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Different variables predicting ovulatory response among clomiphene citrate resistance and clomiphene citrate-sensitive patients with polycystic ovarian syndrome

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

Introduction: Polycystic ovary syndrome (PCOS) is a common endocrinological disorder seen in 6%–10% of women. It is a syndrome that manifests variably from adolescence as oligomenorrhea or hirsutism or obesity and goes on to affect the reproductive performance of the female by causing anovulation. Although lifestyle modification is known to improve reproductive outcomes in females with PCOS, the standard gold treatment for norm-gonadotropic oligo/amenorrheic infertility (WHO Group II) was clomiphene citrate (CC) (3) until 2018.

Background: The purpose of the study was to evaluate the role of clinical, metabolic, hormonal, and ultrasound features of women with PCOS in predicting the response to clomiphene citrate.

Patients & methods: This Prospective Observational study included 100 women with PCOs according to Rotterdam's criteria at Ain Shams University Maternity Hospital from June 2020 to January 2022. All patients were treated with CC (Clomiphene Citrate) according to the stair-step approach. Medroxyprogesterone (10 mg/d Provera for 10 days) was given to induce withdrawal bleeding to start these steps again in a new cycle if the patient was known to have oligomenorrhea. These steps were repeated for 3cycles before declaring the patient CC resistant. Due to the debatable effect of CC on the endometrium, all patients had Estradiol valerate 2 mg pills (cycloprogenova®) from the 11th day of the cycle. Response to CC was ovulation which was assessed either by TVUS or by serum progesterone level.

Results: Of the total 100 PCOS women, 42 (49.4%) were CC resistant and 43 (50.6%) were CC sensitive, and 15 were dropouts. Of the 43 PCOS women who ovulated, maximum, i.e., 25 (58.1%) women ovulated with 100 mg CC. The most significant diagnostic feature of PCOS in this study was a BMI of ≤27.8 (kg/m^2) with a specificity of 88.1%. CC-resistant PCOS women had significantly higher body mass index (BMI), TSH, and Serum Prolactin and were also associated with apple and pear-shaped WHR. Longer menstrual cycles were significantly more common in the CC-resistant group.

Conclusion: Clomiphene-sensitive PCOS women have significantly shorter cycles, lower BMI, Avocado-shaped WHR, and low TSH and Prolactin levels. These parameters should be considered while deciding on the ovulation induction protocol. Trial registration: Clinical Trial registration number is: NCT03206892.

Keywords: Anti-Müllerian hormone; Clomiphene; Ferriman–Gallwey score; Metabolic syndrome; Polycystic ovary syndrome; Body mass index; TSH; Prolactin

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinological disorder seen in 6%–10% of women. In nearly 20% of infertile women, PCOS is said to be the key reason behind infertility [1].

PCOS is a syndrome that manifests variably from adolescence as oligomenorrhea or hirsutism or obesity and goes on to affect the reproductive performance of the female by causing anovulation. Some women may be severely affected by metabolic syndrome, diabetes mellitus, or endometrial carcinoma. It also increases the risk of ovarian and breast carcinoma [2].

Although lifestyle modification is known to improve reproductive outcomes in females with PCOS, the standard gold treatment for norm-gonadotropic oligo/amenorrheic infertility (WHO Group II) was clomiphene citrate (CC) [3] until 2018, when ESHRE and ASRM declared letrozole as the first-line treatment for ovulation induction (OI) [4].

Induction of ovulation using CC could be undergone by either the traditional or the stair-step approach. The advantage of the latter is that when a dose increase is required, it can be done during the same cycle thereby decreasing treatment time and hence patient anxiety [5].

Those who fail to respond to CC are labeled as clomiphene resistant. It is common in approximately 15%–40% of women with PCOS [6]. Major factors postulated for CC resistance include obesity, insulin resistance, (seen in nearly 50%–70% of females with PCOS), and hyperandrogenemia [7]. Moreover, genetic predisposition is suggested to play a role in CC resistance [8]. However, still, the current data available on the causes of CC resistance are not sufficient enough to direct our treatment.

