

# Induction of Ovulation with Combined Glucocorticoid and Clomiphene Citrate Therapy in a Minimally Hirsute Woman

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A very minimally hirsute anovulatory woman who had failed to ovulate with 200 mg clomiphene citrate for five days had a successful ovulation and pregnancy with 150 mg clomiphene citrate plus glucocorticoids for five days.

## INTRODUCTION

For over 20 years, glucocorticoids have been used in certain infertility cases to induce ovulation.<sup>3,6</sup> In most of these cases the women were hirsute and had a diagnosis of mild adrenal hyperandrogenism or polycystic ovaries.<sup>2,5,8</sup> Recently, Greenblatt and co-workers demonstrated that adding prednisone to the therapeutic regimen can induce ovulation in a hirsute woman who previously failed to ovulate with clomiphene citrate alone.<sup>3</sup> They felt that since this woman's main source of androgens was the adrenal, she would respond to glucocorticoids: those patients who respond to glucocorticoids, including those with polycystic ovarian syndrome, have the adrenal as the main source of androgens. However, Kirschner and co-workers demonstrated through bilateral adrenal and ovarian vein catheterization that dexamethasone can suppress ovarian vein and plasma testosterone in 45% of cases, even in the absence of apparent adrenal hyperfunction. This finding suggests the possibility that the adrenal might secrete a hormone that is metabolized by the ovary to testosterone.

Here we are presenting the case of a woman with only very subtle clinical signs and symptoms of increased androgens who failed to ovulate on very high doses of clomiphene citrate but did ovulate and become pregnant when glucocorticoids were added to a smaller dose of clomiphene citrate. She had no evidence of increased adrenal androgens.

## CASE REPORTS

The patient, who was 27 years old, was referred to us because of secondary amenorrhea and primary infertility. Her last spontaneous period was five years previously. She had been on oral contraceptives for four years and after stopping had three spontaneous periods over four months but none since. Before she began taking oral contraceptives, her menstrual frequency was 30 to 38 days. She had monophasic basal temperature charts and had been treated with clomiphene citrate over several months without ovulation induction and without periods. Her last dosage had been 200 mg, days five to nine, for two cycles.

Physical examination revealed a height of 63 inches, weight of 154 pounds and a blood pressure, sitting, of 130/75. Her physical exam was completely normal. She did not have oily skin or pimples and just had a very slight increase of hair on the upper lip. Pelvic examination was normal, and there was abundant cervical mucus, with excellent spinnbarkeit and ferning, acellularity and many motile sperm. Vaginal hormonal cytology revealed 70% superficial cells and 20% large intermediate cells; the remainder were small intermediates with occasional atypical navicular cells. Thus, the smear was not diagnostic but suggested a possible androgen effect.

The following laboratory studies were obtained: serum T<sub>4</sub> was 11.4 µg per 100 ml (4.5 to 13.8); T<sub>3</sub> uptake was 30.3% (25 to 35); testosterone, 233 ng per 100 ml (50 to 100); luteinizing hormone, 30.5 mIU per ml (2 to 30); and follicular stimulating hormone, 19.2 mIU per ml (5 to 20). Her baseline urinary 17 hydroxycorticosteroids were 4.8 mg per 24 hours (2.5 to 8.5), whereas the 17 ketosteroids were 11.2 mg per 24 hours (5 to 15), with a volume of 1550 cc and a creatinine of 1,442 mg per total volume.

The patient was placed on prednisone, 5 mg before bedtime and 2.5 mg in the morning. After one month, repeat 17 hydroxycorticosteroids and 17 ketosteroids were 2.2 mg and 6.7 mg, respectively, whereas the serum testosterone decreased to a level of 32 ng per 100 ml. The patient failed to ovulate with 10,000 units of human chorionic gonadotropin. She was kept on the prednisone, and after five days of medroxyprogesterone acetate, 10 mg, she was started on clomiphene citrate, 150 mg for five days, beginning on her fifth menstrual day. Not only did she ovulate for her first time in five years, but she conceived during that cycle.

#### DISCUSSION

This case demonstrates that glucocorticoids may be quite useful in ovulation induction when used in conjunction with clomiphene citrate, not only when an adrenal source of androgens is apparent, as suggested by Greenblatt,<sup>3</sup> but also when there is increased testosterone, presumably of ovarian origin. As in this case, in view of normal 17 ketosteroids, whether there is an increased adrenal androgen precursor metabolized to testosterone in the ovary is still an unsettled question. We would have preferred to directly measure ovarian and adrenal androgens by catheterization studies, but it was not indicated clinically. This case also reemphasizes that an androgen increase may be present even without significant clinical symptoms and signs.<sup>4</sup> Thus,

in anovulatory cases, we feel that serum testosterone levels, vaginal hormonal cytology and 17 ketosteroids should be performed routinely even without significant androgen symptoms and signs. Combined glucocorticoid and clomiphene citrate therapy may not only prove useful in inducing ovulation when clomiphene alone has failed but may possibly be useful in reducing the clomiphene dosage especially where there is an associated hostile cervical mucus.

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