International Journal of Gynecology and Obstetrics 133 (2016) 59–63

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Predictors of patient responses to ovulation induction with clomiphene citrate in patients with polycystic ovary syndrome experiencing infertility

Hamed E. Ellakwa *, Zakaria F. Sanad, Haitham A. Hamza, Mohamed A. Emara, Mohamed A. Elsayed

Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Menoufia, Egypt

ARTICLE INFO

Article history:
Received 24 February 2015
Received in revised form 14 September 2015
Accepted 2 December 2015

Keywords:
AMH
Clomiphene citrate
HOMA-IR
PCOS
Visceral fat area

ABSTRACT

Objective: To identify predictors of clomiphene citrate-induced ovulation in patients with polycystic ovary syndrome (PCOS). *Methods:* A prospective observational study of patients 18–40 years of age with PCOS experiencing infertility was conducted at Menoufia University Hospital between January 2011 and January 2013. A range of potential predictors of ovulation were recorded before patients received a 50-mg dose of clomiphene citrate. Following ovulation or no response to increasing clomiphene-citrate doses, correlations between predictors and treatment responses were analyzed. *Results:* In total, 150 patients with PCOS experiencing infertility were enrolled. Following treatment, 110 (73.3%) patients ovulated. Highly significant differences were observed between treatment responders and non-responders in baseline amenorrhea, body mass index (BMI), waist circumference, total testosterone, anti-Müllerian hormone, fasting insulin, homeostatic model assessment of insulin resistance, and visceral fat area ($P < 0.001$). Significant differences in mean ovarian volume ($P < 0.009$) and ovarian stromal artery pulsatility index ($P < 0.003$) were also observed. Total testosterone was the best individual predictor of clomiphene citrate treatment response. The area under the receiver operating characteristic curve in a multivariate prediction model was 0.98. *Conclusions:* A combination of patient amenorrhea, BMI, total testosterone, anti-Müllerian hormone, ovarian volume, ovarian stromal artery pulsatility index, and visceral fat area could be used to predict clomiphene-citrate treatment response in patients with PCOS experiencing infertility.
ClinicalTrials.gov: NCT02269306

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine and metabolic disorder with genetic causes [1–3]. The principal features of PCOS include biochemical hyperandrogenemia and/or clinical manifestations of hyperandrogenism [4]. PCOS is observed in 90%–95% of female patients experiencing anovulation attending fertility clinics [5]. Additionally, 90% of patients who have PCOS and experience infertility are overweight [6] and these patients are more likely to have upper-body fat distribution [7]. Moreover, increased abdominal or visceral adiposity is associated with greater insulin resistance, which could exacerbate the reproductive and metabolic anomalies that can occur in PCOS [7].

Clomiphene citrate is considered to be the gold-standard treatment for inducing ovulation in patients with PCOS [8]. Although 60%–85% of patients ovulate after clomiphene-citrate treatment, only approximately 50% of patients go on to conceive [9]. If ovulation is not induced by the administration of clomiphene citrate 150 mg/day, then the patient is said to show clomiphene-citrate resistance [10]. If such patients could be identified early, significant time can be saved in providing these patients with alternative treatments. Many studies have assessed different screening characteristics as possible predictors of clomiphene-citrate treatment outcomes [11–14]. The aim of the present study was to investigate whether the initial screening of clinical, endocrine, sonography, and computed-tomography characteristics could predict clomiphene citrate-treatment response in patients with PCOS experiencing anovulation.

2. Materials and methods

A prospective observational study was performed at the Gynecology Department of Menoufia University Hospital, Egypt, between January 2011 and January 2013. The Institutional Review Committee of the Menoufia Faculty of Medicine provided ethical approval for the study. All study patients gave written informed consent for participation in the present study.