It is seen in various studies [9] that the females who initially failed to respond to CC develop better ovulation and pregnancy outcomes on treatment with insulin-sensitizing agents. This indicates that insulin resistance may cause CC resistance in females with PCOS. Insulin-sensitizing agents [10-12] decrease the dose of ovulation-inducing agents and time for follicular maturation in females with PCOS.

Until now, there is a lack of studies correlating the metabolic profile of women with PCOs and CC resistance. This is unfortunate since predicting CC resistance before induction will save much time by giving alternative

options, aromatase inhibitors for example as the first line of management to this subgroup.

This study aims to identify various parameters of CC resistance in PCOs women using the stair-step approach.

PATIENTS & METHOD

Study design: Prospective Observational Study.

Study setting: Ain shams University Maternity hospital

Study duration: from June 2020 to January 2022

Ethical approval:

All the procedures were approved by the Research Ethical Committee (REC) of Ain Shams University which operates under Federal Wide Assurance No. FWA 000017585 with the number FMASU MD 103/2020 with a progress report every 3 months and a final pre-publication report with the study results.

Informed consent was conducted from the women by the investigator, written consent was obtained from the women after explaining the study's objectives, and they had the right to withdraw at any time.

Inclusion criteria:

The study included women with;

1. PCOS (based on Rotterdam's criteria): oligo/anovulation, hyperandrogenism clinical (hirsutism or less commonly male pattern alopecia) / biochemical (raised Free androgen index or free testosterone) or polycystic ovaries on ultrasound (presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and increased ovarian volume (>10 ml)"1. Unilaterality does not affect diagnosis; neither does the location of the cysts in the ovary.
2. Age <40 years.
3. Women are not on any insulin-sensitizing or lipid-lowering agent.
4. Women with no endocrinal disorders (such as thyroid dysfunction, insulin resistance (DM), and adrenal disorders).
5. Women with a known cause of infertility other than PCO
6. AMH level that reflects the phenotype of PCO

Study cohort:

137 Women were recruited and assessed for eligibility for the study. However, 37 women were excluded because they either not met the inclusion criteria or refused to participate in the study.

The remaining 100 women were subjected to the following after written informed consent:

Initial Assessment included:

- Detailed medical history.
- A routine physical examination that included.
- Body mass index (BMI) was recorded.
- WC and hip circumference were recorded, and Waist Hip Ratio was calculated [13].

https://aishnutritionist.com/calculator/whr/

Signs of androgen excess were looked for such as; excessive hair growth, acne, or alopecia. Excessive hair growth was evaluated by a modified Ferriman and Gallwey [14] (FG) score (<8 normal, 8-15mild hirsutism, >15 moderate/severe hirsutism).

Investigation:

a) Laboratory:

- Free serum testosterone
- AMH (inclusion criteria, AMH that reflects the phenotype of PCOS-one of the inclusion criteria)
- LH (on the 2nd day of the cycle)
- FSH(on the 2nd day of the cycle)
- TSH
- Serum Prolactin
- Fasting and 2hrs postprandial

b) Imaging -Transvaginal ultrasound (on the 2nd day of the cycle):

- Antral follicular count (AFC)
- Ovarian volume [15].
- Endometrial thickness

It was done by the same observer using a Samsung ultrasound machine, HS40 (TVS probe frequency range 5–7 MHZ), same with the folliculometry following induction of ovulation.

Study steps:

Patients were then treated with CC (Clomiphene Citrate) according to the stair-step approach as follows;

An initial course of 50 mg/day on day 2 of their cycle for 5 days, a transvaginal ultrasound was done 1 week after the last pill; if there was no response (all follicles were below 10 mm) the second course of CC,100mg/day for 5 days, was initiated on the same day of the ultrasound. A transvaginal ultrasound was done 1 week after the last pill of the second course and if there was no response, a third and last course of CC, 150mg/day for 5 days was initiated. A transvaginal was done a week from the last pill of the third course and if still no response, the cycle was considered a failure.

The maximum CC dose was 150 mg [11].

Medroxyprogesterone (10 mg/d Provera for 10 days) was given to induce withdrawal bleeding to start these steps again in a new cycle if the patient was known to have oligomenorrhea.

These steps were repeated for 3cycles before declaring the patient CC resistant.

