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Patient Criteria For Successful Induction of Ovulation By Clomiphene Citrate In Patients With Polycystic Ovary Syndrome

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ORIGINAL ARTICLE

Patient Criteria For Successful Induction of Ovulation by Clomiphene Citrate in Patients With Polycystic Ovary Syndrome

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Abstract

Background: **In affluent nations, polycystic ovarian syndrome (PCOS) is the leading cause of an ovulatory infertility, affecting between 5 and 10 % of women of reproductive age. Due to its ease of use, cheap cost, relative safety, and success, clomiphene citrate has been the gold standard therapy for induction of ovulation in women with PCOS for many decades.**

Aim: **To identify patient criteria for successful initiation of oogenesis by PCOS and clomiphene citrate.**

Patients and methods: **In this study, we focused on Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University. The study included 100 patients suffering from PCOS after taking a written informed consent from every patient involved, they were divided into two groups: successful ($n = 65$) and failed ($n = 35$).**

Results: **There were high major dissimilarities in the two groups' ages, weights, BMIs, prevalence of thyroid illness, hormonal profile, follicular diameter and endometrial thickness, and correlations between success and different parameters. There were insignificant differences among groups as regards infertility type and duration, parity, thyroid-stimulating hormone level (μIU/ml), and prolactin (ng/ml).**

Conclusion: **The current study showed that the risk factors for failed clomiphene citrate stimulation of ovulation in PCOS included older age, higher BMI, higher weight, thyroid disease, free testosterone, dehydroepiandrosterone-sulfate, follicle-stimulating hormone, luteinizing hormone level, lower follicle diameter, and endometrial thickness at day 14. PCOS patients who use clomiphene citrate to induce ovulation do not fare better if they meet certain requirements.**

Keywords: Clomiphene citrate, Ovulation, Polycystic ovarian syndrome

1. Introduction

The occurrence of prolonged oligo-ovulation or anovulation, increased androgen production, and polycystic ovaries constitutes a clinical diagnosis known as polycystic ovarian syndrome (PCOS). Menstrual dysfunction and androgen excess symptoms such as hirsutism, acne, and alopecia are common clinical presentations.[1]

Prevalence estimates of PCOS are unreliable since they are definition-specific. In premenopausal women, the prevalence of PCOS ranges from 5 to 10 %, depending on whether the diagnosis is based on the clinical definition that uses chronic anovulation plus androgen excess or the strict research-based definition that relies on endocrine characteristics.[2,3]

Ovulation induction with fertility drugs has been the standard of care for women with PCOS for decades. This is because of the drug's ease of administration, low cost, and relative safety and effectiveness. By signaling low levels of circulating estrogen and so altering the pulsatile release of gonadotropin-releasing hormone, this selective estrogen-receptor

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modulator counteracts the negative feedback of endogenous estrogen on the hypothalamic–pituitary axis (GnRH). Clomiphene treatment should result in normal luteinizing hormone (LH) and a rise in follicle-stimulating hormone (FSH) level secretion, which promotes follicular development and, ultimately, ovulation. Clomiphene users are six times more likely to get pregnant than those using a placebo.[4]

Statistics show that the success of ovulation induction therapy can lead to a singleton live birth rate of above 70 %. Our team has put in a lot of time and effort to evaluate potential determinants of treatment results based on initial screening features. BMI, elevated testosterone levels, advanced maternal age, and insulin resistance were all shown to be quite accurate predictors of ovulation and pregnancy success using multivariate prediction models. These methods have the potential to make ovulation induction more individualized, allowing for better-informed decision-making about which treatment strategy to use and how much of it to provide to each patient.[5]

This work aimed to identify patient criteria for successful initiation of oogenesis by PCOS and clomiphene citrate.

2. Patients and methods

All procedures were conducted in accordance with guiding principles for care of patients and were approved by Al-Azhar University Ethics Board.

One hundred patients of those attending the infertility clinic of Al Hussein University Hospital, all patients with PCOS who agreed to participate after reading and signing an informed consent form were included.

