Drugs in reproductive medicine

Monique D Sterrenburg

Nick S Macklon

Abstract

Reproductive medicine encompasses much beyond the treatment of infertility. However, for the purpose of this article, we will focus primarily on the drugs in current use for the treatment of anovulatory infertility (where the aim of treatment is to achieve monofollicular development) and for in-vitro fertilisation (where multifollicular development in is the goal). Since the discovery and isolation of gonadotrophin (i.e. follicle-stimulating hormone, luteinising hormone and human chorionic gonadotrophin) and gonadotrophin-releasing hormone, an extensive variety of pharmacotherapeutic preparations have been developed. An overview of the different medications used in current practice is provided in this article. In addition to describing their mechanism of action, their clinical application and associated outcomes are also reviewed.

Keywords anti-oestrogens; gonadotrophins; IVF; ovarian stimulation; ovulation

Introduction

The safe and effective use of most drugs used in treating infertility requires an understanding of the endocrinology of normal ovarian follicular development. While early follicle development is considered to be largely independent of gonadotrophins, late follicular development is dependent on follicle-stimulating hormone (FSH). The great majority of human oocytes are destined to undergo atresia. Only those follicles that are able to respond to stimulation by FSH will enter the final stage of development and ovulate.

Each growing follicle possesses a threshold requirement for stimulation by circulating FSH. This threshold level should be passed to ensure ongoing pre-ovulatory development. In the normo-ovulatory cycle only one follicle will become responsive to FSH above this threshold and become capable of converting the theca cell-derived substrate androstenedione to oestradiol by induction of the aromatase enzyme. In response to negative feedback from rising oestradiol and inhibin levels, FSH levels fall in the late follicle phase. The dominant follicle has increased sensitivity to the falling FSH levels and continues growing. Those follicles that commence the latter stages of development after FSH levels start to fall, undergo atresia. The duration of this 'FSH window' during which FSH levels are above the threshold required to stimulate ongoing development, determines the number of follicles that can develop to the pre-ovulatory stage (Figure 1). These advanced stages of follicular development are open to therapeutic intervention with exogenous FSH.

Monique D Sterrenburg *MD is a Fertility Physician and PhD student at the Department of Reproductive Medicine and Gynaecology, University Medical Center Utrecht, Utrecht, The Netherlands.*

Nick S Macklon *MD PhD is Professor in Reproductive Medicine at the Department of Reproductive Medicine and Gynaecology, University Medical Center Utrecht, Utrecht, The Netherlands.*

Oral ovulation induction agents

Ovulatory disorders are identified in the woman in 18–25% of couples presenting with infertility. Most of these women have oligomenorrhoea, arbitrarily defined as menstruation that occurs at intervals of 35 days to 6 months. While ovulation may occasionally occur, spontaneous conception is unlikely.

Induction of ovulation in these women is aimed at inducing monofollicular development, subsequent ovulation and ultimately pregnancy and birth of a healthy newborn.

The method of ovulation induction selected by the clinician should be based on the underlying cause of anovulation and the efficacy, costs, risks and potential complications associated with each method as they apply to the individual woman.

Clomiphene

In 1958, the non-steroidal anti-oestrogen MER-25 was found to induce menstruation in an amenorrheic woman receiving the drug as an experimental treatment for endometrial cancer. The following year, 43 anovulatory women given another anti-oestrogen, clomiphene, also ovulated.

Clomiphene remains the most widely used anti-oestrogen for ovulation induction, and is most effective in normogonadotropic anovulatory women (World Health Organization (WHO) class 2).

The mechanism of action of anti-oestrogens is unclear. These agents are thought to occupy oestrogen receptors in the hypothalamus and pituitary thereby blocking the negative feedback action of oestradiol. Thus, the main mechanism appears to be a rise in serum FSH concentrations by around 50%, resulting in stimulation of follicle growth and follicular oestradiol production. However, other mechanisms – such as induced changes in the insulin-like growth factor system and sex hormone-binding globulin levels – may also contribute.

When clomiphene is administrated to women with a normal menstrual cycle, luteinising hormone (LH) pulse frequency (but not amplitude) increases, suggesting an increase in hypothalamic gonadotrophin-releasing hormone (GnRH) pulse frequency. In women with polycystic ovary syndrome (PCOS), who have a high frequency pattern of LH pulses at baseline, the administration of clomiphene produces an increase in LH pulse amplitude, as well as an increase in the daily plasma concentrations of LH and FSH.

Tamoxifen, like clomiphene, is a non-steroidal anti-oestrogen capable of inducing ovulation. However, it has less of an anti-oestrogenic effect at the uterine level.

Clomiphene acts primarily as an anti-oestrogen in the uterus, cervix and vagina. The normal increase in uterine volume and endometrial thickening that occurs during spontaneous menstrual cycles is largely absent during clomiphene-induced cycles despite higher oestrogen levels. Some studies have found

