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Predictors of Chances to Conceive in Ovulatory Patients during Clomiphene Citrate Induction of Ovulation in Normogonadotropic Oligoamenorrheic Infertility*

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ABSTRACT

The present prospective follow-up study was designed to identify whether clinical, endocrine, or ultrasound characteristics assessed by standardized initial screening of normogonadotropic oligo/amenorrheic infertile patients could predict conception in 160 women who reached ovulation after clomiphene citrate (CC) medication. Additional inclusion criteria were total motile sperm count of the partner above 1 million and a negative history for any tubal disease. Daily CC doses of 50 mg (increasing up to 150 mg in case of absent ovarian response) from cycle days 3–7 were used. First conception (defined as a positive urinary pregnancy test) was the end point for this study. A cumulative conception rate of 73% was reached within 9 CC-induced ovulatory cycles. Patients who did conceive presented more frequently with lower age ($P < 0.0001$) and amenorrhea ($P < 0.05$) upon initial screening. In a univariate analysis, patients with elevated initial serum LH concentrations (>7.0 IU/L) had a higher probability of conceiving ($P < 0.01$). In a multivariate analysis, age and cycle history (oligomenorrhea *vs.* amenorrhea) were identified as the only significant parameters for prediction of conception.

These observations suggest that there is more to be gained from CC ovulation induction in younger women presenting with profound oligomenorrhea or amenorrhea. Screening characteristics involved in the prediction of ovulation after CC medication in normogonadotropic oligo/amenorrheic patients (body weight and hyperandrogenemia, as shown previously) are distinctly different from predictors of conception in ovulatory CC patients (age and the severity of cycle abnormality). This disparity suggests that the FSH threshold (magnitude of FSH required for stimulation of ongoing follicle growth and ovulation) and oocyte quality (chances for conception in ovulatory cycles) may be differentially regulated. (*J Clin Endocrinol Metab* **84:** 1617–1622, 1999)

THE SYNTHETIC antiestrogen clomiphene citrate (CC) represents an easy to use, convenient, inexpensive, and safe first choice medication in normogonadotropic oligo/amenorrheic infertility (WHO group 2) (1). Life-table analysis of pregnancy rates after CC medication and prediction of treatment outcome have been the subject of extensive investigation (2–10). Cumulative pregnancy rates after CC treatment between 37–97% have been reported (3, 4, 6). A positive correlation was established between body weight and the CC dose required to induce ovulation (5, 10). Moreover, recent studies have indicated that body mass index (BMI) is significantly higher in nonresponders (7, 10). Limited information is available, however, concerning the predictive value of initial screening characteristics for treatment outcome (11), and previous investigators were unable to identify predictors for conception after CC induction of ovulation (6, 8, 10). All the above-mentioned studies focused on the prediction of treatment outcome in the entire group of infertile patients who started with CC medication. In contrast, we focused separately on the prediction of ovulation after CC administration (12) and the prediction of conception in ovulatory CC-treated women. This approach seems more appropriate, because statistical bias due to selective drop out from the study for reasons of persistent anovulation despite increasing doses of CC medication is eliminated.

Our group could recently establish that obese hyperandrogenic amenorrheic patients are more likely to be resistant to CC medication (12). We now report on initial clinical, endocrine, and sonographic screening characteristics of normogonadotropic oligomenorrheic or amenorrheic infertile women achieving ovulatory cycles after CC medication in an attempt to identify factors predicting chances for conception in these patients. The separate focus on the prediction of conception and ovulation after CC treatment may allow differentiation among factors affecting oocyte quality independently from follicle development.

