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Original Research Article

Prospective evaluation of screening infertile women using clomiphene citrate challenge test in tertiary care centre of Chengalpattu, Tamil Nadu

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ABSTRACT

Background: The clomiphene citrate challenge test is a sensitive tool for predicting the ovarian reserve and fertility. Thus, we studied the ovarian reserve in infertile patients using the clomiphene citrate challenge test to analyse the outcomes of the study (pregnancy).
Methods: This study included 30 patients with OPD from the Department of Obstetrics and Gynecology at Karpaga Vinayaga Medical College. The study used an Esaote ultrasound machine (Model MyLabSix) as the primary instrument. Infertile women were screened using the Clomiphene Citrate Challenge Test.
Results: In 30 patients undergoing a prospective evaluation using the clomiphene citrate challenge test, the mean age was 31.27±2.38 years, with a BMI of 23.89±3.11. The average duration of infertility was 6.30±2.15 years. Primary infertility was observed in 86.7$ (26/30) of participants, while 13.3% (4/30) had secondary infertility. Menstrual irregularities included regular cycles (43.3%), irregular cycles (46.7%), heavy bleeding (10.0%), and dysmenorrhea (3.3%). Urine pregnancy test results indicated 60.0% negative and 40.0% positive outcomes. Hormonal assessments showed similar cycle day 3 estradiol levels ($p = 0.578$), cycle day 3 FSH levels ($p = 0.236$), cycle day 10 FSH levels ($p = 0.933$), and antral follicle counts ($p = 0.99$) between primary and secondary infertility groups. Additionally, there was no significant difference in the distribution of infertility types by UPT result ($p = 0.661$).
Conclusions: The findings of this study highlight the significance of assessing the ovarian reserve as a crucial factor in predicting pregnancy outcomes. Understanding the ovarian reserve aids clinicians in tailoring personalised treatment strategies for infertility management.

Keywords: Clomiphene citrate challenge test, Fertility, FSH level, Infertility prevalence, Ovarian reserve

INTRODUCTION

The Clomiphene citrate challenge test is a sensitive tool for predicting ovarian reserve and fertility.[1] A couple who fails to conceive within one year of unprotected regular sexual intercourse is defined as infertile. For couples who have had no previous conception, infertility is defined as primary, whereas couples who have had a previous conception and have not conceived again are defined as having secondary infertility. Infertility is commonly divided into five major categories based on the etiopathology results of investigations and prognosis. The proportion of couples in each group varies from population to population.[2]

The diagnostic criteria for infertility include anovulation, tubal, endometriosis, unexplained and male factors. An intact hypothalamic-pituitary-ovarian axis is essential for

normal ovarian function. Gonadotrophin-releasing hormone (GnRH) is released in a pulsatile manner to control the pituitary gland and the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[3] The hormones stimulate the development of follicles, whereas a mid-cycle surge of LH causes rupture of the dominant follicle and release of oocytes (ovulation). Determination of the ovarian reserve is important in the treatment of infertility, and is used to determine the capacity of the ovary to provide eggs that are capable of fertilisation, resulting in a healthy and successful pregnancy. With advanced maternal age, the number of eggs that can be successfully recruited for a possible pregnancy decreases. Generally, FSH levels are expected to be below 10 mIU/ml in women with reproductive potential (levels of 10-15 mIU/ml are considered abnormal).[1,4]

Clomiphene citrate is an orally active synthetic nonsteroidal compound with oestrogenic and antiestrogenic properties and has traditionally been the treatment of choice in women with ovulatory PCOS. It displaces oestrogen from its receptors in the hypothalamic-pituitary axis, reduces the negative feedback effect of oestrogen, and encourages GnRH secretion.[5] The clomiphene citrate challenge test is a provocative and even more sensitive test of ovarian reserve.[4] In this test, women who have been trying to conceive are advised to come on day 2 of their menstrual cycle wherein they will be advised to undergo an ultrasound to check for their ovary status and also evaluate the levels of FSH and oestradiol.

