

## Clomiphene citrate and intrauterine insemination: analysis of more than 4100 cycles

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**Objective:** To evaluate the outcomes of a large cohort of patients undergoing fertility treatment with clomiphene citrate and intrauterine insemination.

**Design:** A retrospective cohort study.

**Setting:** Boston IVF, a large university-affiliated reproductive medicine practice.

**Patient(s):** A total of 4,199 cycles performed in 1,738 infertility patients between September 2002 and July 2007.

**Intervention(s):** All patients received oral clomiphene citrate, and patients with completed cycles had intrauterine insemination performed.

**Main Outcome Measure(s):** Cumulative and per cycle pregnancy rates achieved among subsets of patients defined by age, completed cycles, and intention to treat (ITT).

**Result(s):** For women under age 35 years, 2,351 cycles were initiated in 983 patients. A total of 238 pregnancies ensued, yielding a pregnancy rate (PR) per completed cycle of 11.5% and 10.1% per cycle initiated with ITT. In women aged 35–37 years, 947 cycles in 422 women lead to a PR per completed cycle and ITT of 9.2% and 8.2%, respectively. For patients aged 38–40 years, 614 cycles in 265 women lead to a PR per completed cycle and ITT of 7.3% and 6.5%, respectively. In women aged 41–42 years, 166 cycles in 81 patients lead to a PR per completed cycle and ITT of 4.3% and 3.6%, respectively. For women above age 42 years, 120 cycles in 55 patients lead to a PR per completed cycle and ITT of 1.0% and 0.8%, respectively. On a per-patient treated basis, cumulative PRs were 24.2% under age 35, 18.5% ages 35–37, and 15.1% ages 38–40, whereas only 7.4% ages 41–42 and 1.8% above 42 became pregnant (one pregnancy in 55 patients).

**Conclusion(s):** As anticipated, younger patients have a higher PR per cycle than older patients. The PR per cycle for patients who initiate only one or only two treatment cycles is notably higher than the corresponding per cycle rates for cycles 3 through 9. The drop in success per patient among 41- and 42-year-olds is sharp, but the exceptionally low success rate above age 42 suggests that CC with IUI has virtually no place in their treatment. (*Fertil Steril*® 2008;90:2281–6. ©2008 by American Society for Reproductive Medicine.)

**Key Words:** Clomiphene citrate, intrauterine insemination, infertility, assisted reproductive technology, artificial insemination, ART outcomes

Clomiphene citrate (CC) has been a treatment of choice to help correct ovulatory dysfunction and treat infertility for over 40 years. Clomiphene citrate is both an agonist and antagonist of estrogen, generally acting as a competitive estrogen antagonist at physiologic female estrogen levels (1). Clomiphene citrate is able to stimulate ovulation by competing with estrogen for binding to the hypothalamic estrogen

receptors. By effectively diminishing the pool of available estrogen receptors within the hypothalamus, the negative feedback signal induced by estrogen is blocked, which in turn, alters pulsatile GnRH secretion. This altered GnRH secretion then enhances gonadotropin release from the pituitary. Increased gonadotropin release ultimately drives folliculogenesis at the level of the ovary (2).

Given its ability to induce ovulation in oligo-ovulatory and anovulatory females, CC is considered a first-line medical approach to improve fertility in this patient population (3–5). Hammond et al. (6) demonstrated that, in a group of anovulatory and oligomenorrheic women treated with CC, 86% ovulated and 49% of those patients conceived. More recently, in a compilation of seven published studies looking at CC and ovulation, Homburg (7) reported an ovulation rate of 73% with a pregnancy rate (PR) of 36%. In addition, Beck

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et al. (5) analyzed 12 randomized controlled trials regarding oral antiestrogen treatment in patients with anovulatory infertility and concluded that CC is effective in increasing the PR when compared with placebo. Thus, CC effectively stimulates both ovulation and greatly improves fertility success in most anovulatory women.

