clomiphene citrate

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Prognostic Factors of Ovarian Response to Clomiphene Citrate in Patients with Polycystic Ovarian Syndrome

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= Abstract =

Objectives : To determine whether the body weight, body mass index (BMI), and basal serum level of LH, FSH, testosterone (T), dehydroepiandrosterone sulfate (DHEA-S) are related to the ovarian response to clomiphene citrate (CC) in patients with polycystic ovarian syndrome (PCOS)

Materials and Method : From January 1996 to June 1997, total 57 patients with PCOS were enrolled in the present study. Women who had other infertility factors were excluded from our study. The ovulation induction using CC was used in all patients. The patients were grouped into 50 mg group, 100 mg group, and 150 mg group according to their daily CC dose. The patients were also grouped to ovulatory and non-ovulatory group. The body weight, BMI, and basal serum level of LH, FSH, T, DHEA-S were measured in all patients on the 2nd or 3rd day of the menstrual cycle. Results were analysed with Student's t-test and Fisher's exact test.

Results: The body weight and BMI of the nonovulating group were significantly higher than those of the ovulating group in all groups (50, 100, 150 mg of CC). However, there were no significant differences of the level of LH and FSH between ovulating and nonovulating groups in all CC groups (50, 100, 150 mg). The level of T of nonovulating group was significantly higher in 50 and 100 mg of CC groups, but not in 150 mg group. The level of DHEA-S of the non-ovulating group is significantly higher in 50 mg group, but not in 100 and 150 mg groups.

Conclusion: The body weight and BMI could be useful predictors of ovarian response to CC in patients with PCOS, and basal T and DHEA-S also might be useful in cases of low-dose CC treatment.

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(polycystic ovarian syndrome, PCOS) - -
(hypothalamus-pituitary-ovarian axis, HPO axis) (adrenal gland)

(oligomenorrhea), (amenorrhea) (mentsrual disorder),
(chronic anovulation) (infertility) (hirsutism)
.

(hyperandrogenism) (luteinizing hormone, LH)
(follicle stimulatinf hormone, FSH) LH/FSH 2-3
, (polycystic) (stroma)
(Adams et al., 1985; Conway et al., 1989).

PCOS (ovulation induction)
,
(in viro fertilization and embryo transfer, IVF-ET) (assisted
reproductive technology, ART) .

, clomiphene citrate(CC) 1960
, PCOS
. CC 75-80% PCOS
(Frank et al., 1988), 6 (cumulative pregnancy rate) 40-50%
(Mahesh & Mills, 1986). PCOS 20% CC 250 mg
(Buvat et al., 1989),
(Bider et al., 1993).

PCOS CC ,   ,
LH testosterone(T) (Lobo et al., 1982;
Garcia-Flores & Vanquez-Mendez, 1984) , CC
.

PCOS CC
CC , (body mass index, BMI), LH, FSH,
dehydroepiandrosterone sulfate(DHEA-S), testosterone(T) ,

PCOS CC
.

.

1.

1996   1   1997   6

                                        PCOS   57   .

                                                                        PCO

                (Adams et al., 1985), PCOS

                                        ,

        .   CC

                        (intrauterine insemination, IUI)   .

2.

                        PCOS

        57   .   progesterone in
oil(Progest, Samil pharm., Korea) 200 mg   .
        2-3   BMI   ,   LH,
FSH, T, DHEA-S   (Leopard, B & K, Denmark)   PCO
                                                .   LH   FSH   SPAC-S LH
and FSH immunoradiometric assay(IRMA)(Jeil, Japan)   .   LH
FSH   0.5-200 mIU/ml   interassay variance   3.7%   2.4%   ,
intraassay variance   2.8%   1.5%   .   T   TESTOSTERONE MAIA
radioimmunoassay(Biodata,   Italy)   0.064 ng/ml   , interassay
variance   2.41%, intraassay variance   4.49%   .   DHEA-S   Coat-A-Count
DHEA-SO4 radioimmunoassay(DPC, U.S.A.)   1.1   /dl
        interassay variance   4.6%, intraassay variance   3.8%   .
                        5   50 mg   CC(Serophene, Serono, Switzerland)   5
                        . CC
        (leading follicle)   18 mm   17 mm   2
                                                CC   LH
                        LH   human chorionic gonadotropin(Pregnyl, Organon,