The criterion for inclusion was all of these patients have been diagnosed with PCOS using the Rotterdam criteria: irregular menstrual cycles (oligomenorrhea and/or amenorrhea), infrequent or no menstrual bleeding (menses that occur at intervals greater than 35 days), lack of menstrual periods or amenorrhea (absence of menstruation for >6 months), and excess androgen activity. Clinically: hirsutism, Biochemically: elevated single-serum androgen and polycystic ovaries.

Exclusion criteria were any participant with a medical issue from the list below: hyperprolactinemia, thyroid dysfunction, adnexal mass, diabetes mellitus, adult-onset congenital adrenal hyperplasia, and androgen-secreting ovarian or adrenal tumors.

Patients had comprehensive history taking, physical examinations, laboratory tests, and ultrasonography.

2.1. Statistical analysis

Data were statistically characterized using the range, mean, SD, median, frequencies (number of occurrences), and % as needed. Using the Mann–Whitney *U* test for independent samples, numerical variables between research groups were compared. Statistical significance was defined as *P* values below 0.05. Computers were used for all statistical computation programs' SPSS version 15 for Microsoft Windows (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA).

3. Results

Table 1 shows that in the successful group, the mean age was 28.1 ± 2.5, weight was 80.2 ± 7.19, and BMI was 28.8 ± 2.2. In the failed group, the mean age was 33.4 ± 3.8, weight was 88.8 ± 10.54, and BMI was 32.2 ± 4.6. In terms of age, weight, and BMI, there is a huge gap between the two groups.

Table 2 shows that in the successful group, the mean free testosterone level was 0.72 ± 0.17, dehydroepiandrosterone-sulfate (DHEA) was 210.1 ± 157.2, FSH was 4.1 ± 0.83, and LH was 11.43 ± 1.15. The average free testosterone concentration in the unsuccessful group was 1.6 ± 0.4, DHEA was 227.7 ± 80.5, FSH ws 4.6 ± 1.51, and LH was 13.1 ± 1.61. There was high significant gap between the two groups as regards free testosterone, DHEA, FSH, and LH level.

Table 3 shows that in the successful group, the mean follicle diameter at day 10 was 9.15 ± 1.01, follicle diameter at day 12 was 14.8 ± 1.75, follicle diameter at day 14 was 15.85 ± 2.35, number of mature follicle was 0.28 ± 0.55, end thick day 10 was 6.2 ± 0.88, end thick day 12 was 8.28 ± 1.20, and end thick day 14 was 10.75 ± 1.10.

In the failed group, the mean follicle diameter at day 10 was 9.31 ± 0.75, follicle diameter at day 12 was 11.9 ± 1.9, follicle diameter at day 14 was

Table 1. Sociodemographic data among successful and failed cases.

Variables	Successful ($N = 65$)		Failed ($N = 35$)		Z	P
	Mean ± SD	Range	Mean ± SD	Range		
Age	28.1 ± 2.5	18–35	33.4 ± 3.8	23–39	2.31	0.003*
Weight	80.2 ± 7.19	70.0–100.0	88.8 ± 10.54	80.0–120.0	2.14	0.008*
BMI	28.8 ± 2.2	23.1–34.5	32.2 ± 4.6	25.4–38.5	4.37	<0.0001*

*P value <0.05.

Table 2. Comparison between both successful and failed groups concerning hormonal profile.

Variables	Successful ($N = 65$)		Failed ($N = 35$)		Z	P
	Mean ± SD	Range	Mean ± SD	Range		
Free testosterone	0.72 ± 0.17	0.30–0.90	1.6 ± 0.4	0.5–2.1	5.53	<0.0001*
DHEA	210.1 ± 157.2	100.0–300.0	227.7 ± 80.5	200.2–350.3	3.81	<0.0001*
FSH	4.1 ± 0.83	3.1–5.6	4.6 ± 1.51	3.0–9.0	3.30	<0.0001*
LH	11.43 ± 1.15	9.0–14.0	13.1 ± 1.61	9.5–16.0	1.96	0.02*

DHEA, dehydroepiandrosterone-sulfate; FSH, follicle-stimulating hormone; luteinizing hormone.
*P value <0.05.