Given the fertility success seen in the anovulatory population, CC has more recently been used as an approach to initial treatment in patients with unexplained infertility, on the premise that CC will increase the number of mature follicles that develop every month and thus increase the likelihood of pregnancy. Additionally, it has been postulated that CC may help to overcome subtle ovulatory defects (1, 7). In a retrospective analysis of 45 published studies on CC success in patients with unexplained infertility, Guzick (8) reported a 5.6% PR per cycle in patients undergoing CC treatment with timed intercourse, and an 8.3% PR per cycle in CC plus intrauterine insemination treatment (CC/IUI). Furthermore, in one of the largest series to date, Dickey et al. (9) reported a 9.2% PR per cycle in 3,381 CC/IUI cycles in a population of infertility patients that included both ovulatory and anovulatory patients. Thus, given that CC is an orally administered, cost-effective means of improving PRs among a variety of patients, it can be reasonably argued that it should be the first therapy offered to patients seeking infertility treatment.

However, the reported efficacy of CC varies widely in the published literature. In the ovulatory infertility population, published PRs per cycle with CC range anywhere from 12% to 35% (10–12). In an infertility population consisting of both ovulatory and anovulatory patients, efficacy rates of CC are even more variable, with published PRs ranging from 4% to 27% per cycle (13–16). In this study, we report the largest series of CC data to date in a population of infertile patients who were either ovulatory or oligo-anovulatory, with at least one open fallopian tube undergoing IUI. We also stratify the efficacy of CC by age groups and examine outcome on a per-cycle and per-patient-treated basis to highlight when CC is effective and when it should be bypassed in favor of other treatment alternatives that may better maximize pregnancy success.

## MATERIALS AND METHODS

### Patient Population

All patients in the present study were evaluated and treated at Boston IVF, a large university affiliated reproductive medicine practice. The data analysis was performed under an institutional review board protocol approved by Beth Israel Deaconess Medical Center. Patients in the data set ranged in age from 20–48 years, with a mean age of 34.5 years. All patients underwent a comprehensive fertility evaluation. At Boston IVF a comprehensive fertility evaluation includes cycle day 3 measurement of estradiol, FSH, TSH, free thyroxin, and prolactin. Women aged 40 and older also undergo a CC challenge test to further assess their ovarian reserve. Assessment of uterine anatomy and fallopian tube patency

is achieved through a hysterosalpingogram. A semen analysis is also performed. In 2007, a basal antral follicle ultrasound was added to the evaluation. Upon completion of the initial evaluation patients with evidence of thyroid dysfunction or hyperprolactinemia were further evaluated as indicated, and treated medically before proceeding with fertility therapy. Men with severe semen parameter abnormalities were referred for urologic evaluation. Patients were deemed eligible for ovulation induction and IUI if they had a structurally normal uterine cavity with at least one open fallopian tube without radiographic evidence of peritubal adhesions, were ovulatory or oligo-anovulatory, and had adequate sperm available for insemination defined as the presence at least 5 million total motile sperm postprocessing. Thus, the patients treated in the present analysis represent multiple infertility diagnoses. Treatment with CC began at a dose of 50 mg in oligo-anovulatory patients or 100 mg in ovulatory infertile patients for 5 consecutive days. Cycles were cancelled when the patient [1] failed to respond to the prescribed dose of CC as evidenced by the absence of an LH surge using a home-based urine ovulation predictor kit and confirmed by the absence of at least one follicle >15 mm by pelvic ultrasound, [2] ovulated spontaneously before scheduled cycle monitoring as evidenced by a serum progesterone >3 ng/mL, or [3] had no motile sperm detected following sperm-washing procedures. Patients whose treatment cycles were completed underwent IUI.

### Data Set

In September 2002, Boston IVF began using an electronic medical record (eIVF, PracticeHwy.com, Inc, Irving, TX) to track cycles of ovulation induction and IUI. All patients undergoing ovarian stimulation with or without IUI at Boston IVF between September 2002 and the present are in the database. The database contains in excess of 10,000 ovarian stimulation cycles. Using the eIVF database query tool, data from all cycles of CC with IUI were exported in July 2007 to a Microsoft Excel spreadsheet for analysis.