Holland) 10,000 IU   12- 18   ,   36- 40   IUI

      .   IUI   percoll gradient   .   Percoll   (Pharmacia
Inc., Sigma Chemical Co., St. Louis, MO, U.S.A.)   90%, 70%, 50% percoll
            15 ml polypropylene centrifuge tube   1 ml
600 g   15   .   .
Tube   IUI   (Markler cannula, Sefi Medical, Israel)   IUI
      .

      ,   CC 50 mg   CC 100 mg
                        ,   CC 150 mg
                              .

            IUI   11- 12   β- hCG   ,   3 mIU/ ml   1
                                  (gestational sac)

                              (clinical pregnancy)   .
                                                      .   β- hCG
hCG MAIACLONE kit(Serono Diagnostics, MA)   IRMA   ,
interassay variance   intraassay variance   10%   5%   .
                                  Student t- test
Fisher's exact test   CC
regression analysis   . P < 0.05   .

.

1996   1   1997   6

PCOS   57   .   CC

50 mg   1   , 50 mg   100 mg

2   100 mg   150 mg

3   .   ,

,

.

1 (CC 50 mg)   57   14   24%   3

.   2 (CC 100 mg)   43   22   (51%), 4

3   21   10   (47%)   1   (Table 1).

CC   (   )   (   )

, BMI,   LH, FSH, T,   DHEA-S   .

1   43   67.7 ± 9.0 kg   14   54.6 ± 5.2 kg

(p   0.0001) BMI   35.3 ± 2.2 kg/m^2 40.5 ± 3.1

kg/m^2 (p   0.0001).

.   T   0.7 ± 0.1 ng/ml

1.3 ± 0.5 ng/ml   (p   0.001), DHEA-S

907.2 ± 248.2 ng/ml   1478.3 ± 560.1 ng/ml   (p

0.0001),   LH   FSH

(Table 2, Fig. 1, 2, 3).

2   58.3 ± 6.6 kg   68.6 ±

10.1 kg   (p   0.0003). BMI

36.8 ± 2.4 kg/m^2 40.2 ± 3.4 kg/m^2 (p

0.0001)   .   T

1.0 ± 0.4 ng/ml   1.5 ± 0.5 ng/ml   (p

0.0004),   1   DHEA-S   .   LH   FSH   1

(Table 3, Fig. 1, 2, 3).

,   3   64.5 ± 7.1 kg   75.7 ±

7.5 kg   (p   0.001), BMI   38.5 ± 2.2 kg/m^2 42.5

± 2.3 kg/m^2 (p   0.001),

.   T, DHEA-S, LH,   FSH

(Table 4, Fig. 1, 2, 3).

CC   (r =
0.91; p   0.05), BMI   CC   (r =
0.93; p   0.05).

Table 1. Clinical characteristics of patients

	Group I	Group II	Group III
No. of patients	57	43	21
Age of patients (yrs)	28.7 ± 5.5	29.2 ± 4.0	29.1 ± 3.8
Age of husbands (yrs)	31.8 ± 6.8	32.4 ± 5.7	33.2 ± 4.0
Duration of infertility (mos)	86.9 ± 68.0	64.9 ± 41.8	72.2 ± 43.0
No. of ovulating patients	14(24%)	22(51%)	10(47%)
No. of pregnancy	3	4	1

Values are means ± SD.