Subsequently, the patient was started on a clomiphene citrate 100 mg/day tablet from day 5 to day 9. Repeat FSH levels and ultrasound will be performed on day 10. Clomiphene citrate typically stimulates a transient increase in gonadotropin levels.[1,4,6]

FSH level from 10-12.5 mIU/ml predicts resistance to fertility medications and a diminished prognosis. At 12.5-15 mIU/mL, the prognosis is poor, but pregnancies occur with aggressive treatment. Levels greater than 15 mIU/ml indicate that infertility treatment with the patient's eggs is unlikely to succeed and that egg donation should be offered. Patients with FSH levels of > 10 mIU/ml should undergo further evaluation.

A poor Clomid challenge test indicates that it is unlikely that the couple will be successful using in vitro fertilization, IVF.[7]

This study aimed to investigate the ovarian reserve in infertile patients using the clomiphene citrate challenge test and analyse the outcome of the study (pregnancy).

METHODS

This quasi-experimental study was performed on 30 patients with OPD at the Department of Obstetrics and Gynecology in Karpaga Vinayaga Medical College from May 2022 to June 2023.

Inclusion criteria

All patients aged between 20- and 45-years seeking infertility treatment were included in the study.

Exclusion criteria

Previously failed Clomiphene citrate challenge test, primary ovarian insufficiency, thin endometrial lining, hormone-reactive tumour, and husband-male factor infertility were excluded from the study.

Study instruments

Ultrasound machine - Esaote, Model- MyLabSix was used in this study.

Operational definitions

Infertility is defined as the failure to conceive within one year of unprotected, regular sexual intercourse. For couples who have had no previous conception, infertility is defined as primary, whereas couples who have had a previous conception and have not conceived again are defined as having secondary infertility.

Clomiphene citrate challenge test

This is a provocative and even more sensitive test of ovarian reserve that probes the endocrine dynamics of the cycle under both basal and stimulated conditions before (cycle day 3 FSH and oestradiol) and after (cycle day 10 FSH) clomiphene citrate treatment (100 mg/day, cycle days 5-9).

Statistical analysis

Data were collected from hospital records, including demographic information, surgical details, and outcome measures. The collected data were analysed using appropriate statistical methods such as t-tests and chi-square tests. Statistical significance was set at $p<0.05$.

Informed consent was obtained from all the patients before the initiation of the study. Participation in the study remained unaffected by treatment in any manner. This study was approved by the institution's ethics committee (KIMS). Prior permission regarding the privacy and confidentiality of the data was obtained from the department of obstetrics and gynaecology.

RESULTS

The study participants had a mean age of 31.27±2.38 years. Their body mass index (BMI) averaged 23.89±3.11. Additionally, the duration of infertility among the participants was 6.30±2.15 years (Table 1).

The study included 30 patients, of whom 26 (86.7%) had primary infertility and 4 (13.3%) had secondary infertility. Regarding menstrual history, 13 patients (43.3%) reported regular cycles, 14 patients (46.7%) reported irregular cycles, 3 patients (10.0%) experienced heavy menstrual bleeding, and 1 patient (3.3%) had dysmenorrhea. Urine pregnancy test (UPT) results showed that 18 patients (60.0%) were negative, while 12 patients (40.0%) were positive (Table 2).

Table 1: Demographic and baseline characteristics of participants.

	Mean	Standard deviation
Age	31.27	2.38
BMI	23.89	3.11
Duration of infertility	6.30	2.15

Table 2: Patient characteristics and reproductive health history.

		Number of patients	Percentage
Primary infertility		26	86.7
Secondary infertility		4	13.3
Menstrual history	Regular cycles	13	43.3
	Irregular cycles	14	46.7
	Heavy menstrual bleeding	3	10.0
	Dysmenorrhea	1	3.3
UPT	Negative	18	60.0
	Positive	12	40.0

Table 3: Hormonal and follicular measurements by urine pregnancy test (UPT) result.

