

- **Dexamethasone-clomiphene citrate (CC) treatment in CC-resistant PCOS patients**
- **The effect of oral contraceptives on conception**

THE QUESTION: Does dexamethasone-clomiphene citrate (CC) treatment improve ovulation rates in CC-resistant patients with polycystic ovary syndrome?

PAST STUDIES This paper pays homage to the pioneering work of Riddick and colleagues who, almost 20 years ago, demonstrated that dexamethasone (DEX) therapy increased the rate of ovulation and conception in clomiphene citrate (CC)-resistant anovulatory patients with normal serum dehydroepiandrosterone sulfate (DHEAS) levels.¹ Since then, several mechanisms have been proposed to explain this phenomenon, including the ability of glucocorticoids to lower hypothalamo-pituitary luteinizing hormone (LH) secretion,^{2,3} suppress adrenal androgen production,⁴ and therefore reduce circulating androgen levels in hyperandrogenic women.^{5,6} Reducing ovarian androgen production while suppressing circulating DHEAS as a prohormone for ovarian steroidogenesis⁴ presumably lowers elevated intrafollicular androgen levels, which appear to impair folliculogenesis.

THIS STUDY Parsanezhad et al examined the efficacy of DEX in conjunction with CC for inducing ovulation in CC-resistant polycystic ovary syndrome (PCOS) patients. Two hundred thirty infertile PCOS patients who failed to ovulate during CC therapy (250 mg/day orally for 5 days) and human chorionic gonadotropin (hCG) administration (10,000

units, intramuscularly) were randomized to CC (200 mg/day, cycle days 5-9) with or without DEX (2 mg/day, cycle days 5-14). Serum DHEAS levels, semen analysis, postcoital testing, and hysterosalpingography were normal in all cases. Basal serum hormone levels were measured before CC therapy (cycle days 3-5). Clinicians performed ultrasound-timed hCG administration on cycle days 16 and 17, and serum hormone determinations 1 week later. Treatment persisted for a maximum of 6 cycles.

Eighty-eight percent of PCOS patients receiving combined DEX-CC therapy ovulated, as determined by serum progesterone values, compared with 20% of PCOS patients receiving CC alone. Participants receiving DEX-CC therapy also demonstrated significant decreases in serum levels of LH, DHEAS, and testosterone, with a significant increase in serum progesterone concentrations. In addition, 40.5% and 4.2% of PCOS patients conceived while receiving CC with and without DEX, respectively. The authors conclude that the combination of DEX and CC in the treatment of CC-resistant anovulatory PCOS patients should be considered before gonadotropin therapy or surgical intervention.

FIND THIS STUDY Parsanezhad EM, Alborzi S, Motazedian S, Omrani G. Use of dexamethasone and clomiphene citrate in the treatment of clomiphene citrate-resistant patients with polycystic ovary syndrome and normal dehydroepiandrosterone sulfate levels: a prospec-

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tive, double-blind, placebo-controlled trial. *Fertil Steril*. 2002;78:1001-1004.

WHO MAY BE AFFECTED BY THESE FINDINGS? CC-resistant PCOS patients who have difficulty conceiving.

EXPERT COMMENTARY This study confirms the previous observation that DEX therapy can increase the rate of ovulation and conception in CC-resistant anovulatory patients with normal serum DHEAS levels.¹ While 88% of the PCOS patients receiving combined DEX-CC therapy in this study ovulated and had “regular” menstrual cycles, the proportion of women resuming normal menstrual cyclicity on a monthly basis is not addressed. Using weekly serum progesterone measurements, the ratio of luteal phase weeks to total observed weeks (with a ratio of 0.5 denoting a 4-week ovulatory menstrual cycle)⁷ along with a description of menstrual cycle intervals (by days) would address this important question.