Information recorded in the database for each stimulation cycle included a unique numeric patient identifier, the patient's name, age at cycle start, treatment start date, last menstrual period, peak estradiol level, pregnancy outcome, and cancellation date and cancellation reason (if applicable). The cycle outcome descriptions logged within the database included the following: pregnant, not pregnant, cancelled, stopped, in progress, blank, or awaiting results. Pregnancy as defined in our study include only those patients who had ultrasound evidence of a gestational sac. A separate field in the database "pregnancy test" with possible entries of positive or negative was not included in this analysis. We found that a large percentage of subjects had a blank entry in the "pregnancy test" field, indicating that the field was not consistently recorded at the time of cycle closure.

The eIVF Query tool identified 4,229 cycles of CC with IUI. Thirty cycles were removed from the analysis as they

belonged to hypothetical test patients placed into the electronic medical record for training purposes.

Each record in the database represented an individual cycle. Because each patient undergoing treatment has a unique identifier it was possible to identify each patient. There were a total of 1,738 patients who initiated 4,199 treatment cycles. It was further possible to determine the number of cycles each patient undertook. The data shows that 95% of the patients initiated four cycles of CC/IUI or fewer. In this analysis we chose to examine individual cohorts of patients as a function of the number of treatment cycles initiated. Therefore, patients who initiated three cycles are not a nested subset of those who initiated four cycles.

The data was stratified by patient age at cycle start into five categories. Four of the categories are concordant with the age strata used by the United States Department of Health and Human Services, Centers for Disease Control and Prevention in their annual Assisted Reproductive Technology Report. They are: [1] <35 years of age, [2] 35 to 37, [3] 38 to 40, and [4] 41 to 42. The final stratum in the present study was >42 years of age.

The data is further stratified by the number of cycles initiated by each patient, ranging from 1 to 9. Outcomes are reported in three ways for each age stratum by number of cycles initiated: [1] pregnancy rate per cycle of known outcome (pregnant or not pregnant), [2] pregnancy rate per cycle initiated regardless of outcome status (intention to treat), and [3] pregnancy rate per patient.

## Statistics

The statistical package available in Excel was used to calculate mean pregnancy rates.

## RESULTS

For women under age 35 years, 2,351 cycles were initiated in 983 patients. A total of 238 pregnancies ensued yielding a pregnancy rate (PR) per completed cycle of 11.5% and 10.1% per cycle initiated with intention to treat (ITT). Among the 938 patients in this age category treated, 24.2% became pregnant.

In women aged 35–37 years, 947 cycles in 422 women lead to a PR per completed cycle and ITT of 9.2% and 8.2%, respectively. The 422 patients in this age category achieved 78 pregnancies for a rate of 18.5%.

For patients aged 38–40 years, 614 cycles in 265 women lead to a PR per completed cycle and ITT of 7.3% and 6.5%, respectively. There were 40 pregnancies in the 265 patients treated, a rate of 15.1%.

In women aged 41–42 years, 166 cycles in 81 patients lead to a PR per completed cycle and ITT of 4.3% and 3.6%, respectively. Only 6 of the 81 patients (7.4%) became pregnant.

For women above age 42 years, 120 cycles in 55 patients yielded one pregnancy, a rate of 1.8% per patient. The PR per completed cycle and ITT were 1.0% and 0.8%, respectively (Table 1).

With the exception of ages 41–42, approximately 90% or more of the pregnancies seen in each age stratum was achieved in three initiated CC/IUI cycles or fewer (Table 2).

## DISCUSSION

This study is the largest single-center study to date reporting on the efficacy of CC and IUI. Although the variation among CC success rates in the literature is wide, our PR per cycle does correlate closely with some of the larger published trials (8, 9).