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Subjects and Methods

Subjects and study protocol

Between February 1993 and December 1997, 160 couples presenting with oligomenorrhea (bleeding intervals between 35 days and 6 months) or amenorrhea (bleeding interval >6 months) and infertility attending our unit were included in the present study. Additional inclusion criteria were 1) serum FSH levels within normal limits (1–10 IU/L) (1, 13, 14)

and normal serum PRL and TSH levels, 2) spontaneous menses or positive bleeding response to progestagen withdrawal, 3) ovulatory cycles after CC induction of ovulation, 4) BMI (weight divided by height squared) greater than 18, 5) age between 19–40 yr, 6) a total motile sperm count [TMC = ejaculate volume (milliliters) × sperm concentration (10^6/mL) × percentage of progressive motile sperm] of the partner above 1 million (15), 7) negative history for any tubal pathology, and 8) no indication for intrauterine insemination. Study approval was obtained from the human subject committee of the Dijkzigt Hospital/Erasmus University, and informed consent was obtained from all subjects included. A standardized clinical, endocrine, and sonographic screening took place before initiation of induction of ovulation with CC medication.

Ovulation after CC treatment was assessed by midluteal serum progesterone (P) levels above 25 nmol/L, combined with transvaginal sonographic monitoring of follicle growth until visualization of a preovulatory follicle (mean diameter, >18 mm) and subsequent disappearance or biphasic basal body temperature charts, as described previously (12). Clomiphene citrate was administered at a daily dose of 50 mg (increased to 100 and 150 mg in subsequent cycles in the case of absent ovarian response) from cycle days 3–7 after initiation of spontaneous or progestin-induced withdrawal bleeding. Conception was defined as a positive urinary pregnancy test (Clearview, hCG II, Unipath Ltd., Bedford, UK) more than 3 days after the expected menses, and ongoing pregnancy was defined as sonographic assessment of an intrauterine gestational sac with positive heart beat.

History and clinical screening included assessment of duration of infertility, whether infertility was primary or secondary, cycle history, previous medication and/or surgery, and BMI. Endocrine screening included serum assays of FSH, LH, estradiol (E_2), testosterone (T), androstenedione (AD), sex hormone-binding globulin (SHBG), and P. Fasting venous blood samples were taken on a random day between 0800–1000 h, as indicated previously (12). Blood samples were centrifuged within 2 h after withdrawal and were stored at −20 C until assayed. Serum LH and FSH levels were measured by immunofluorometric assay (Amerlite, Ortho-Clinical Diagnostics, Amersham, Aylesbury, UK), as described previously (14). P levels were measured by RIA, as described previously (16). Serum E_2, T, AD, and SHBG levels were estimated using RIA kits provided by Diagnostic Products (Los Angeles, CA), as described previously (17). Intra- and interassay coefficients of variation were less than 3% and 8% for FSH, less than 5% and 15% for LH, less than 16% and 17% for P, less than 5% and 7% for E_2, less than 3% and 5% for T, less than 8% and 11% for AD, and less than 4% and 5% for SHBG, respectively. Transvaginal pelvic ultrasound (model EUB-415, Hitachi Medical Corp., Tokyo, Japan) was performed by a single observer (B.I.) and included the assessment of ovarian stroma amount and echogenicity (arbitrarily classified from one to three per ovary), ovarian volume (milliliters), and total number of follicles (both ovaries), as described previously (13, 18). Semen analyses were performed according to WHO guidelines (1992) and comprised ejaculate volume (milliliters), number of spermatozoa per mL (10^6 spermatozoa/mL), percentage of progressive motile spermatozoa, and percentage of normal forms (19).