In addition, the authors do not discuss the proportion of patients who experienced side effects from intermittent DEX therapy or the rate of patient dropout over the study interval, leaving some practical aspects of this DEX administration unresolved. The authors do recommend that clinicians use combined DEX-CC therapy to treat CC-resistant anovulatory PCOS patients before gonadotropin therapy or surgical intervention, but this is not new. What is new, however, is how this recommendation fits with other advice regarding the use of insulin sensitizers in similar PCOS patients to reduce ovarian hyperandrogenism for ovulation induction.^{7,8} This issue is crucial because reversal of hyperinsulinemia in anovulatory PCOS women receiving insulin sensitizers may improve both ovulation and pregnancy outcome by ameliorating possible adverse effects of insulin excess on oocyte development.^{9,10}

BOTTOM LINE Future studies examining the safety, side effects, and efficacy of these agents will determine whether combined DEX-CC therapy for treating CC-resistant anovulatory

PCOS patients may be a possible alternative to insulin sensitizers.

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THE QUESTION: Does prolonged use of oral contraceptives delay planned conception?

PAST STUDIES Several earlier studies have shown that women who stop oral contraceptives (OCs) have a short-term decrease in fertility that begins the first month after discontinuing use and lasts up to a year. It took 3 months to several years for pregnancy rates to equal those of comparison groups.¹⁻⁵

A smaller study of women discontinuing OCs showed a delay in conception related to OC composition, with higher estrogen doses associated with longer intervals from discontinuation to conception.⁶ Additional investiga-

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tions have shown a decrease in fertility rates after OCs, but have not controlled as well for other factors such as age (OC users tend to be older than non-users). Still, multiple studies indicate that the rate of post-pill amenorrhea is low, and therefore unlikely to affect pregnancy rates.⁷⁻⁸

THIS STUDY This investigation is part of a larger study of environmental and genetic influences on pregnancy outcome. The study enrolled 85% of couples in southwest England expecting a child during the study period. Researchers collected information on various aspects of the women's health, including tobacco use, alcohol consumption, body size, and occupational and educational status. The study population included a total of 12,106 couples—8,497 of which had planned pregnancies.

Researchers found the pregnancy rate at 1 year was significantly higher for OC users than for non-users. Although the absolute difference was not large (89.5% of women using OCs for more than 5 years versus 85.4% of never-users), it is consistently related to the length of exposure. Stepwise regression analysis showed that the higher pregnancy rates persisted even when other factors, such as smoking and maternal age, were considered.

FIND THIS STUDY Farrow A, Hull MGR, Northstone K, Taylor H, Ford WCL, Golding J. Prolonged use of oral contraception before a planned pregnancy is associated with a decreased risk of delayed conception. *Human Reprod.* 2002;17:2754-2761.

WHO MAY BE AFFECTED BY THESE FINDINGS? Current OC users planning future pregnancy.

EXPERT COMMENTARY The ideal contraceptive would be highly effective and readily reversible; planned pregnancy would not be delayed or prevented. However there are persistent beliefs that women need a break from prolonged use of OCs before they are able to conceive. Post-OC amenorrhea is presented as a usually reversible complication of OC use that may delay conception. Unfortunately, the alternative may be a contraceptive with a

higher failure rate (leading to unplanned pregnancy) or one with fewer noncontraceptive benefits.

The women in the comparison group included users of other contraceptives as well as women who used no contraception at all. Other studies of post-OC fertility have used various comparison groups. Several have suggested that OCs may decrease the rate of upper genital infection.^{9,10} Thus, OC users may have a higher subsequent fertility rate, since users of nonhormonal methods may experience more tubal infertility.

The current study does not demonstrate a dip in fertility, but it doesn't address the possibility of a short-term decrease with prompt recovery. Still, the findings strongly support the thesis that pregnancy rates for women who stop OC use are the same, if not higher, than rates for women using no contraceptives or another birth control method.

BOTTOM LINE Women who want to become pregnant should discontinue contraception when they are ready, and OC users shouldn't anticipate a longer period from discontinuation to conception. ■

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