	UPT		P value
	Negative	Positive	
	Mean±Standard deviation	Mean±Standard deviation	
Cycle day 3-estradiol	62.41±10.31	19.00±1.53	<0.0001
Cycle day 3 FSH	11.29±2.05	11.69±3.84	0.717
Cycle day 10 FSH	12.71±2.66	5.69±1.44	<0.0001
Antral follicle count	6.24±1.71	12.00±1.35	<0.0001

Table 4: UPT results and infertility types.

		UPT				P value
		Negative		Positive		
		Count	Row N %	Count	Row N %	
Infertility	Primary	16	61.5	10	38.5	0.661
	Secondary	2	50.0	2	50.0	

The mean cycle day 3 estradiol levels were 42.65±23.70 pg/mL for primary infertility patients and 49.75±21.56 pg/mL for secondary infertility patients (p=0.578). The mean cycle day 3 FSH levels were 11.62±3.07 mIU/ml and 10.50±1.29 mIU/ml for primary and secondary infertility patients, respectively (p=0.236). The mean cycle day 10 FSH levels were 9.69±4.17 mIU/ml for primary infertility patients and 9.50±4.65 mIU/ml for secondary infertility patients (p=0.933). Lastly, the mean antral follicle count was 8.73±3.46 for primary infertility patients and 8.75±2.22 for secondary infertility patients (p=0.99), indicating similar hormone levels and follicle counts between the groups (Table 3).

There was no significant difference found (p=0.661) in the distribution of infertility types between those with negative UPT results (61.5% primary, 38.5% secondary) and positive UPT results (50.0% each for primary and secondary infertility) (Table 4).

DISCUSSION

In our study, we observed that the mean age of women seeking treatment for primary infertility was 31.27±2.38. This figure slightly exceeds the findings of Adamson et al who, in their investigation of the prevalence and factors associated with primary infertility among young women in Mysore, India, reported an average age of 25.9±3.12 years for women experiencing infertility.[8] Additionally, the BMI data (23.89±3.11) revealed that all patients fell within the normal body mass index (BMI) range (18.5-25), consistent with the findings of Baby et al. In their study, they noted that 68.80% of females were categorized as having a normal BMI.[9]

Polycystic ovary syndrome is the major cause of infertility, with a wide spectrum of symptoms, clinical and biological manifestations, menstrual irregularities, obesity, and hirsutism. Several factors, such as a sedentary lifestyle, family history, and hormonal imbalance, actively cause PCOS.[9] Magendzo et al discovered that among young patients, a noteworthy one-third (34%) exhibited diminished ovarian reserve, as evidenced by an abnormal CCCT.[10] This prevalence surpasses the 24% rate observed in a cohort of patients under 38 years of age undergoing high-complexity assisted reproduction treatment, as reported by Csemiczky et al.[11] The elevated occurrence of diminished ovarian reserve in Magendzo's study can be attributed to its focus on couples grappling with unexplained infertility, devoid of anatomical, endocrine, or male factors. Consequently, this cohort may have had a higher concentration of women with diminished ovarian reserves.[10]

The literature presents some inconsistencies regarding the necessity of measuring stimulated FSH concentration. Jain et al. concluded in their review that basal FSH and CCCT exhibit similar predictive abilities for achieving clinical pregnancy in women undergoing infertility treatment.[12] Conversely, Yanushpolsky et al investigated young women undergoing high-complexity assisted reproduction treatment and found that those with normal basal FSH concentrations but elevated FSH on day 10 experienced comparably low pregnancy rates as those with elevated basal FSH concentrations. Notably, both groups had significantly lower pregnancy rates than women with low basal and stimulated FSH concentrations, as revealed by Yanushpolsky et al.[13]

Magendzo et al noted that among 50 women with abnormal CCCT results, 16 exhibited normal basal FSH levels, but abnormal post-stimulation FSH concentrations. Interestingly, this subgroup experienced a similarly low pregnancy rate per cycle in women with abnormal basal FSH levels. Thus, these findings validate the significance of stimulated cycle day 10 FSH concentration in providing crucial insights for assessing ovarian reserve and, consequently, treatment prognosis.[10]

The findings from the comparison of hormonal and antral follicle count parameters between the negative and positive urine pregnancy test (UPT) groups revealed several important insights. The significant difference in oestradiol levels on day 3 between the negative and positive UPT groups suggests a potential association between early oestradiol levels and pregnancy status. However, the lack of a significant difference in cycle day 3 FSH levels between the negative and positive UPT groups was unexpected. FSH levels, which are crucial for follicular development, typically increase in the early follicular phase. On cycle day 10, the substantial difference in FSH levels between the groups supports FSH as a predictive marker.