Our study is unique in that we have analyzed both the PR per cycle but further stratified by the number of initiated cycles. Patients continue or discontinue treatment with CC/IUI for a number of reasons. Treatment-dependent pregnancy is clearly one reason for discontinuation, but other reasons for discontinuation include treatment-independent pregnancy, moving on to alternative treatment options or child-free living, financial constraints, and stress (17–19).

We chose to report PRs where the results were clearly known as well as by ITT. By doing so we hoped not to bias the results by showing only completed cycles. If there was a significant dropout or cancellation rate at a particular age or cycle number we believed that studying the two extreme ends of outcome calculation that we would be able to detect such an anomaly, if it existed. The largest difference between % pregnant with known outcome and % pregnant by ITT was seen in all age strata (except those >42) among patients who initiated only one cycle. This is not a surprise in that patients, who for one reason or another, had a cycle cancelled, would be less likely to proceed on to another cycle. The lack of difference in the oldest age stratum is because of the lack of pregnancy among any of the 25 patients who initiated their first cycle of CC/IUI at that age.

Our data demonstrated a PR per cycle that is higher than the PR among natural cycles in patients with unexplained infertility. In a retrospective analysis of 45 published reports looking at the efficacy of various ovulation induction protocols, Guzik et al (8) described a natural PR per cycle of only 1.3%–4.1% in an unexplained infertility population. Thus, we can infer that CC/IUI increases the chance of pregnancy two- to 10-fold over timed intercourse in this patient population.

In addition, patients who initiate any treatment are interested in knowing if their chance of conception declines over repeated months of treatment. We looked at the % of all pregnancies achieved in each age stratum as a function of the number of cycles initiated. For women aged 40 and younger 89%–95% are achieved with three or fewer cycles initiated with 92%–98% achieved with four or fewer cycles initiated. The same was not observed for patients aged 41–42; however, there were only six pregnancies achieved in the 166 cycles initiated in 81 patients. Thus, the overall low