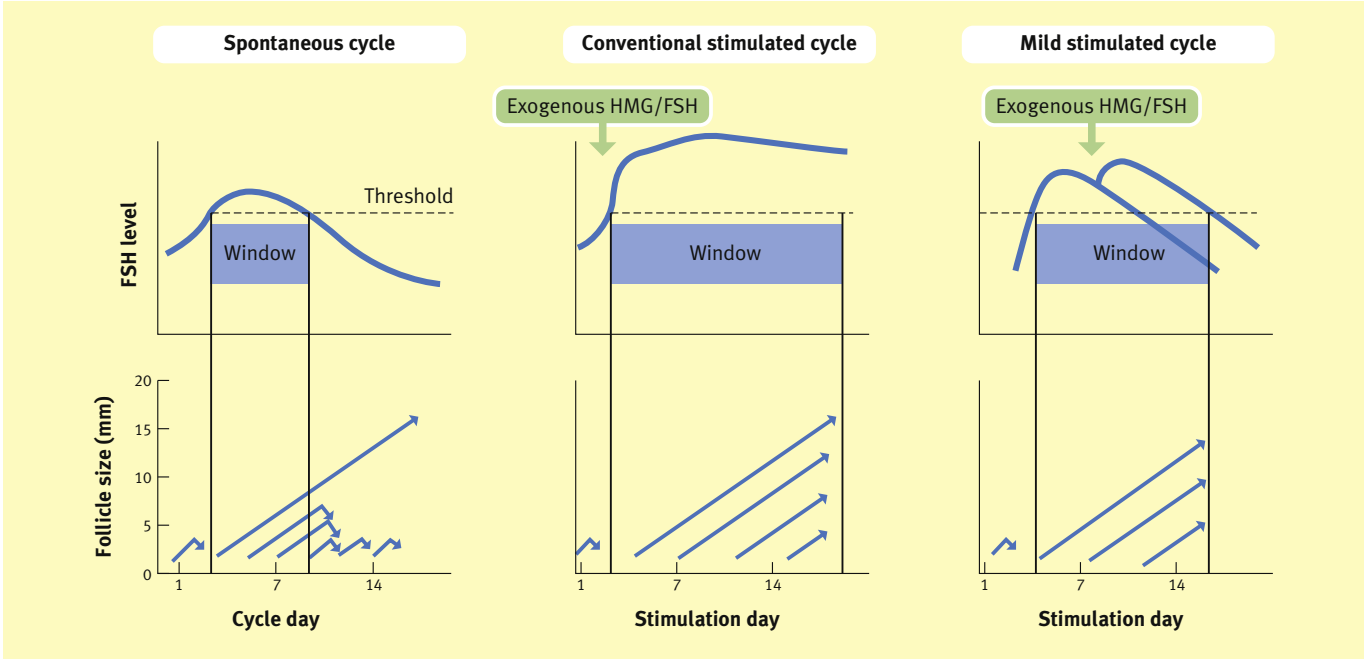

Figure 1 The follicle-stimulating hormone (FSH) threshold and window concept for monofollicular selection (left panel) as conventionally applied to achieve multifollicular development (middle panel). Each arrow represents a developing follicle. The right panel represents the concept of extending the FSH window by administering exogenous FSH in the midfollicular phase to maintain FSH levels above the threshold allowing multifollicular development.

abnormal luteal phase endometrial morphology in clomiphene-induced cycles.

Clomiphene therapy for ovulation induction is typically started on the fifth day of a cycle, following either spontaneous or induced bleeding. It is initially begun at a dose of 50 mg daily for 5 days. If ovulation does not occur in the first cycle of treatment, the dose is increased to 100 mg. Thereafter, dosage is increased by increments of 50 mg to a maximum daily dose of 250 mg. However, most authorities do not encourage the use of more than 150 mg. Drug-induced side effects are hot flushes (occurring in 10–20% of women), abdominal distention and pain (5.5%), nausea and vomiting (2.2%) and breast discomfort (2%).

There are a number of methods to suggest or confirm ovulation including:

- a biphasic basal body temperature (although this method is not encouraged in practice as it is frequently inaccurate and frustrating for the patient)
- evidence of a pre-ovulatory increase in urinary LH on a home monitoring kit
- an elevated serum progesterone concentration during the mid-luteal phase of the cycle
- pelvic ultrasound evidence of pre-ovulatory follicular growth followed by collapse of the follicle.

Transvaginal ultrasound can also be used to monitor for the presence of multiple follicular development and the potential risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). Some advocate ultrasound monitoring of just the first clomiphene cycle in order to exclude hyper-response.

Around 60–85% of anovulatory women ovulate in response to clomiphene (most typically WHO class 2 patients). Of those who ovulate, approximately 50% do so at a dose of 50 mg. Predictors of ovulation include the lower free androgen index, lower body mass index (BMI), presence of oligomenorrhoea (as opposed to amenorrhoea) and lower ovarian volume. Of those who ovulate, 30–40% conceive. Predictors of pregnancy with clomiphene include younger age, low BMI, low free androgen index and oligomenorrhoea rather than amenorrhoea.

After 6 months of treatment, the pregnancy rate per cycle falls substantially despite regular ovulation. In addition, pregnancy rates are lower among women who ovulate only after receiving higher doses of clomiphene. Failure to conceive despite ovulatory cycles, particularly at higher doses, may be due to clomiphene's anti-oestrogenic effects on the quantity and quality of cervical mucus and on the endometrium.

Of clomiphene-induced pregnancies, twin and triplet gestations occur in approximately 7–9% and 0.3%, respectively. The incidence of miscarriage and birth defects appears to be similar to that in spontaneous pregnancies and the rate of ectopic pregnancy is probably not increased. The risk of OHSS is less than 1%.

Aromatase inhibitors

Aromatase inhibitors are a class of drugs that block the conversion of testosterone and androstenedione to oestradiol and estrone, respectively (unlike clomiphene which blocks oestrogen action), thereby reducing negative oestrogenic feedback at the pituitary. The resultant increase in gonadotrophin secretion should stimulate growth of ovarian follicles. As the dominant follicle grows and oestrogen levels rise, normal negative feedback occurs centrally because aromatase inhibitors do not deplete oestrogen receptors in the brain. FSH is suppressed and the smaller growing follicles become atretic. Mono-ovulation of a single dominant follicle should occur in most cases. In contrast to clomiphene, they appear to be free of the adverse affects on endometrial and cervical mucus attributed to clomiphene.

Letrozole and anastrozole are triazole derivatives that are potent, reversible, competitive, non-steroidal aromatase