Our prospective evaluation of CCCT as a screening tool for the general infertile population offers valuable insights. While CCCT demonstrates utility in assessing ovarian reserve, its effectiveness as a standalone screening tool for predicting fertility outcomes in the general infertile population remains inconclusive. Additional factors, such as age, medical history, and ovarian morphology, should be considered alongside CCCT results for comprehensive fertility assessment. Future research should explore the integration of CCCT with other diagnostic modalities to enhance the predictive accuracy and inform personalised infertility management strategies.

CONCLUSION

Our study evaluating ovarian reserve in infertile women through the clomiphene citrate challenge test provides valuable insights into fertility potential. These findings underscore the importance of assessing ovarian reserve in guiding personalized infertility treatment plans. While women with FSH levels ≤ 10 IU/l were considered to have normal ovarian reserve and those with FSH levels >10 IU/L were classified as having diminished ovarian reserve, further research is needed to refine these cut-offs and develop more accurate predictive models. Larger, longitudinal studies are warranted to corroborate our findings and optimize fertility interventions for improved patient outcomes.

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REFERENCES

1. Wu JM, Takahashi DL, Ingram DK, Mattison JA, Roth G, Ottinger MA, et al. Ovarian reserve tests and their utility in predicting response to controlled ovarian stimulation in rhesus monkeys. Am J Primatol 2010;72(8):672-80.
2. Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem 2018;62:2-10.
3. Carson SA, Kallen AN. Diagnosis and management of infertility: A review. JAMA 2021;326(1):65.
4. Sharma N, Chakrabarti S, Sharma N, Chakrabarti S. Ovarian Reserve. In: Innovations In Assisted Reproduction Technology IntechOpen; 2019.
5. Brown J, Farquhar C. Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome. Cochr Libr. 2016;2017.
6. Ulrich ND, Marsh EE. Ovarian reserve testing: A review of the options, their applications, and their limitations. Clin Obstet Gynecol. 2019;62(2):228-37.
7. In Vitro Fertilization. HRC Fertility. Available at: https://www.havingbabies.com/in-vitro-fertilization/. Accessed 01 March 2024.
8. Adamson PC, Krupp K, Freeman AH, Klausner JD, Reingold AL, Madhivanan P. Prevalence & correlates

of primary infertility among young women in Mysore, India. Indian J Med Res. 2011;134(4):440-6.
9. Baby A, Varghese AA, Jose C, Kandasamy K, Rajagopal SS. A prospective evaluation of causes and treatment of infertility in a tertiary care hospital, Erode. Asian J Pharm Clin Res 2018;11(2):149-53.
10. Magendzo A, Schwarze J-E, de la Vega CD, Altieri E, Zegers-Hochschild F, Balmaceda JP. Clomiphene citrate challenge test predicts outcome of intrauterine insemination in women aged under 37 years. Reprod Biomed Online. 2006;12(4):423-7.
11. Csemiczky G, Harlin J, Fried G. Predictive power of clomiphene citrate challenge test for failure of in vitro fertilization treatment. Acta Obstet Gynecol Scand. 2002;81(10):954-61.
12. Jain T, Soules MR, Collins JA. Comparison of basal follicle-stimulating hormone versus the clomiphene citrate challenge test for ovarian reserve screening. Fertil Steril. 2004;82(1):180-5.
13. Yanushpolsky EH, Hurwitz S, Tikh E, Racowsky C. Predictive usefulness of cycle day 10 follicle-stimulating hormone level in a clomiphene citrate challenge test for in vitro fertilization outcome in women younger than 40 years of age. Fertil Steril. 2003;80(1):111-5.

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