**TABLE 1**

<b>Outcomes of CC/IUI treatment.</b>										
<b>Outcomes &lt; 35</b>	<b>1 Cycle</b>	<b>2 Cycles</b>	<b>3 Cycles</b>	<b>4 Cycles</b>	<b>5 Cycles</b>	<b>6 Cycles</b>	<b>7 Cycles</b>	<b>8 Cycles</b>	<b>9 Cycles</b>	<b>Total</b>
Intention to treat	74	61	71	45	18	4	11	1	0	285
Patient not pregnant	118	328	876	299	107	29	49	14	8	1,828
Patient pregnant	101	57	55	12	5	3	3	1	1	238
Total cycles initiated <sup>a</sup>	293	446	1002	356	130	36	63	16	9	2,351
% pregnant per completed cycle	46.1%	14.8%	5.9%	3.9%	4.5%	9.4%	5.8%	6.7%	11.1%	11.5%
% pregnant per cycle start	34.5%	12.8%	5.5%	3.4%	3.8%	8.3%	4.8%	6.3%	11.1%	10.1%
Total unique patients	293	223	334	89	26	6	9	2	1	983
% pregnant per patient	34.5%	25.6%	16.5%	13.5%	19.2%	50.0%	33.3%	50.0%	100.0%	24.2%
<b>Outcomes 35-37</b>	<b>1 Cycle</b>	<b>2 Cycles</b>	<b>3 Cycles</b>	<b>4 Cycles</b>	<b>5 Cycles</b>	<b>6 Cycles</b>	<b>7 Cycles</b>	<b>8 Cycles</b>	<b>9 Cycles</b>	<b>Total</b>
Intention to treat	24	19	35	14	2	2				96
Patient not pregnant	81	150	412	97	19	14				773
Patient pregnant	29	25	17	1	4	2				78
Total cycles initiated <sup>a</sup>	134	194	464	112	25	18				947
% pregnant per completed cycle	26.4%	14.3%	4.0%	1.0%	17.4%	12.5%				9.2%
% pregnant per cycle start	21.6%	12.9%	3.7%	0.9%	16.0%	11.1%				8.2%
Total unique patients	134	97	155	28	5	3				422
% pregnant per patient	21.6%	25.8%	11.0%	3.6%	80.0%	66.7%				18.5%
<b>Outcomes 38-40</b>	<b>1 Cycle</b>	<b>2 Cycles</b>	<b>3 Cycles</b>	<b>4 Cycles</b>	<b>5 Cycles</b>	<b>6 Cycles</b>	<b>7 Cycles</b>	<b>8 Cycles</b>	<b>9 Cycles</b>	<b>Total</b>
Intention to treat	18	10	11	18	3	2	3			65
Patient not pregnant	45	123	212	93	17	15	4			509
Patient pregnant	16	11	11	1	0	1	0			40
Total cycles initiated <sup>a</sup>	79	144	234	112	20	18	7			614
% pregnant per completed cycle	26.2%	8.2%	4.9%	1.1%	0.0%	6.3%	0.0%			7.3%
% pregnant per cycle start	20.3%	7.6%	4.7%	0.9%	0.0%	5.6%	0.0%			6.5%
Total unique patient	79	72	78	28	4	3	1			265
% pregnant per patient	20.3%	15.3%	14.1%	3.6%	0.0%	33.3%	0.0%			15.1%
<b>Outcomes 41-42</b>	<b>1 Cycle</b>	<b>2 Cycles</b>	<b>3 Cycles</b>	<b>4 Cycles</b>	<b>5 Cycles</b>	<b>6 Cycles</b>	<b>7 Cycles</b>	<b>8 Cycles</b>	<b>9 Cycles</b>	<b>Total</b>
Intention to treat	11	7	4	3	3	0				29
Patient not pregnant	20	43	40	16	2	11				132
Patient pregnant	1	2	1	1	0	1				6
Total cycles initiated <sup>a</sup>	32	52	45	20	5	12				166
% pregnant per completed cycle	4.8%	4.4%	2.4%	5.9%	0.0%	8.3%				4.3%
% pregnant per cycle start	3.1%	3.8%	2.2%	5.0%	0.0%	8.3%				3.6%

*Dovey. Clomiphene/intrauterine insemination results in 4100 cycles. Fertil Steril 2008.*

<b>TABLE 1</b>							
<b>Continued.</b>							
<b>Outcomes 41–42</b>	<b>1 Cycle</b>	<b>2 Cycles</b>	<b>3 Cycles</b>	<b>4 Cycles</b>	<b>5 Cycles</b>	<b>6 Cycles</b>	<b>Total</b>
Total unique patient	32	26	15	5	1	2	81
% pregnant per patient	3.1%	7.7%	6.7%	20.0%	0.0%	50.0%	7.4%
<b>Outcomes &gt; 42</b>	<b>1 Cycle</b>	<b>2 Cycles</b>	<b>3 Cycles</b>	<b>4 Cycles</b>	<b>6 Cycles</b>	<b>8 Cycles</b>	<b>Total</b>
Intention to treat	9	3	4	3	1	0	20
Patient not pregnant	16	19	29	17	11	7	99
Patient pregnant	0	0	1	0	0	0	1
Total cycles initiated <sup>a</sup>	25	22	34	20	12	7	120
% pregnant per completed cycle	0.0%	0.0%	3.3%	0.0%	0.0%	0.0%	1.0%
% pregnant per cycle start	0.0%	0.0%	2.9%	0.0%	0.0%	0.0%	0.8%
Total unique patient	25	11	11	5	2	1	55
% pregnant per patient	0.0%	0.0%	9.1%	0.0%	0.0%	0.0%	1.8%

<sup>a</sup> Total cycles initiated = intention to treat + patient not pregnant + patient pregnant.

