day 8 had a negative impact on pregnancy rates.[18] However, a recent meta-analysis found that the probability of live birth was not affected by the administration of recombinant LH during ovarian hyperstimulation.[19]

Follicular development under gonadotrophin stimulation is monitored using vaginal ultrasound to measure the growth and number of follicles.[7] Serum oestradiol may also be measured in some clinics. When the dominant follicles have reached a certain size (~18 mm) hCG at a dose of 5,000 IU to 10,000 IU is commonly given to replicate the mid-cycle LH surge. In comparison with LH, hCG has a longer half-life, which may promote ovarian hyperstimulation syndrome (OHSS).[20] Recombinant LH, GnRH or a GnRH agonist may be used as a substitute for the mid-cycle LH surge.[6] Of the available options, recombinant LH is as effective as hCG, but carries a reduced risk of OHSS and improved local tolerance.[21]

Following egg collection, insemination and embryo transfer, progesterone supplementation (via vaginal pessaries, suppositories, intramuscular injections or orally) is usually given until menses occurs or the woman has a positive pregnancy test.[22] In natural cycles, the ovary produces progesterone following ovulation. Following ovarian hyperstimulation, there is some evidence that premature luteolysis occurs, thus necessitating progesterone supplementation.[22] Alternatively, hCG can be given two to three times a week, but this may promote OHSS in some women.[22]

Adverse effects

Approximately 10% of IVF cycles are cancelled before the planned egg collection because the response to ovarian hyperstimulation is excessive and the risk of OHSS is significant, or because the response to ovarian hyperstimulation is poor.[22] The OHSS occurs as a result of gonadotrophin stimulation, and occurs in less than 5% of IVF cycles.[5] Symptoms include ovarian swelling, pelvic pain and haemodynamic fluid shifts, which are often accompanied by ascites.[5] While the syndrome often resolves within weeks, there is a risk of thromboembolism, and death has occurred in some cases.[5]

There do not appear to be any definite long-term adverse effects of IVF on a woman's health.[5] A large Australian cohort study found that women who have been exposed to IVF medications do seem to have a transient increase in the risk of breast and uterine cancer diagnosed in the year following treatment.[23] However, the overall incidence of ovarian, breast and uterine cancer was no greater than that expected based on age-standardised population rates.

Conclusions

ART is a rapidly growing area; the number of ART treatment cycles has increased by 47% between 2002 and 2006.[3] IVF treatment is a highly specialised area. We have attempted to provide an overview of the principles of treatment and the medications involved. However, there are many treatment protocols available for IVF. Alternative strategies with fewer adverse effects and improved cost-benefit ratios will continue to be developed.

References

1. Pandian Z, Bhattacharya S, Vale L, et al. In vitro fertilisation for unexplained subfertility. Cochrane Database of Systematic Reviews. 2005; Issue 2: Art. No.: CD003357.
2. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. Lancet. 1978;2:366.
3. Wang YA, Dean JH, Badgery-Parker T, et al. Assisted reproduction technology in Australia and New Zealand 2006. Sydney: AIHW National Perinatal Statistics Unit; 2008.
4. Australian Bureau of Statistics. Births 2006. Canberra: Australian Bureau of Statistics; 2007.
5. Van Voorhis BJ. Clinical practice. In vitro fertilization. NEJM 2007;356:379-86.
6. Hulme JA, Lambalk CB, van Loenen AC, et al. Contemporary pharmacological manipulation in assisted reproduction. Drugs. 2004;64:297-322.
7. Rowell P, Braude P. Assisted conception. I-general principles. BMJ. 2003;327:799-801.
8. Templeton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. NEJM 1998;339: 573-7.
9. Kolibianakis EM, Collins J, Tarlatzis BC, et al. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. Hum Reprod Update. 2006;12:651-71.
10. Out HJ, Braat DD, Lintsen BM, et al. Increasing the daily dose of recombinant follicle stimulating hormone (Puregon) does not compensate for the age-related decline in retrievable oocytes after ovarian stimulation. Hum Reprod. 2000;15:29-35.
11. Out HJ, David I, Ron-El R, et al. A randomized, double-blind clinical trial using fixed daily doses of 100 or 200 IU of recombinant FSH in ICSI cycles. Hum Reprod. 2001;16:1104-9.
12. Wikland M, Bergh C, Borg K, et al. A prospective, randomized comparison of two starting doses of recombinant FSH in combination with cetrorelix in women undergoing ovarian stimulation for IVF/ICSI. Hum Reprod. 2001;16:1676-11.
13. Fauser BC, Devroey P, Yen SS, et al. Minimal ovarian stimulation for IVF: Appraisal of potential benefits and drawbacks. Hum Reprod. 1999;14:2681-6.
14. Hohmann FP, Macklon NS, Fauser BC. A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol. J Clin Endocrinol Metab. 2003;88:166-73.
15. Daya S. Methodologic pitfalls in assessing the efficacy of recombinant follicle-stimulating hormone versus human menopausal gonadotropin in assisted reproduction. Fertil Steril. 2003;80:1100-4.
16. Harlin J, Aanesen A, Csemiczky G, et al. Delivery rates following IVF treatment, using two recombinant FSH preparations for ovarian stimulation. Hum Reprod. 2002;17:304-9.
17. Fleming R, Lloyd F, Herbert M, et al. Effects of profound suppression of luteinizing hormone during ovarian stimulation on follicular activity, oocyte and embryo function in cycles stimulated with purified follicle stimulating hormone. Hum Reprod. 1998;13:1788-92.
18. Humaidan P, Bungum L, Bungum M, et al. Ovarian response and pregnancy outcome related to mid-follicular LH levels in women undergoing assisted reproduction with GnRH agonist down-regulation and recombinant FSH stimulation. Hum Reprod. 2002;17:2016-21.
19. Kolibianakis EM, Kalogeropoulou L, Griesinger G, et al. Among patients treated with FSH and GnRH analogues for in vitro fertilization, is the addition of recombinant LH associated with the probability of live birth? A systematic review and meta-analysis. Hum Reprod Update. 2007;13:445-52.
20. Weissman A, Lurie S, Zalel Y, et al. Human chorionic gonadotropin: Pharmacokinetics of subcutaneous administration. Gynecol Endocrinol. 1996;10:273-6.
21. Manau D, Fabregues F, Arroyo V, et al. Hemodynamic changes induced by urinary human chorionic gonadotropin and recombinant luteinizing hormone used for inducing final follicular maturation and luteinization. Fertil Steril. 2002;78:1261-7.
22. Braude P, Rowell P. Assisted conception. II-in vitro fertilisation and intracytoplasmic sperm injection. BMJ. 2003;327:852-5.
23. Venn A, Watson L, Bruinsma F, et al. Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet. 1999;354:1586-90.