Data analysis

A *P* value of 0.05 was chosen as the threshold level for statistical significance. Cox regression has been used for life-table analysis of conception rates during CC treatment (20). The number of ovulatory CC treatment cycles was the time variable for multivariate analyses. Censoring was defined as definitive discontinuation of CC therapy without conception or end of follow-up (February 1998). To analyze the effect of the severity of cycle abnormality on chances of conceiving after CC treatment, we arbitrarily divided the cycle histories of the patients into four categories; 5–6 weeks (n = 56), 6–9 weeks (n = 50), 9–26 weeks (n = 25), and greater than 26 weeks (*i.e.* amenorrhea) (n = 29). The univariate relation was assessed between the variables listed in Table 1 and the time interval between the first ovulation after CC medication and conception using the Kaplan-Meier method (21) for categorical and the Cox regression (20) for continuous variables. The log-rank test has been used to denote statistical significance in life-table analyses. The multivariate analysis was performed with the method of forward stepwise selection to gain a better insight into the interdependence between initial screening parameters. This method can explain why a variable that was significantly different in univariate analysis was not selected in the final model. The prognostic impact of variables was expressed as a fecundability ratio, which is equivalent to the hazard ratio in survival analysis. For instance, a fecundability ratio of 0.9 for an unfavorable group means that the conception rate per ovulatory CC treatment cycle is 10% lower compared to that in the favorable group. In some couples (n = 25), no sperm analysis was performed because of the short time interval between initiation of CC medication and conception. A statistical imputation technique has been applied using multiple conditional mean imputation to fill in these missing sperm parameters (22). The value of semen parameters was estimated using the time until conception and patient characteristics related to sperm parameters in the nonmissing group. Data were analyzed using the commercially available software package SPSS, Inc. (Chicago, IL).

Results

A total of 82 women (51% of the ovulatory group) conceived, and 73 (46%) reached an ongoing pregnancy from the total of 160 patients fulfilling the in/exclusion criteria. Sixty-nine were singleton and 4 were twin pregnancies (data not shown). Initial screening parameters of 9 patients who had a miscarriage after CC (11% of overall CC conceptions) were not different from those of the remaining 73 patients who reached an ongoing pregnancy (data not shown). One woman who conceived (twin pregnancy) during her first CC treatment cycle was frequently monitored on an out-patient basis due to abdominal discomfort

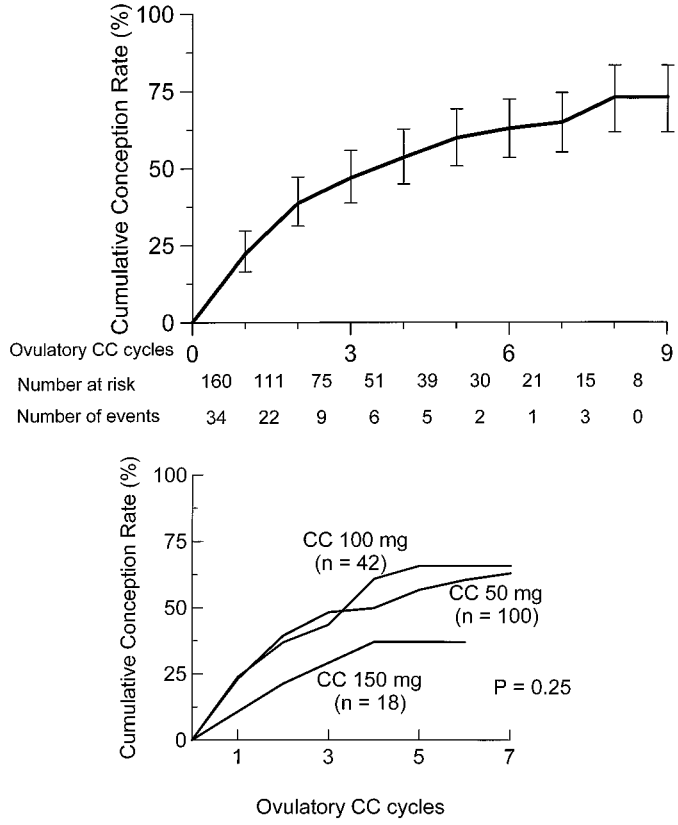

FIG. 1. Life-table analysis of CCR in 160 normogonadotropic oligoamenorrheic infertile patients who ovulated after CC medication. CCR (including absolute number of patients at risk and number of events (conceptions)) are presented for the total study group (*upper panel*; *vertical lines* represent 95% confidence intervals) and separately for women who reached ovulatory CC cycles with 50, 100, or 150 mg daily for 5 subsequent days (*lower panel*). N represents the initial number of patients at risk per dose group. *P* = log-rank test *P* value.

and enlarged ovaries. There was no case of severe ovarian hyperstimulation syndrome.