Table 2. Comparison of clinical and endocrine parameters between ovulating
and nonovulating groups in daily CC 50 mg group

	Ovulating	Nonovulating	p value
No. of patients	14	43	
Age of patients (yrs)	29.2 ± 2.6	28.3 ± 2.8	NS
Age of husband (yrs)	32.1 ± 3.5	32.4 ± 3.5	NS
Body weight (kg)	54.6 ± 5.2	67.7 ± 9.0	p < 0.0001
Height (cm)	162.5 ± 3.9	162.8 ± 4.2	NS
BMI (kg/m^2)	35.3 ± 2.2	40.5 ± 3.1	p < 0.0001
Basal hormone level			
LH (mIU/ml)	8.9 ± 1.6	9.1 ± 1.5	NS
FSH (mIU/ml)	5.2 ± 0.7	5.6 ± 1.0	NS
T (ng/ml)	0.7 ± 0.1	1.3 ± 0.5	p < 0.0001
DHEA-S (ng/ml)	907.2 ± 248.2	1478.3 ± 560.1	p < 0.0001

Values are means ± SD.

NS : not significant

BMI : body mass index, LH : lutenizing hormone, FSH : follicule stimulating hormone,

T : testosterone, DHEA-S : dehydroandrostenedione sulfate

Table 3. Comparison of clinical and endocrine parameters between ovulating
and nonovulating groups in daily CC 100 mg group

	Ovulating	Nonovulating	p value
No. of patients	22	21	
Age of patients (yrs)	28.2 ± 2.3	28.4 ± 3.2	NS
Age of husband (yrs)	30.1 ± 2.3	32.5 ± 3.9	NS
Body weight (kg)	58.3 ± 6.6	68.6 ± 10.1	p < 0.0003
Height (cm)	161.6 ± 4.1	162.3 ± 4.4	NS
BMI (kg/m^2)	36.8 ± 2.4	40.2 ± 3.4	p < 0.0005
Basal hormone level			
LH (mIU/ml)	9.0 ± 1.4	9.1 ± 1.5	NS
FSH (mIU/ml)	5.6 ± 1.3	5.3 ± 1.0	NS
T (ng/ml)	1.0 ± 0.4	1.5 ± 0.5	p < 0.0004
DHEA-S (ng/ml)	1332.8 ± 444.1	1411.7 ± 626.3	NS

Values are means ± SD.

NS : not significant

BMI : body mass index, LH : lutenizing hormone, FSH : follicule stimulating hormone,

T : testosterone, DHEA-S : dehydroandrostenedione sulfate

Table 4. Comparison of clinical and endocrine parameters between ovulating
and nonovulating groups in daily CC 150 mg group

	Ovulating	Nonovulating	p value
No. of patients	10	11	
Age of patients (yrs)	29.4 ± 3.6	29.6 ± 2.5	NS
Age of husband (yrs)	32.6 ± 3.9	32.1 ± 3.4	NS
Body weight (kg)	64.5 ± 7.1	75.7 ± 7.5	p < 0.0013
Height (cm)	163.3 ± 3.6	163.1 ± 5.7	NS
BMI (kg/m^2)	38.5 ± 2.2	42.5 ± 2.3	p < 0.0008
Basal hormone level			
LH (mIU/ml)	9.3 ± 1.3	8.9 ± 1.3	NS
FSH (mIU/ml)	5.1 ± 0.7	5.7 ± 1.0	NS
T (ng/ml)	1.4 ± 0.3	1.6 ± 0.3	NS
DHEA-S (mg/ml)	1379.2 ± 428.1	1453.7 ± 657.3	NS

Values are means ± SD.

NS : not significant

BMI : body mass index, LH : lutenizing hormone, FSH : follicule stimulating hormone,

T : testosterone, DHEA-S : dehydroandrostenedione sulfate

Fig. 1. Comparison of the body weight and BMI between the ovulating and nonovulating groups in three groups according to the CC doses

Fig. 2. Comparison of the level of T and DHEA-S between the ovulating
and nonovulating groups in three groups according to the CC doses

Fig. 3. Comparison of the level of LH and FSH between the ovulating
and nonovulating groups in three groups according to the CC doses

IV .