Due to the debatable effect of CC on the endometrium, all patients had Estradiol valerate 2 mg pills (cycloprogenova®) from the 11th day of the cycle till fetal pulsation is documented.

Response:

The response to CC was ovulation which was assessed by TVUS.

A scan was done 1 week after the last pill of each course. If follicles >10mm, follow up till ovulation.

Ovulation was also followed up using serum progesterone levels to decrease the number of dropouts. Serum progesterone above 10 ng/mL indicates ovulation.

In the case of known regular cycles, serum progesterone was withdrawn 2 weeks after the follicle reaches the size of 12mm if the results indicated ovulation a BHCG titer was withdrawn two weeks later. However, if the results were negative for ovulation and the patient is known to have regular cycles, the current cycle was dropped by physiological menstruation.

On the other hand, if she was known to have oligomenorrhea the same steps as aforementioned are followed but weekly serum progesterone was withdrawn till menses occur [12].

Based on the ovulation pattern, these patients were divided into two groups, one who ovulated with a CC maximum of 150 mg and others who did not ovulate and were considered CC resistant. The patients who ovulated were further classified into three subgroups based on whether they ovulated with 50 mg or 100 mg or 150 mg of CC.

The various parameters were compared between the CC-resistant and CC-sensitive groups.

Statistical methods

Quantitative variables were tested for normality using the Kolmogorov– Smirnoff tests. The normally distributed variables of the patients were recorded as mean ± standard deviation (SD) while skewed continuous variables were statistically analyzed using Mann–Whitney U-test. Qualitative variables were expressed as proportions.

The independent t-test was used to compare normal continuous variables between (clomiphene-sensitive and clomiphene-resistant). For qualitative variables, Chi-square or Fisher's exact test was used, whichever was applicable. All statistical tests are two-sided and performed at a significance level of α =0.05. The analysis of the data was done using online software 'IBM, SPSS Statistics (version 24.0, Armonk, NY: IBM Corp).

RESULTS

A total of 100 women met the inclusion/exclusion criteria of the study (**Tab. 1.**).

BMI statistically was significantly lower in responder cases. Apple and fat pear distribution statistically was significantly less frequent in responder cases. No statistically significant difference according to induction response regarding infertility duration or age (**Tab. 2.**).

Oligomenorrhea statistically was significantly less frequent in responder cases. Ovarian volume, AFC ≥ 12, (US PCO criteria), and Hirsutism and hirsutism grade were non-significantly less frequent in responder cases. No statistically significant difference according to induction response regarding free testosterone. TSH and prolactin statistically were significantly lower in responder cases. No statistically significant difference according to induction response regarding FSH, LH, LH/FSH, and AMH (**Tab. 3.**).

BMI had significantly moderate diagnostic performance in predicting good induction response, while TSH and prolactin had a significantly low diagnostic performance (**Tab. 4.**).

BMI ≤ 27.8 (kg/m^2) had higher diagnostic characteristics than fat distribution, TSH, and prolactin; had high specificity and positive predictive value (**Tab. 5.**).

BMI ≤ 27.8 (kg/m^2), Avocado fat distribution, TSH ≤ 2.0 (mIU/L), and Prolactin ≤ 14.5 (μg/L) statistically were significant independent factors that favor the occurrence of good induction response (**Tab. 6.**).

DISCUSSION

Clomiphene resistance may result from multiple more sophisticated equations with metabolic, endocrinal, and ultrasound criteria contributing to it.

This study's purpose was to shed light on the factors associated with CC resistance using the stair-step approach and to embrace those that may predict the patients who

Tab. 1. Demographic characteristics among the studied groups.

Characteristics		Mean ± SD	Range
Age (years)		27.1 ± 4.7	18.0 – 38.0
Infertility duration (years)		3.9 ± 2.7	1.0 – 12.0
BMI (kg/m^2)		30.6 ± 5.1	20.6 – 46.9
		N	%
Fat distribution	Avocado	41	41.0
	Apple	37	37.0
	Pear	22	22.0

Tab. 2. Comparison according to induction response regarding demographic characteristics.