Table 3. Comparison between both successful and failed groups in the first cycle concerning follicular diameter and endometrial thickness.

Variables of C1	Successful ($N = 65$)		Failed ($N = 35$)		Z	P
	Mean ± SD	Range	Mean ± SD	Range		
Follicle diameter at day 10	9.15 ± 1.01	8–12	9.31 ± 0.75	8–10	1.8	0.061
Follicle diameter at day 12	14.8 ± 1.75	10–15	11.9 ± 1.9	9–14	1.17	0.5
Follicle diameter at day 14	15.85 ± 2.35	10–20	14.8 ± 1.25	12–17	3.53	0.0001*
Number of mature dollicles	0.28 ± 0.55	0–2	0.0 ± 0.0	0	–	<0.001*
End thick day 10	6.2 ± 0.88	4–7	5.18 ± 0.98	4–7	1.24	0.45
End thick day 12	8.28 ± 1.20	6–10	7.25 ± 1.85	6–9	2.37	0.002*
End thick day 14	10.75 ± 1.10	9–12	9.42 ± 1.18	7–11	1.15	0.61

*P value <0.05.

14.8 ± 1.25, number of mature follicle was 0.00 ± 0.00, end thick day 10 was 5.18 ± 0.98, end thick day 12 was 7.25 ± 1.85, and end thick day 14 was 9.42 ± 1.18.

There were major differences between the two groups as regards follicle diameter at day 14, number of mature follicle, and end thick day 12.

Table 4 shows that in the successful group, the mean follicle diameter at day 10 was 10 ± 0.77, follicle diameter at day 12 was 13.49 ± 1.28, follicle diameter at day 14 was 16.88 ± 3.68, number of mature follicle was 0.75 ± 0.80, end thick day 10 was 5.32 ± 0.99, end thick day 12 was 7.75 ± 1.40, and end thick day 14 was 9.89 ± 1.40.

In the failed group, the mean follicle diameter at day 10 was 9.91 ± 0.95, follicle diameter at day 12 was 12 ± 1.69, follicle diameter at day 14 was 14.53 ± 1.53, number of mature follicle was 0.00 ± 0.00, end thick day 10 was 5.08 ± 0.98, end thick day 12 was 7 ± 1.26, and end thick day 14 was 8.89 ± 2.66.

Table 4. Comparison between both successful and failed groups in the second cycle concerning follicular diameter and endometrial thickness.

Variables of C2	Successful ($N = 65$)		Failed ($N = 35$)		Z	P
	Mean ± SD	Range	Mean ± SD	Range		
Follicle diameter at day 10	10 ± 0.77	9–12	9.91 ± 0.95	9–11	1.52	0.14
Follicle diameter at day 12	13.49 ± 1.28	11–18	12 ± 1.69	10–14	1.74	0.07
Follicle diameter at day 14	16.88 ± 3.68	11–22	14.53 ± 1.53	12–16	5.78	<0.0001*
Number of mature follicle	0.75 ± 0.80	0–3	0 ± 0	0	–	<0.0001*
End thick day 10	5.32 ± 0.99	4–7	5.08 ± 0.98	4–7	1.02	0.97
End thick day 12	7.75 ± 1.40	6–10	7 ± 1.26	5–9	1.23	0.5
End thick day 14	9.89 ± 1.40	7–12	8.89 ± 2.66	3–11	3.61	<0.0001*

*P value <0.05.

Table 5. Comparison between both successful and failed groups in the third cycle concerning follicular diameter and endometrial thickness.