The life-table analysis of cumulative conception rates (CCR) of patients who ovulated after CC are indicated in Fig. 1 for the total group, and separately for different dose groups. A cumulative conception rate of 47% was reached within three cycles from first ovulation, and a CCR of 73% was reached within nine CC-induced ovulatory cycles. Patients using daily doses of 50, 100, and 150 mg CC reached cumulative conception rates of 57%, 66%, and 38% within 5 ovulatory cycles, respectively ($P_{\log\ rank} = 0.25$; Fig. 1). At higher doses, chances for conception and ongoing pregnancy are not statistically significantly reduced, although absolute CCR (n = 18) were low in the 150-mg CC group. The overall mean duration of follow-up was 4 ± 3 months and 3.2 ± 2.6 ovulatory CC cycles. Initial screening characteristics of the overall group of patients who ovulated after CC and separately for those women who conceived (n = 82) *vs.* those who did not (n = 78) are depicted in Table 1. Age, the severity of cycle abnormality (oligomenorrhea *vs.* amenorrhea), and cycle duration, arbitrarily classified in four categories (see also *Materials and Methods*), were significantly different in univariate analysis. Age (cut-off of 30 yr), cycle history (oligomenorrhea *vs.* amenorrhea), and initial serum LH level (cut-off level of 7.0 IU/L) in univariate analyses for CCR are depicted in Fig. 2. The percentages of ongoing pregnancies per conception for patients with elevated (initial serum LH level ≥7.0 IU/L) or normal initial serum LH levels were 84.8% and 94.4%, respectively (*P* value for difference in proportion ongoing pregnancies = 0.16, and 95% confidence interval for difference = −3% to 23%). The cut-off value for normal (*i.e.* 7.0 IU/L) was chosen on the basis of a previous study from our group in normoovulatory controls (mean ± 1 SD) (23).

A total number of 159 patients had complete data on the variables used in the multivariate analyses. Univariate analysis and forward stepwise multivariate analyses of all initial parameters for the prediction of chances to conceive in ovulatory patients treated with CC are depicted in Table 2. During the stepwise multivariate analysis for the prediction of chances to conceive, age, and cycle history (amenorrhea *vs.* oligomenorrhea) entered into the model (steps 1 and 2, respectively). The multivariate-adjusted fecundability ratio for age was 0.90 (95% confidence interval, 0.85–0.95), and that for amenorrhea was 0.54 (95% confidence interval, 0.32–0.93).

Discussion

The present prospective follow up study was designed to evaluate whether initial screening characteristics of 160 normogonadotropic oligo/amenorrheic infertile women could predict conception during ovulatory CC-induced cycles. Although CC medication has been the focus of prevalent research, limited information is available regarding the prediction of conception as treatment outcome (11). Reported cumulative pregnancy rates vary between 37–97%. Most studies, however, suffer from methodological difficulties and different inclusion/exclusion criteria. For the first time, our group has focused on ovulation and conception in sep-

TABLE 1. Initial clinical, endocrine, and ultrasound screening characteristics and sperm parameters of partners (median and range) of 160 normogonadotropic oligomenorrheic or amenorrheic infertile women who ovulated after CC induction of ovulation (overall group) and did or did not (CC failure) conceive

