

Clomiphene Citrate: An Old Favourite Lives On

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It's a simple truism, but nothing beats experience. Those of us in contemporary practice are fortunate indeed to have the experience of our clinical forebears to depend on.

Consider the work done by Stein and Leventhal, summarized in their paper "Amenorrhea associated with bilateral polycystic ovaries," which was read at a meeting of the Central Association of Obstetricians and Gynecologists in New Orleans in November 1934.¹ In this report they describe the cases of seven young women, four of whom had chief complaints of "sterility and amenorrhea" and the others a combination of amenorrhea, irregular menses, abnormal hair growth, and lower abdominal pain.

Much time and effort (and, I'm sure, head scratching) must have gone into the clinical management of these women. All of them had undergone transabdominal or transuterine pneumoperitoneum with subsequent X-ray in order to allow some visualization of the ovaries, as well as the other pelvic structures. Initially their management had consisted of injections of "estrogenic hormone preparations . . . reputed to be more or less potent," but ultimately all seven women underwent surgery. The surgical procedures were described as wedge resections, although the authors acknowledge that in fact they resected from one half to three quarters of each ovary, followed by suture of the hilus using "the finest catgut." Postoperatively, all the women developed regular and apparently ovulatory cycles, and two of them (at the time of the report) had successfully conceived.

Contrast this with how these women would be managed today, leaving aside the possibility that they would make their own diagnosis and provide their own management via Internet sources. Not for them the pain and uncertainty of induction of a pneumoperitoneum or the hazards of laparotomy under general anaesthesia. Depending on their wishes regarding pregnancy and contraception, women presenting with amenorrhea and signs of hyperandrogenism would be unlikely to experience more than venepuncture

(for some hormone assays) and possibly endovaginal ultrasound examination before polycystic ovary syndrome (PCOS) is diagnosed and treatment discussed. In the great majority of cases, such treatment would be medical rather than surgical. The risks associated with such treatment are minimal and well known. And if such women were seeking pregnancy, standard practice for 30 years was to offer them treatment with clomiphene citrate.

This impressively resilient and effective medication has actually been used to induce ovulation since 1965.² Although initial impressions were that it had potential to inhibit fertility, because much of its clinical action is anti-estrogenic, it subsequently proved to have real potential to induce ovulation in anovulatory women. Randomized trials of clomiphene therapy compared with placebo or no treatment in women with oligo-ovulation and infertility showed the likelihood of ovulation increased almost seven times and the pregnancy rate per treated cycle increased over three times.³

So treatment with clomiphene in women with PCOS will increase the potential for such women to conceive. But women with PCOS also experience higher than average rates of early pregnancy loss,⁴ later pregnancy complications,⁵ and obesity,⁶ leading to the frustrating conclusion that induction of ovulation does not address the root cause of the condition. The recognition that women with PCOS have significant insulin resistance that is independent of obesity, changes in body composition, and impairment of glucose tolerance,⁷ and that insulin resistance in PCOS appears to arise from a defect in the insulin receptor or in postreceptor signal transduction⁸ raised the possibility that PCOS was essentially a metabolic syndrome based on reduced insulin sensitivity. Whether or not this is so remains unresolved, partly because there is no universally agreed set of diagnostic criteria for PCOS. Most North American investigators use the National Institutes of Health (1990) criteria of hyperandrogenism, oligo-ovulation, and exclusion of known disorders, but many others use the Rotterdam (2003) criteria, which require two of oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and ultrasound demonstration of

polycystic ovaries (assuming that other causes have been excluded).⁹ This lack of certainty has not, however, stopped numerous investigators and primary care providers from treating women with PCOS with insulin sensitizers such as metformin.

Nevertheless, so far as infertility is concerned, it looks as though clomiphene is still the preferable treatment. In a multicentre randomized study of metformin and clomiphene citrate (or a combination) treatment in 626 women with PCOS and infertility, women treated with metformin for up to six months had a live-birth rate of 7.2%, and the rate in those treated with clomiphene was 22.5%—a highly significant difference.¹⁰ Users of metformin had more gastrointestinal side effects but no multiple pregnancies; the multiple pregnancy rate in women taking clomiphene alone was 6%. It is evident from the findings of this study that women with PCOS who wish to conceive and who seek treatment should first be offered clomiphene.

But the consistent gap between ovulation rates and pregnancy rates in anovulatory women treated with clomiphene has always vexed clinicians and clinical investigators. This has most commonly been attributed to the relatively long-lasting anti-estrogenic effect of clomiphene, in the endometrium especially,¹¹ although other factors could be involved. The effect of clomiphene in the endometrium has been one of the key reasons behind the search for anti-estrogenic agents that either have no atrophic effect in the endometrium or have a short half-life. This search resulted in the introduction of letrozole, an aromatase inhibitor, for inducing ovulation. So far, letrozole appears to have similar efficacy to clomiphene citrate in achieving pregnancy in both anovulatory¹² and ovulatory¹³ women. But concerns have persisted about fetal safety with use of letrozole.

In the present issue, Rachel Forman and colleagues describe the history of using letrozole for ovulation induction in both ovulatory and anovulatory women and the controversy about the relative safety to the fetus of letrozole and clomiphene citrate. On the basis of their study, they conclude that the use of letrozole to induce ovulation does not

appear to increase the risk of fetal abnormalities and does not affect birth weight.

So it appears that clomiphene citrate has a viable challenger for its position as drug of choice in primary management of anovulatory infertility; letrozole is at least a potentially effective alternative therapy if clomiphene fails. What clomiphene does have, however, is a 40-year history of clinical use. In this evidence-based era, that is a very reassuring base.

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