The present study enrolled patients attending the hospital for fertility treatment who had been diagnosed with PCOS according to the following predefined criteria [15]; clinical hyperandrogenism, defined as hirsutism or acne vulgaris, and/or biochemical hyperandrogenism (total testosterone >880 ng/L or dehydroepiandrosterone sulfate

* Corresponding author at: Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Menoufia 32511, Egypt. Tel.: +20 482 222 731; fax: +20 482 235 691.
E-mail address: drhamedellakwa@yahoo.com (H.E. Ellakwa).

http://dx.doi.org/10.1016/j.ijgo.2015.09.008
0020-7292/

[DHEA-S] >2750 μg/L) [16]; the presence of menstrual disturbances, mainly oligomenorrhea or amenorrhea; and polycystic ovaries, visualized by transvaginal ultrasonography (either 12 or more follicles measuring 2–9 mm in diameter or an increase in ovarian volume >10 cm^3). Patients were excluded if they were younger than 18 years old or older than 40 years of age, had a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) lower than 18.5 or higher than 35, were pregnant, had any endocrine disorders or systemic diseases, were currently using or in the last 3 months had used oral contraceptives, glucocorticoids, antiandrogens, any ovulation-inducing agents, dopaminergic agents, antidiabetes drugs, antiobesity drugs, or if patients had a history of adnexal surgery.

Following consultation and study enrollment, patient histories (including information on patients' cycles) were taken and a clinical examination was performed on day three of a spontaneous cycle or of progestin-induced menses in patients with amenorrhea; anthropometric measures were recorded, including BMI and waist circumference, defined as the smallest circumference at the level of the umbilicus.

An early-morning blood sample was obtained from patients during the follicular phase (at the same time as clinical examination). Samples were used to determine serum levels of follicle stimulating hormone, luteinizing hormone, anti-Müllerian hormone (AMH), total testosterone, DHEA-S, insulin, and glucose. Patients' insulin resistance was calculated using the homeostasis model assessment (HOMA-IR) as follows [17]:

$$HOMA\text{–}IR = \frac{fasting\ \ insulinemia\ (\mu IU/mL) \times fasting\ \ glucose\ (mg/dL)}{450}$$

The initial clinical examination included an ultrasonographic examination of the uterus and ovaries, performed using a 6.5-MHz transvaginal transducer (Sonata Plus; IBE Technologies, Al Agouzah, Egypt). Ovarian volume and the number, diameters, and distribution of follicles were recorded. The average value of both ovaries was used for the statistical analyses. Doppler measurements of the uterine and intraovarian vessels were obtained. Patients assumed a semi-recumbent position for all ultrasonographic and Doppler measurements. Patients were evaluated between 08:00 am and 11:00 am to exclude any effects of circadian rhythms on uterine blood flow [18]. Further, patients were required to rest in a waiting room for at least 15 minutes before measurements were taken and patients were asked to completely void the bladder to minimize external effects on pelvic blood flow [19]. Color signals were sought in the stroma at the maximum distance from the surface of the ovary (Supplementary Material S1). Color-flow images of the ascending branches of the uterine arteries were sampled laterally to the cervix in a longitudinal plane (Supplementary Material S2). The pulsatility index, defined as the difference between peak systolic and end diastolic blood flow, divided by the mean maximum flow velocity, was calculated for the ovarian stromal and uterine arteries. In each patient examination, the mean value of three consecutive waveforms was obtained. The average value of the pulsatility indices of the right and left ovarian stromal and uterine arteries was used for all further calculations.

Computed tomography was performed to measure each patient's visceral fat area using a SOMATOM Spirit (Siemens, Berlin, Germany) scanner, with all patients in a supine position with their arms above their head and their legs elevated by a cushion to reduce the curve of their back. Images corresponding to the L4-L5 level were analyzed using ImageJ software version 1.43 (National Institutes of Health, Bethesda, USA) (Supplementary Material S3).