Screening parameters	Overall group (n = 160)	Conceived (n = 82; 51%)	CC failure (n = 78; 49%)	*P* value[a]
Clinical				
Age (yr)	28 ± 4	27 ± 4	29 ± 4	0.0001
Infertility duration (yr)	1.9 ± 2.3	1.6 ± 1.4	2.2 ± 2.9	0.23
Primary infertility (n)	116	62	54	0.40
Amenorrhea (n)	29	18 (62)	11 (38)	0.04
Bleeding interval in 4 categories				0.05
5–6 weeks, n (%)	56 (35)	22	34	
6–9 weeks, n (%)	50 (31)	29	21	
9–26 weeks, n (%)	25 (16)	13	12	
>26 weeks, n (%)	29 (18)	18	11	
BMI (kg/m^2)	26 ± 6	26 ± 6	25 ± 6	0.46
Endocrine				
LH (IU/L)	7.6 ± 4.2	8.2 ± 4.3	6.9 ± 4.0	0.11
T (nmol/L)	2.3 ± 1.0	2.3 ± 1.0	2.3 ± 1.0	0.85
AD (nmol/L)	15.0 ± 6.9	15.8 ± 7.9	14.0 ± 5.7	0.16
FAI[c]	5.4 ± 3.9	5.5 ± 4.1	5.1 ± 3.7	0.20
SHBG (nmol/L)	56 ± 31	54 ± 27	58 ± 35	0.24
E_2 (pmol/L)	259 ± 175	229 ± 145	290 ± 198	0.10
Ultrasound				
Mean ovarian vol (mL)	9.3 ± 3.7	9.2 ± 3.7	9.4 ± 3.7	0.97
Mean follicle no.	12 ± 5	12 ± 5	12 ± 5	0.48
Total stroma score[d]	3.2 ± 1.1	3.1 ± 1.1	3.3 ± 1.2	0.66
Total motile sperm count (TMC)	73 (1.1–492)	75 (1.5–303)	72 (1.1–492)	0.32[e]
% Normal morphology	24 (1–50)	20 (1–50)	25 (1–50)	0.34[e]

Values are the mean ± SD. Underlined values are statistically significant.
[a] Comparison of CC-conceived *vs.* CC failure (univariate Cox regression).
[b] Chances to conceive differ among four categories of bleeding interval.
[c] FAI = T × 100/SHBG.
[d] Arbitrarily defined as one to three per ovary (both ovaries added).
[e] Computed with multiple imputation of missing values.