Characteristics		Responder (N=52)	Resistant (N=48)	p-value
Age (years)		27.6±4.8	26.5±4.5	^0.272
Infertility duration (years)		3.8±2.7	4.0±2.8	^0.730
BMI (kg/m^2)		29.2±5.4	32.1±4.3	^0.004*
Fat distribution	Avocado	28 (53.8%)	11 (22.9%)	#0.007*
	Apple	16 (30.8%)	23 (47.9%)	
	Pear	8 (15.4%)	14 (29.2%)	

^ Independent t-test. #Chi square test. *Significant

Tab. 3. Comparison according to induction response regarding clinical characteristics and laboratory findings.

Characteristics		Responder (N=52)	Resistant (N=48)	p-value
Ovarian volume (mL)		9.7±1.3	10.1±1.5	^0.095
AFC	<12	5 (9.6%)	1 (2.1%)	§0.207
	≥12	47 (90.4%)	47 (97.9%)	
Irregular menses		38 (73.1%)	43 (89.6%)	#0.036*
US PCO criteria		47 (90.4%)	47 (97.9%)	§0.207
Hirsutism		29 (55.8%)	26 (54.2%)	#0.872
In hirsute cases;		N=29	N=26	
-Testestosterone		0.5±1.3	0.4±0.9	^0.823
-Hirsutism grade		15.1±6.1	18.1±5.9	^0.072
TSH (mIU/L)		1.9±0.8	2.5±1.0	^0.001*
FSH (mIU/L)		6.0±2.5	5.7±1.9	^0.514
LH (mIU/L)		8.3±6.2	7.5±4.2	^0.487
LH/FSH		1.4±0.9	1.6±1.8	^0.681
AMH (ng/mL)		6.0±3.8	7.2±3.5	^0.124
Prolactin (μg/L)		9.9±5.3	13.7±5.8	^0.001*

^ Independent t-test. *Significant ^ #Chi square test. §Fisher's Exact test. *Significant

Tab. 4. Diagnostic performance of BMI, TSH, and prolactin in predicting good induction response.

Factors	AUC	SE	p-value	95% CI	Cut off
BMI	0.764	0.054	0.001*	0.659 – 0.870	≤ 27.8
TSH	0.668	0.054	0.004	0.562 – 0.775	≤ 2.0
Prolactin	0.683	0.053	0.002	0.579 – 0.786	≤ 14.5

AUC: Area under the curve. SE: Standard error. CI: Confidence interval, *significant

Tab. 5. Diagnostic characteristics of BMI, fat distribution, TSH, and prolactin in predicting good response.

Characteristics	Value	95% CI	Value	95% CI
	BMI ≤ 27.8 (kg/m^2)		Avocado fat distribution	
Sensitivity	51.2%	35.5%–66.7%	55.8%	41.3% – 69.5%
Specificity	88.1%	74.4%–96.0%	75.0%	60.4% – 86.4%
Accuracy	69.4%	58.5% – 79.0%	65.0%	54.8% – 74.3%
Youden's index	39.3%	21.4% – 57.1%	30.8%	12.5% – 49.0%
PPV	81.5%	61.9% – 93.7%	70.7%	54.5% – 83.9%
NPV	63.8%	50.1% – 76.0%	61.0%	47.4% – 73.5%
LR+	4.30	1.80 – 10.29	2.23	1.29 – 3.85
LR-	0.55	0.40 – 0.77	0.59	0.42 – 0.83
LR	7.75	2.56 – 23.50	3.78	1.61 – 8.87
	TSH ≤ 2.0 (mIU/L)		Prolactin ≤ 14.5 (μg/L)	
Sensitivity	67.4%	51.5% – 80.9%	79.1%	64.0% – 90.0%
Specificity	64.3%	48.0% – 78.4%	50.0%	34.2% – 65.8%
Accuracy	65.9%	54.8% – 75.8%	64.7%	53.6% – 74.8%
Youden's index	31.7%	11.6% – 51.9%	29.1%	9.7% – 48.5%
PPV	65.9%	50.1% – 79.5%	61.8%	47.7% – 74.6%
NPV	65.9%	49.4% – 79.9%	70.0%	50.6% – 85.3%
LR+	1.89	1.20–2.98	1.58	1.13 – 2.22
LR-	0.51	0.31 – 0.82	0.42	0.22 – 0.81
DOR	3.73	1.52 – 9.15	3.78	1.46 – 9.78

CI: Confidence interval. PPV: Positive Predictive Value. NPV: Negative Predictive Value. LR+: Positive likelihood ratio. LR-: Negative likelihood ratio. DOR: Diagnostic odds ratio

might ovulate. This will most certainly aid in the choice of induction of ovulation protocol.