PCOS   LH   (theca

cell)   androstenedione   T   LH   DHEA-S

              ,   .

                      (insulin receptor disorder)

(peripheral   insulin   resistance)   ,

(hyperinsulinemia)   ,

insulin-like growth factor-I(IGF-I

                           (Bergh et al., 1993).   insulin-like growth

factor binding protein-1(IGFBP-1)   IGF-I

                     (Conover et al., 1992), sex hormone binding globulin(SHBG)

                                                                          (Tiitinen et

al., 1993).   PCOS

                                                            .   PCOS

                                                                      ,

                                               CC   .

    CC   (gonadotropin releasing

hormone, GnRH)   (gonadotropin; LH, FSH)

               .

                                                         (negative feedback)

                          .   CC   FSH   LH

                                                                        .

CC   .

              CC   GnRH   (pulse frequency)

    , GnRH   (Kerin et al., 1985), PCO

                                         ,   (pulse amplitude)

                      (Kettel et al., 1993).

              CC   1960

100-200 mg   5   5   75-80%   ,

                                                          (Rust et al., 1974; Frank et al.,

1988).   20%   PCOS   CC 250 mg

(Buvat et al., 1989),

(Bider et al., 1993). PCOS CC

, ,

(Lobo et al., 1982; Garcia-Flores & Vanquez-Mendez, 1984)

.

PCOS 35% 80% ,

BMI 27 . BMI 25

PCOS 31% ,

(, 1994). PCOS

. androstenedione extraglandular aromatization

- (acyclic estrogen feedback)

LH (Chang et al., 1982),

(Barbieri et al., 1986) LH

. IGFBP-1 IGF-I

(Tiitinen et al., 1993).

CC ,

(Barbieri et al., 1986)

CC

(Tiitinen et al., 1993; Armstrong, 1996). ,

IGF-I, IGFBP-1 SHBG CC

. PCOS , ,

LH, FSH

(Harlass et al., 1984;

Pasquali et al., 1986; Guzick et al., 1994). BMI 34.6 58

BMI 31.6 80% ,

29% androstenedione (Hollmann

et al., 1996). IGFBP-1 ,

CC (r = 0.91; p 0.05),

BMI CC (r = 0.93;

p 0.05), 50, 100, 150 mg

(p 0.05), PCOS CC

. , BMI

CC ,

.

, Poretsky Kalin(1988) CC 100mg

T

, androstenedione DHEA-S , Tiitinen

(1993) PCOS 25 CC 100mg

CC

LH, FSH, .

T 1 (50 mg) 2 (100 mg)

(p 0.05; p 0.05), 3 (150 mg)

. DHEA-S 1 (50 mg)

(p 0.05), 2, 3 (100, 150 mg)

. IGF-I

IGFBP-1 (Barbieri et al., 1986)

(peripheral conversion) SHBG

. LH FSH

,

LH, FSH

. T DHEA-S

T DHEA-S

. T

T T (1-2%)

T

. T CC T

.

,

.

.

PCOS CC BMI CC

, T DHEA-S

CC

.

V.

1996   1   1997   6

                              PCOS   57   , BMI,
LH, FSH, T, DHEA-S   CC

                                                           .

1. CC   50 mg, 5   (1   )   57   14 (24%)
             , 43 (76%)   . CC   100 mg, 5   43
(2   ) 22 (51%)   , CC   150 mg, 5   21   (
3   ) 10 (47%)   .

2.   CC   (r = 0.91;
p   0.05), BMI   CC   (r = 0.93; p
   0.05).

3.   (p
   0.05; p   0.05; p   0.05).

4.   T   1   (50 mg   )   2   (100 mg   )
                 (p   0.05; p   0.05),   3   (150 mg   )
             .

5.   DHEA-S   1   (50 mg   )
      (p   0.05),   2, 3   (100, 150 mg   )   .

6.   LH, FSH
   .

                    , PCOS   CC   BMI   CC
                 ,   T   DHEA-S   CC
                 .

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