Variables of C3	Successful ($N = 65$)		Failed ($N = 35$)		Z	P
	Mean ± SD	Range	Mean ± SD	Range		
Follicle diameter at day 10	10.26 ± 0.8	8–11	9.43 ± 0.79	8–10	1.02	0.95
Follicle diameter at day 12	14 ± 1.02	11–16	12 ± 1.29	10–13	1.59	0.10
Follicle diameter at day 14	18.79 ± 1.68	15–20	15.5 ± 1	13–15	2.82	0.003*
Number of mature follicle	1.30 ± 0.75	0–3	0 ± 0	0	–	<0.0001*
End thick day 10	5.80 ± 0.8	4–7	5.20 ± 1.25	4–7	2.44	0.002*
End thick day 12	7.85 ± 1.25	4–10	7.7 ± 1.59	5–10	1.61	0.09
End thick day 14	10.65 ± 0.89	9–12	10.1 ± 1.32	8–12	2.19	0.006*

*P value <0.05.

Table 6. Correlations between success and different parameters.

Correlations	
	Success
Age	
r	−0.764**
P	0.000
BMI	
r	−0.688**
P	0.000
TSH	
r	−0.147
P	0.144
Follicle diameter at day 14	
r	0.841**
P	0.000
End thick day 14	
r	0.659**
P	0.000

***P* value <0.05.

Significant differences existed between the two groups as regards follicle diameter at day 14, number of mature follicle, and end thick day 14.

Table 5 shows that in the successful group, the mean follicle diameter at day 10 was 10.26 ± 0.8, follicle diameter at day 12 was 14 ± 1.02, follicle diameter at day 14 was 18.79 ± 1.68, number of mature follicle was 1.30 ± 0.75, end thick day 10 was 5.80 ± 0.8, end thick day 12 was 7.85 ± 1.25, and end thick day 14 was 10.65 ± 0.89.

In the failed group, the mean follicle diameter at day 10 was 9.43 ± 0.79, follicle diameter at day 12 was 12 ± 1.29, follicle diameter at day 14 was 15.5 ± 1, number of mature follicle was 0.00 ± 0.00, end thick day 10 was 5.20 ± 1.25, end thick day 12 was 7.7 ± 1.59, and end thick day 14 was 10.1 ± 1.32.

There were substantial variations between the two groups as regards follicle diameter at day 14, number of mature follicle, and end thick days 10 and 14.

There were significant correlations between success and age, BMI, follicle diameter at 14, and end thick day 14 (Table 6, Fig. 1).

4. Discussion

The current study showed that there were 65 (65 %) induction success of ovulation by clomiphene citrate and there were 35 (35 %) failures.

Based on the current study, Areetheerapas and Singwongsa[6] showed that the response rate of clomiphene citrate was 66 %. While Sachdeva et al.[7] showed that the response rate of clomiphene citrate was 53.7 %. However, Ellakwa et al.[8] revealed that the response rate of clomiphene citrate was 73.3 %.

The comparison between the success group and failed group showed that the failed group was significantly older and has higher weight and BMI. In agreement with this study, Ellakwa et al.[8] revealed that the failed group was significantly older and has higher weight and BMI.

In concordance with the current study, Setiani et al.[9] showed that there was an association between obesity with successful ovulation induction with