During the course of the thesis, pregnancy rates were encouraging, Pregnancy occurred in about one-tenth of the studied cases, to exploit this opportunity to present new topics for future cohorts.

Tab. 6. Logistic regression for factors affecting good induction response.

Factors	β	SE	p-value	Odds ratio (95% CI)
BMI ≤27.8 (kg/m^2)	1.34	0.50	0.008*	3.82 (1.45–10.11)
Avocado fat distribution	0.99	0.54	0.013*	2.70 (0.93–7.82)
TSH ≤2.0 (mIU/L)	1.04	0.50	0.042*	2.84 (1.07–7.49)
Prolactin ≤14.5 (μg/L)	1.41	0.51	0.017*	4.10 (1.51–11.11)
Constant	-2.19	0.57	<0.001*	

β: Regression coefficient. SE: Standard error. CI: Confidence interval, *significant

PCOs criteria impact

Oligomenorrhea was significantly lower in responders, while clinical hyper-androgenemia (hirsutism and hirsutism grade), biochemical hyper-androgenemia, and ultrasound criteria (ovarian volume and AFC >12) were non-significantly less in the responders.

Sachdeva and his colleagues, who held a prospective observational study on 164 PCOs patients, concluded results were in concordance with this study. Showing that cycles were significantly longer (oligomenorrhea) in CC-resistant patients [16-18].

Ellakwa and his colleagues and Sachdeva and his colleagues both disagree in that higher Ferriman Gallway score and free testosterone were observed in CC-resistant women as compared to those who were CC-sensitive [18,19]. This contradiction might be explained by the number of patients recruited in this study (100) and the studies mentioned above (150 and 164 respectively). Other causes that might have resulted in this contradiction include; the difference in the number of patients under different subgroups of BMI and WHR secondary to demographic differences; this study used free testosterone while the aforementioned used total, different exclusion criteria, and methodology as seen in Ellakwa and his colleagues' study who excluded patient with BMI >35kg/m^2 and used the standard method of CC, not the stair-step approach [19].

Sachdeva and his colleagues also proved in their study that CC-resistant women had significantly higher mean ovarian volume and AFC on the contrary to this study which was non significantly higher [18]. Yet again this might be due to the larger sample size.

Metabolic impact

Body mass index is significantly lower in responders. It was also noticed that the significance in the fat distribution, apple, and pear-shaped bodies were significantly lower in responders.

Sachdeva and his colleagues and Akpinar and his colleagues both had study results that postulate the same conclusion as this one; BMI is statistically significantly higher in the resistant group [18-20].

Sachdeva and his colleagues and Areetheerapas and his colleagues had also similar results to this study which points out that waist-hip ratio(WHR) is an indispensable parameter in determining the response to CC, concluding that high WHR is significantly elevated in the resistant group [18,21].

The latter point, although it enforces the point this study had reached which is; WHR is significantly high in the resistant group. That is interestingly the same point it contradicts this study's result.

In this study, Apple and pear-shaped bodies were significantly higher in the resistant group making the Avocado shaped body the ideal body for CC sensitivity. This is opposed by the previous study which illustrates that the pear shape is the ideal WHR; this may have been due to the difference in the demographics in the study population since in Egypt the vast majority is the Avocado shape, and thus the majority of the patients collected in this study.

Hormonal impact

TSH and serum prolactin were statistically significantly lower in responders and pregnant, while FSH, LH, FSH/LH ratio, and AMH were statistically non-significantly lower.

Woo and his colleagues conducted a retrospective study on 312 monitored cycles. They revealed that elevated LH/FSH ratio was only significant in patients who underwent treatment with letrozole compared to those who took CC [22]. Leading to a debatable point on whether or not a high level of LH/FSH level is a certain parameter to predict the response to clomiphene citrate.