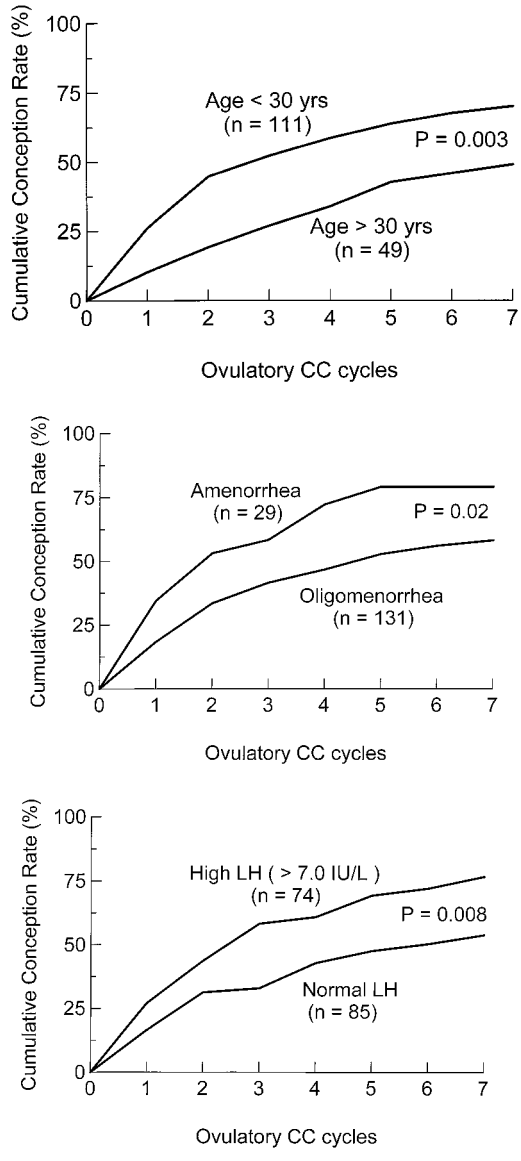

FIG. 2. Univariate analysis of CCR in 160 normogonadotropic oligoamenorrheic infertile patients per ovulatory CC cycle. Initial screening parameters shown are 1) patient's age (cut-off level at 30 yr; *upper panel*), 2) cycle history (oligomenorrhea *vs.* amenorrhea; *middle panel*), and 3) initial serum LH concentrations (cut-off level of 7.0 IU/L; *lower panel*). n represents the initial number of patients at risk. P = log-rank test P value.

arate steps, taking into account that a significant proportion (23%) of patients who remain anovulatory after CC medication (12) have no chance of conception. Inclusion of these patients in a study focusing on conception causes statistical bias. This separate focus may offer a better insight into the potential predictive power of initial screening characteristics in a heterogeneous group of normogonadotropic oligo/amenorrheic infertile women (WHO class 2) for CC-induced follicle growth and ovulation, separately from conception.

In the present study, CCR of 63% within six cycles and 73% within nine ovulatory CC-induced cycles have been reached. Two thirds of patients who conceived reached this end point within the first three ovulatory CC treatment cycles. This is

TABLE 2. Forward stepwise multivariate analyses of initial screening characteristics for the prediction of chances to conceive in 159 normogonadotropic oligo-amenorrheic infertile women who ovulated after CC induction of ovulation

Analyses steps	Univariate: 0[a]	Multivariate	
		1	2
Screening parameters			
Clinical			
Age (yr)	0.0001	In model	In model
Amenorrhea (n = 29)	0.04	0.02	In model
Bleeding interval (in four categories)	0.05	0.06	0.30
Endocrine			
LH (IU/L)	0.11	0.36	0.26
FAI[b]	0.20	0.56	0.38
AD (nmol/L)	0.16	0.38	0.15
E_2 (pmol/L)	0.10	0.26	0.39

Numbers are P values for inclusion in the model. *Underlined* numbers are significant at $P < 0.05$.

[a] Only screening parameters with a univariate $P \leq 0.2$ (see Table 1) are shown. In the univariate analysis (step 0), three variables reach statistical significance (*underlined*). In step 1 of the multivariate analysis the variable with the highest prognostic information (age) is selected. After the first step, amenorrhea still reaches statistical significance and, therefore, is selected in the second step. Thereafter, no additional variable is statistically significant anymore, indicating that the model cannot be improved by selecting a subsequent parameter.

[b] FAI = T × 100/SHBG.

in agreement with previous reports in the literature regarding CC (3, 24, 25) and is similar to spontaneous conception chances in normoovulatory women (26). This is also comparable to conception rates reported for exogenous gonadotropin induction of ovulation (27–29) in anovulatory infertile patients. These observations strongly suggest that the overall detrimental effects of CC on cervical mucus production or endometrial receptivity and subsequent implantation are limited with daily CC doses up to 150 mg. Although the CCR seems to be lower in the high dose CC group, this finding was not statistically significant. It should be noted that the sample size of this group was limited, so actual differences cannot be excluded.

Previous studies were unable to identify predictors for conception in CC induction of ovulation in normogonadotropic infertile women (6, 8, 10). In the present study, age and cycle history (amenorrhea or oligomenorrhea) were significantly different comparing patients who conceived *vs.* those who did not during CC-induced ovulatory cycles. Multivariate analyses revealed a final model including age and cycle history. The predictive power of age was highest. The area under the receiver operating characteristics curve of the final model including these two factors reached 0.68 (data not shown), which is substantially lower than that in the previous model predicting ovulation after CC (0.82) (12). For reasons of clarity, the forward stepwise approach was chosen. Backward stepwise analysis was also applied, resulting in the same final model (data not shown). Young patients have a higher probability to conceive during CC-induced ovulatory cycles. The fecundability rate of the patient decreases by approximately 10%/yr. This is in agreement with reports that indicate that age is an important factor for the prediction of chances for spontaneous conception in untreated nor-

moovulatory subfertile patients (30–32). Similar findings have been reported for the prediction of chances to conceive after exogenous gonadotropin induction of ovulation (27) and *in vitro* fertilization treatment (33).