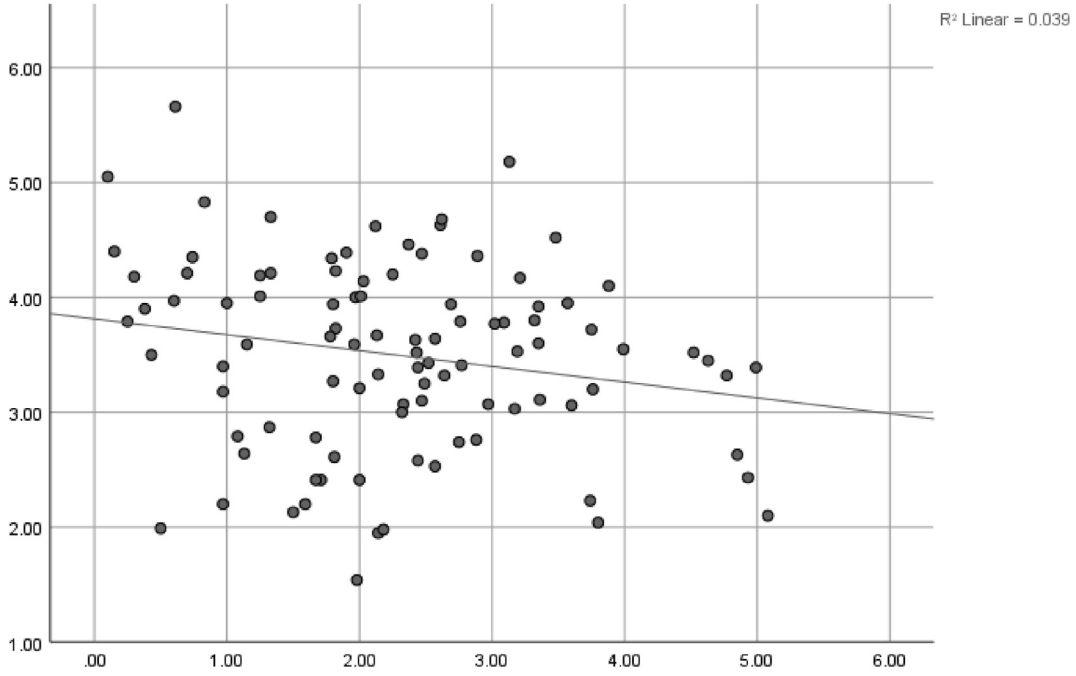

Fig. 1. Correlations between success and end thick day 14.

clomiphene citrate ($P = 0.009$). Also, Sachdeva et al.[7] in univariate regression analysis showed that higher BMI and waist circumference were found to be independent predictors of nonresponsiveness to clomiphene citrate.

Regarding the concerning hormonal profile in the studied groups, it was found that in the successful group, the mean free testosterone level was 0.72 ± 0.17, DHEA was 210.1 ± 157.2, FSH was 4.1 ± 0.83, and LH was 11.43 ± 1.15. In the failed group, the mean free testosterone level was 1.6 ± 0.4, DHEA was 227.7 ± 80.5, FSH was 4.6 ± 1.51, and LH was 13.1 ± 1.61. High-significance differences existed between the two groups as regards free testosterone, DHEA, FSH, and LH level. In concordance with the current study, Xia et al.[10] showed that there was a significant association between response to clomiphene citrate with LH, testosterone, and DHEA.

As well, in agreement with the current study, Sachdeva et al.[7] in univariate regression analysis showed that testosterone, LH, and FSH/LH were found to be independent predictors of nonresponsiveness to clomiphene citrate.

Also, Palomba et al.[11] showed that there was a significant association between response to clomiphene citrate with testosterone. But in contrast to our results, LH, LSH, and DHEA were nonsignificantly associated with response. This was identical to the outcomes of Ellakwa et al.[8]

However, Gaba et al.[12] showed that there was a significant association between response to clomiphene citrate with LH. But in contrast to our results, testosterone, LSH, and DHEA were nonsignificantly associated with response.

During the first cycle, concerning follicular diameter and endometrial thickness, the current study showed that in the successful group, the mean follicle diameter at day 10 was 9.15 ± 1.01, follicle diameter at day 12 was 14.8 ± 1.75, follicle diameter at day 14 was 15.85 ± 2.35, number of mature follicle was 0.28 ± 0.55, end thick day 10 was 6.2 ± 0.88, end thick day 12 was 8.28 ± 1.20, and end thick day 14 was 10.75 ± 1.10.