After recording patient characteristics, clomiphene citrate was administered according to a previously described method [13]. Briefly, clomiphene-citrate therapy began at an initial dose of 50 mg/day for 5 days from day three of spontaneous or progestin-induced menses. Treatment response was defined as ovulation in response to any dose of clomiphene citrate, assessed by midluteal serum progesterone measurement (ovulation was indicated by progesterone >10 ng/mL) combined with ultrasonographic monitoring of follicle growth until the appearance and subsequent rupture of a preovulatory follicle (mean diameter ≥18 mm). If ovulation did not occur (no response), the dose was increased by 50 mg/day during the next cycle, up to a maximum dose of 150 mg/day. Patient follow-up continued for at least three treatment cycles for all patients, after which any patients who had not responded to treatment were defined as experiencing clomiphene-resistant anovulation.

Patient characteristics were recorded as mean ± SD. The Mann–Whitney *U* test was used to make initial comparisons of the studied parameters between responding and non-responding patients. A logistic-regression analysis was conducted to examine univariate and multivariate relationships between the study parameters and patient responses. A multivariate logistic analysis incorporating backward elimination was used to evaluate the significance of using different patient parameters in predicting clomiphene-resistant anovulation in patients; $P < 0.10$ was used as the cut-off level for eliminating non-significant predictors from the final model. Receiver operating characteristic (ROC) curve and the area under the curve (AUC) analyses were used to assess the discriminative ability of each of the predictive characteristics. SPSS version 17.0 (SPSS Inc, Chicago, IL, USA) and MedCalc version 12.4, (MedCalc Software, Ostend, Belgium) were employed for data analyses.

3. Results

The present study enrolled 150 patients with PCOS experiencing oligo/anovulation. The age of the study population was 23.95 ± 3.26 years (range 19–35 years). All study patients reported experiencing infertility; 113 (75.3%) patients had been diagnosed with primary infertility and 37 (24.7%) reported experiencing secondary infertility. Of the study participants, 30 (20.0%) patients had a BMI of 18–24.9 and 120 (80.0%) patients were overweight or obese (BMI 25–34.9). The mean BMI of the participants was 27.99 ± 3.4. Among the study participants, 28 (18.7%) and 122 (81.3%) patients were experiencing amenorrhea or oligomenorrhea, respectively. Among the 126 (84.0%) patients with hyperandrogenemia, both clinical and biochemical hyperandrogenemia were reported by 66 (52.4%) patients, clinical hyperandrogenemia only was reported by 44 (34.9%) participants, and biochemical hyperandrogenemia only was reported by 16 (12.7%) patients.

Patient responses to increasing doses of clomiphene-citrate therapy are detailed in Fig. 1. Following treatment with a dose of 150 mg/day, 40 (26.7%) patients were classified as not responding to clomiphene citrate.

Significant differences were observed between patients who experienced a response to clomiphene citrate-induced ovulation and those who did not in cycle history (presence or absence of amenorrhea), BMI, waist circumference, total serum testosterone, serum AMH level, fasting insulin level, HOMA-IR, mean ovarian volume, ovarian stromal artery pulsatility index, and visceral fat area. However, no significant differences were observed with regards to patient age, type of infertility

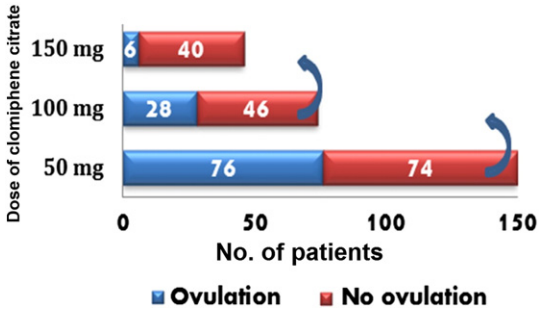

Fig. 1. Patient responses to ovulation induction with clomiphene citrate. Patients not responding to clomiphene-citrate treatment received increasing daily doses of clomiphene citrate.