Amenorrheic patients exhibit a 2-fold higher probability to conceive after ovulatory CC cycles compared to oligomenorrheic patients. Patients with longer bleeding intervals also exhibit higher conception chances. We have been unable to find similar reports in the literature regarding induction of ovulation. The most likely explanation seems to be the following. Patients with amenorrhea have an extremely low probability to conceive without intervention due to anovulation before seeking help by a physician. Presumably, the major subfertility factor in these patients is chronic anovulation, which can be resolved temporarily by the use of CC medication. These patients are more likely to be at low risk for any other subfertility factor, such as tubal or sperm dysfunction. Some oligomenorrheic patients may have spontaneous ovulations (34), and some of these women may never seek medical intervention because of spontaneous pregnancies. Their benefit from ovulation induction is an increased chance for conception due to an increased number of ovulations with a fixed interval in a given period of time. Similar observations were made for pregnancy chances after artificial insemination with donor sperm in relation to the sperm quality of the partner. Donor insemination outcome is significantly better in cases with very poor sperm quality (35). One should consider that amenorrheic patients also have a higher probability to remain anovulatory after CC, as demonstrated previously (12). In contrast, regular ovulatory cycles are easier to induce with CC in oligomenorrheic patients, but there is less chance of pregnancy.

In the present study, patients with elevated initial serum LH levels have a significantly higher probability to conceive once ovulatory cycles have been achieved by CC. A recent study also indicated higher initial LH levels in patients who conceived after CC medication (10). In contrast, a poor treatment outcome has been observed in patients with high LH levels during the follicular phase of CC-induced cycles (8). It should be realized that we report on initial LH levels before initiation of CC medication, rather than during CC-induced cycles. Indeed, elevated LH levels may normalize only during CC-induced ovulatory cycles (36). These observations are in sharp contrast with reports regarding patients with elevated LH who perform poorly during gonadotropin induction of ovulation (28) or *in vitro* fertilization (37). We previously showed that initial LH concentrations did not predict patients who would remain anovulatory after CC medication (12). The present observation seems to dispute previous beliefs concerning the detrimental effects of elevated LH levels on oocyte maturation and capacity for fertilization. In addition, we did not observe a higher spontaneous abortion rate in patients with high LH levels who conceived after CC medication. This finding is also in contrast with previous reports on the effects of high LH concentrations on chances for spontaneous abortion after exogenous gonadotropins (38, 39). The predictive power of the initial LH level is poor in case age enters in the final model, which may be due to a correlation of initial LH with age (data not shown). The mechanism of action of CC is not fully elucidated, and the role of LH in the pathogenesis of ovarian abnormalities remains open for speculation. As an example, female siblings of male patients described with an activating mutation of the LH receptor (so-called familial male testotoxicosis) seem to be without a clear phenotype (40).

Total motile sperm count is not a predictor in univariate or multivariate analyses of prediction of conception in the present study population. This is in agreement with the observation that a large overlap exists between semen characteristics of males from fertile *vs.* subfertile couples (15). Moreover, it can be speculated that couples with better sperm parameters have already conceived spontaneously before seeking medical intervention.

In summary, it can be concluded that body weight and hyperandrogenemia are the predominant predictors for ovulation after CC treatment, whereas age and cycle history dictate pregnancy chances in ovulatory women. This stresses for the first time the important concept that follicle growth and oocyte quality (and subsequent capacity to be fertilized *in vivo*) are differentially regulated during induction of ovulation, confirming observations during *in vitro* fertilization.

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