In the failed group, the mean follicle diameter at day 10 was 9.31 ± 0.75, follicle diameter at day 12 was 11.9 ± 1.9, follicle diameter at day 14 was 14.8 ± 1.25, number of mature follicle was 0.00 ± 0.00, end thick day 10 was 5.18 ± 0.98, end thick day 12 was 7.25 ± 1.85, and end thick day 14 was 9.42 ± 1.18.

There were significant differences between both groups as regards follicle diameter at day 14, number of mature follicle, and end thick day 12. During the second cycle, the current study showed that in the successful group, the mean follicle diameter at day 10 was 10 ± 0.77, follicle diameter at day 12 was 13.49 ± 1.28, follicle diameter at day 14 was 16.88 ± 3.68, number of mature follicle was 0.75 ± 0.80, end thick day 10 was 5.32 ± 0.99, end thick day 12 was 7.75 ± 1.40, and end thick day 14 was 9.89 ± 1.40.

In the failed group, the mean follicle diameter at day 10 was 9.91 ± 0.95, follicle diameter at day 12 was 12 ± 1.69, follicle diameter at day 14 was 14.53 ± 1.53, number of mature follicle was 0.00 ± 0.00, end thick day 10 was 5.08 ± 0.98, end thick day 12 was 7 ± 1.26, and end thick day 14 was 8.89 ± 2.66.

There were significant differences between both groups as regards follicle diameter at day 14, number of mature follicle, and end thick day 14. During the third cycle, the current study showed that in the successful group, the mean follicle diameter at day 10 was 10.26 ± 0.8, follicle diameter at day 12 was 14 ± 1.02, follicle diameter at day 14 was 18.79 ± 1.68, number of mature follicle was 1.30 ± 0.75, end thick day 10 was 5.80 ± 0.8, end thick day 12 was 7.85 ± 1.25, and end thick day 14 was 10.65 ± 0.89.

In the failed group, the mean follicle diameter at day 10 was 9.43 ± 0.79, follicle diameter at day 12 was 12 ± 1.29, follicle diameter at day 14 was 15.5 ± 1, number of mature follicle was 0.00 ± 0.00, end thick day 10 was 5.20 ± 1.25, end thick day 12 was 7.7 ± 1.59, and end thick day 14 was 10.1 ± 1.32.

Significant variances were between the two groups as regards follicle diameter at day 14, number of mature follicle, and end thick days 10 and 14. The study showed that through the cycles, the follicle diameter was gradually increased and reached more than 18 mm (success in induction of ovulation) at day 14 of the third cycle in the success group. So, the current study showed that the use of clomiphene citrate for three cycles results in a success in ovulation induction in 65 % of patients.

Success of ovulation after receiving 150 mg of clomiphene citrate/day for 5 days per cycle, for at least three cycles, is common and occurs in 60–85 % in PCOS patients.[13]

In concordance with this study, Elkhateeb et al.[13] showed that through the three treatment cycles, there were significant increases in the mature follicles 18 mm or more. Consonant to the current study, Areetheerapas and Singwongsa[6] showed that three cycles result in 66 % success in induction of ovulation.

The current study showed that there were significant correlations between success and age, BMI, follicle diameter at day 14, and end thick day 14.

In agreement with the current study, Ellakwa et al.[8] revealed that there was a significant correlation between success and age, but in contrast, Areetheerapas and Singwongsa[6] and Sachdeva et al.[7] showed that the response for clomiphene citrate was nonsignificantly correlated with age.

4.1. Conclusion

The current investigation revealed the risk factors for unsuccessful ovulation induction with clomiphene citrate in PCOS patients, including older age, higher BMI, higher weight, thyroid disease, free testosterone, DHEA, FSH, LH level, lower follicle diameter, and endometrial thickness at day 14. Patients' criteria have no significant effect on the outcome of ovulatory stimulation by clomiphene citrate in cases with PCOS. The current study was restricted by its small sample size, being a single-center study and short follow-up duration. Further research with bigger sample sizes and longer follow-up periods is required to confirm our findings and discover independent risk factors for failure.

Conflicts of interest

There is no conflict.

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