*Dovey. Clomiphene/intrauterine insemination results in 4100 cycles. Fertil Steril 2008.*

PR in that age group makes the percentage less relevant. Because the overwhelming majority of pregnancies to be achieved with each age stratum occur within three to four initiated cycles, there seems to be little benefit to continued use of CC/IUI beyond this cycle number.

Our data also highlights a significant reduction in efficacy of CC/IUI with advancing maternal age. This finding is not surprising, given that an overall decline in fertility with advancing age has been well documented (20, 21). In our population, women 41 and 42 years old only had a 3.6%–4.3% PR per cycle with CC/IUI, and only 7.4% of the patients ever achieved pregnancy with this modality. This rate is less than half the pregnancy incidence per patient of women aged 38–40.

Patients who were 43 years of age and older only had a 1% or less PR per cycle. More pointedly, only 1 patient of 55 treated ever achieved a pregnancy. This suggests the absence of efficacy of CC/IUI for patients age 43 years and older.

Although CC/IUI has been the mainstay of initial therapy for both oligo-anovulatory infertility as well as unexplained infertility for many years, concerns have been raised in the literature regarding its overall efficacy in certain patient populations (1, 6, 22). Specifically, some studies have identified a subset of anovulatory women who are resistant to CC (4, 6, 22). The incidence of CC resistance is approximately 25%, and although the etiology behind failure to ovulate is unclear, studies have demonstrated that these patients tend to be obese and insulin resistant (4, 6, 22, 23). However, several therapies are being studied in this patient population to use in conjunction with CC, such as insulin-sensitizing agents, glucocorti-

coids, and gonadotropins, with promising preliminary findings (1).

Another concern broached in recent publications is whether the antiestrogen effects of CC interfere with implantation and pregnancy (1, 6, 24). Several investigators have noted that PRs with CC are less than expected based on achieved ovulation rates, and this discrepancy has been theorized to be secondary to CC's antiestrogenic effects on cervical mucus and endometrial differentiation. It has been suggested that the aromatase inhibitor class of medications, which are not associated with such adverse antiestrogen effects, may thus replace CC as the mainstay of infertility therapy (6). However, trials comparing the efficacy of CC to letrozole, one of the most

<b>TABLE 2</b>		
<b>Pregnancies with CC/IUI.</b>		
<b>Age stratum</b>	<b>% of all pregnancies achieved within</b>	
	<b>3 Cycles</b>	<b>4 Cycles</b>
<35	89.5%	94.5%
35–37	91.0%	92.3%
38–40	95.0%	97.5%
41–42	66.7%	83.3%
>42	100%	

*Dovey. Clomiphene/intrauterine insemination results in 4100 cycles. Fertil Steril 2008.*

commonly used aromatase inhibitors, have yet to demonstrate any advantage of the aromatase inhibitors over CC in inducing ovulation or increasing PRs (10, 13).

A limitation of our study is that it was not randomized, and this limits the ability to directly compare these results with outcomes of other therapies. The lack of accurate attribution within the database of which patients were ovulatory and which were oligo-anovulatory limits a direct comparison of these two populations within each stratum. One might postulate that oligo-anovulatory patients who do ovulate with CC are more likely to become pregnant overall and pregnant sooner than those with unexplained infertility. On the other hand, oligo-anovulatory patients who are more likely to be resistant to CC than ovulatory infertile patients could account for earlier dropout from treatment.

The strength of this study is its large size. This is a population-based study of sorts in that all patients treated in our facility are included. This facilitates comparison within and between age strata. Although the diagnoses of the patients varied, the generally good outcomes in most age strata suggest that it is reasonable to offer CC/IUI as first-line therapy to patients without regard to ovulatory status, with at least one open fallopian tube and with at least 5 million motile sperm following preparation; in other words, a simplified fertility evaluation. This study demonstrates the utility of a limited number of CC/IUI treatments in this population under age 41. Further study of patients aged 41 and older is critically needed to determine the most effective treatment modality for those patients. For the foreseeable future, CC/IUI will remain the mainstay of initial treatment for wide range of infertile women <41 years of age.

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