Ibrahim and Nofal, had a prospective observational study on 204 PCOs patients to find an association between subclinical hypothyroidism and response to CC induction of ovulation. Since still there is a debate on the cut-off value for subclinical hypothyroidism, they followed the United States Preventive Services Task Force (USPSTF) Guidelines which defined subclinical hypothyroidism SCH as high serum TSH (2.5-10 mIU/L) with a normal FT4 concentration [23].

The study conducted did reach a conclusion that subclinical hypothyroidism negatively affects the response to induction of ovulation by CC and thereby pregnancy and thereby increasing the percentage of the clomiphene resistance group [23].

Sachdeva and his colleagues and Xi and his colleagues have study results contradicting this study. Both the mentioned study proved that LH, LH/FSH ratio, and AMH were elevated in the resistant group [18,24].

Sachdeva and his colleagues studied 164 patients with the same approach as this study, the stair-step approach with the definition of clomiphene resistance when a dose of 150mg has been tried. Therefore a larger sample size may have been the cause of this contradiction [18].

On the other hand, Xi and his colleagues had a study on 81 patients only studying the level of AMH and the response to CC accordingly, withdrawing AMH level on the 3rd day of the cycle, and declaring clomiphene resistance when the patient had a maximum dose of 100 with no ovulation and not using the stair-step approach, adding multiple variables to the comparison between this study and Xi and his colleagues study. Yet, these findings and conclusions were supported by several other studies regardless of the approach [24].

Tripathy and his colleagues conveyed a prospective randomized study on PCOS patients with normal prolactin levels. They studied their response to CC as regards ovulation and pregnancy by dividing the recruited patients into 2 groups one receiving CC only while the other had bromocriptine added. The outcome of this study showed that a normal level of prolactin had no adverse effect on ovulation and pregnancy [25].

Significant predictive factors

Among all the parameters measured, four were identified to have statistical significance in predicting good induction response. These were BMI, fat distribution, TSH, and Prolactin.

BMI had significantly higher diagnostic performance in predicting induction response than TSH, Prolactin, and Fat distribution.

TSH and prolactin; had high specificity and positive predictive value.

BMI ≤ 27.8 (kg/m^2), Avocado fat distribution, TSH ≤ 2.0 (mIU/L), and Prolactin ≤ 14.5 (μg/L) were statistically significant independent factors that favor the occurrence of a good induction response

The above data were elicited in previous studies; Sachdeva and his colleagues and Areetheerapas and his colleagues discussed the predictors of CC response, concluding that BMI and Fat distribution are of major impact on the response [18,21].

Sachdeva and his colleagues did not mention a cut-off value for each parameter but proved that a high BMI and Waist Hip ratio is of essence impact [18].

Whereas Areetheerapas and his colleagues reached a cut-off value for Waist hip ratio of 0.775 to predict drug responsiveness with 90.8% sensitivity and 20.2% specificity. However, in their study, BMI had no significant statistical difference [21].

No literature was found discussing a cut-off value for both TSH and prolactin levels as predictors of CC response except for the information discussed formerly.

It is worth mentioning that due to the small sample size, we were unable to develop a regression model.

We admit that the pregnancy rate is superior to the ovulation rate, but again due to the small sample size it was difficult to correlate predictable variables with clinical pregnancy.

According to the outcome of this study we are now able to categorize PCOS patient and start them on the most appropriate dose of Clomiphene Citrate for them or even counsel them that CC will not be the right choice for them depending on their demographic and lab criteria.

To further benefit from what this study revealed so far more studies should be held on larger population so that a regression model could be developed.

CONCLUSION

PCOs patients with BMI ≤ 27.8 (kg/m^2), Avocado fat distribution, TSH ≤ 2.0 (mIU/L), and Prolactin ≤ 14.5 (μg/L) were found to have a high response to CC induction by the stair-step approach as compared to their counterparts. The clinical pregnancy levels were similarly relatively low.

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CONFLICT OF INTEREST

No conflict of interest to declare about this work.

SUBJECT CONFIDENTIALITY

All evaluation forms, reports, and other records that leave the site would not include unique personal data to maintain subject confidentiality.

AUTHORS' CONTRIBUTIONS

All authors had put the plan, collected data, and followed up with the patients.

DATA AND MATERIALS

All data and materials are available on request.

FUNDING

No available.

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