Clomifene’s role in fertility treatment has never been usurped by its rivals

In this month’s article on landmark drugs, Jenny Bryan takes a look at how clomifene became one of the most successful fertility pills of all time.

Lost in the late 20th century maze of pharmaceutical takeovers is William S. Merrell, a US chemical company that went from selling uterine tonics in the 1890s to developing the most successful fertility pill of all time — clomifene (Clomid).

Still the most commonly used drug to treat ovulatory problems related to polycystic ovary syndrome, clomifene — unlike Merrell’s earlier potions, perhaps — does what it says on the pack.

“Clomifene is a vital part of our armoury to help women with polycystic ovaries to become pregnant, although weight loss should be the first-line treatment for most of these women, and we don’t like to start a woman on clomifene until she has achieved a body mass index of under 30,” explains Virginia Beckett, consultant obstetrician and gynaecologist at Bradford Teaching Hospitals NHS Foundation Trust. “Getting women pregnant when they are overweight with a diabetic body type can lead to significant perinatal morbidity for both the mother and the baby,” she adds.

One in six couples has fertility problems and, in 30 per cent of cases, the female partner has polycystic ovaries. Dr Beckett, who is a spokeswoman for the Royal College of Obstetricians and Gynaecologists, points out that, owing to rising levels of obesity, a quarter of Caucasian women have polycystic ovaries, and half of these have the full syndrome, with signs and symptoms such as anovulation, male pattern baldness, acne, hirsutism and abnormal endocrine findings. In the south Asian population, the condition is even more common, with 50 per cent of women having polycystic ovaries and two thirds of these having the full syndrome, often related to diabetes.

From tonics to twins

Clomifene citrate emerged from a programme of hormone research at William S. Merrell in the 1940s and ’50s aimed at finding drugs with oestrogenic activity that could be suitable for oral contraception or ovulation induction. Initial animal testing demonstrated promising oestrogenic, gonadotrophin inhibition and anti-ovulatory effects.1

However, it was only after researchers found that doses of a related compound required to induce ovulation in amenorrhoeic women were too high for safety, that they looked again at clomifene. Results of the first clinical use of the drug were published in 1961 when clomifene was shown consistently to induce ovulatory cycles in previously anovulatory women.2 Further studies from other groups confirmed the effects, and editorial in JAMA, The Lancet and the BMJ supported the promising new approach to infertility treatment.3

Before long, smiling new mothers who safely gave birth to multiple babies after taking clomifene were featured in the media, and clomifene pioneer Robert Greenblatt predicted that around 70 per cent of women with ovulatory problems could be helped by the drug.1 Subsequent studies carried out over the next 30 years confirmed that clomifene treatment could achieve ovulation rates of 60–85 per cent and pregnancy rates of 30–40 per cent.4

In the 1960s, when the devastating effects of thalidomide were making headlines, it was not surprising that fears of congenital abnormalities were raised during the early days of clomifene use. But these proved unfounded. Clomifene was one of the first products to go through new drug regulatory procedures introduced by the US Food and Drug Administration in the wake of thalidomide, and was licensed in 1967.

Likely mode of action

Debate over the precise mechanism of action of clomifene continued for many years after its use as an infertility treatment became widespread, with both oestrogenic and anti-
Proportion of women with polycystic ovaries respond to the 150mg dose. For the small don't respond to that dose are unlikely to above the 100mg dose, because women who starts women on the lowest (50mg) dose of of them twins. cent of women now have multiple births, most reduced births of quadruplets and above since risk of clomifene treatment, although careful development, and luteinising hormone. production of follicle stimulating hormone occurs five to 10 days after the last day of the menstrual cycle, and ovulation usually. Clomifene is typically given on days 2 to 6 of Clomifene in clinical practice today relieved oestrogenic activity being shown. As an anti-oestrogen, clomifene is a competitive inhibitor of oestradiol for receptors in many oestrogen-dependent tissues, including the ovaries and endometrium. Blockage of oestrogen receptors in the hypothalamus reduces natural oestrogen production, leading to interruption of the normal negative feedback mechanism from the ovaries to the hypothalamus, and increased pulsatile gonadotrophin-releasing hormone secretion.2,4 This, in turn, results in increased production of follicle stimulating hormone (FSH), with accompanying follicle development, and luteinising hormone.

Clomifene in clinical practice today

Clomifene is typically given on days 2 to 6 of the menstrual cycle, and ovulation usually occurs five to 10 days after the last day of treatment.7 Because prolonged use has been linked to epithelial ovarian cancer, the National Institute for Health and Clinical Excellence recommends that clomifene should not continue beyond 12 months to achieve a pregnancy.5 Multiple pregnancy remains a potential risk of clomifene treatment, although careful dose tailoring to individual women has reduced births of quadruplets and above since the early days of treatment. About 10–15 per cent of women now have multiple births, most of them twins.

Like other fertility specialists, Dr Beckett starts women on the lowest (50mg) dose of clomifene, taken once daily: “We rarely go above the 100mg dose, because women who don’t respond to that dose are unlikely to respond to the 150mg dose. For the small proportion of women with polycystic ovaries who are thin, we may start with a 25mg daily dose,” she explains.

NICE currently advises that all women should undergo ultrasound monitoring during at least their first cycle of clomifene so that their dose can be adjusted to prevent production of too many follicles. But this guidance is under review;8 and the cost of tracking cycles for the growing number of women undergoing treatment is prohibitive for many units.

Other adverse effects of clomifene treatment include flushing, sweats and heavy periods and, rarely, ovarian hyperstimulation syndrome, resulting in ovarian enlargement, bloating, abdominal or pelvic pain and nausea. Miscarriage rates are not significantly different from those in women not using clomifene.

For those who ovulate in response to clomifene, but do not become pregnant after six months, NICE recommends clomifene treatment with intrauterine insemination. Combining clomifene with the type 2 diabetes treatment metformin has been shown to increase ovulation and pregnancy rates compared with clomifene alone, but without evidence of improved live birth rates.8

When clomifene does not work

Ovarian drilling — creating lesions on the surface of the ovary in order to trigger ovulation — is offered to women who do not respond to clomifene, and appears to be as effective as the other option for such patients — gonadotrophin treatment — and less likely to result in multiple pregnancies.6 “Drilling is invasive as it requires a laparoscopy, but it can be carried out at the same time that you check a woman’s tubes if she hasn’t become pregnant after, say, three cycles of clomifene. About 40 per cent of women will become pregnant by six months following a combination of ovarian drilling and stimulation,” says Dr Beckett.

If drilling and clomifene fail, FSH treatment, usually with in vitro fertilisation, is the next option. FSH injections need intensive monitoring because of the significant risk of severe ovarian hyperstimulation and, as Dr Beckett explains, there is a narrow therapeutic window between doses that fail to stimulate follicle production and those that cause over-stimulation.

“Unlike clomifene, the purpose of FSH treatment is to stimulate multiple follicles but, if you get too many, women can be very sick, and it’s particularly difficult to judge the best dose for women with PCOS,” she says.

Continuing role for clomifene

In contrast to many products featured in the landmark drugs series, clomifene’s role at the forefront of fertility treatment has never been usurped by newer rivals. Dr Beckett concludes: “Clomifene’s days are far from over, and if we didn’t have it, we’d be very limited in what we could offer couples whose infertility is caused by ovulatory failure or infrequent ovulation. I can’t see our need for clomifene disappearing any time soon.”

References