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LIFESTYLE FACTORS

Influence of smoking on outcome of COH and IUI in subfertile couples

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Abstract
Aim To evaluate the influence of smoking on the outcome of COH and IUI in subfertile couples.
Patients and methods We reviewed the medical files of all consecutive women, age ≤35 years, attending our infertility clinics over an eigth-year period. Data on patient age, smoking habits, and variable related to infertility-treatment were collected from the files.
Results A total of 2,318 cases were evaluated: 1,803 in non-smoking patients (n=679) and 515 in smokers (n=206). The smokers used significantly more gonadotropin ampoules and gained a thinner endometrium on the day of hCG administration than the nonsmokers (p<0.016 for both). There were no between-groups differences in patient age, duration of gonadotropin stimulation, number of follicle >14 mm in diameter, or E2 levels on the day of hCG administration.
Conclusion Smokers undergoing COH with IUI required a significantly higher gonadotropin dosage than nonsmokers in order to achieved a comparable pregnancy rate.

Keywords Smoking · COH · IUI · Infertility · Pregnancy rate

Capsule Smokers undergoing COH with IUI required a significantly higher gonadotropin dosage than nonsmokers in order to achieved a comparable pregnancy rate.

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Introduction

Lifestyle and environmental factors are well-known contributors to reproductive failure. Therefore, clinicians suggest that they be identified and corrected during preconception counseling of infertile couples prior to initiation of treatment.

Cigarette smoking, with its widely recognized deleterious health effects, accounts for an estimated 13% of causes of female infertility [1]. The underlying mechanism is presumed to involve a toxic effect of the various tobacco chemicals on follicular development, gamete mutagenesis or inhibition of granulose cell aromatase. This, in turn, leads to accelerated follicular depletion, reduced fecundity, increased miscarriages, and accelerated onset of menopause [2–4].

Cigarette smoking also has a significant negative effect on the clinical outcome of assisted reproduction treatment (ART). Several meta-analyses and reviews have investigated the effect of smoking in patients undergoing IVF treatment [5–7]. They all found that compared to nonsmokers, smokers required a higher mean gonadotropin doses for ovarian stimulation, and had lower peak E2 levels, fewer oocytes retrieved, lower fertilization and implantation rates, and lower pregnancy and live-birth rates. Moreover, smokers required nearly twice the number of IVF cycles to conceive.

Controlled ovarian hyperstimulation (COH) combined with intrauterine insemination (IUI) has been considered a key factor in the success of infertility treatment for subfertile couples [8–10], because it enables the recruitment of multiple healthy fertilizable oocytes [11] and the correction of subtle ovulatory dysfunction. Moreover, while various COH protocols have been used for ovarian stimulation, a recent meta-analysis demonstrated that based on the limited available literature, gonadotropins might be the most effective drugs [12].

Surprisingly, however, despite the widespread studies of the effect of smoking on reproductive outcome after IVF treatment [6, 13–16], there is no information in the literature on the influence of smoking on COH and IUI.

The aim of the present study was to attempt to fill this gap in order to clarify the proper approach to COH in smokers and to aid fertility specialists and their patients in the decision-making process.

Patients and methods

We reviewed the medical files of all consecutive women who attended two infertility clinics of a single national-health maintenance organization over an eigth-year period. At admission, all women and their partners underwent a basic fertility workup, including the completion of a referral status form that consisted of demographic characteristics, including smoking habits and medical history. Following the first assessment and prior to gonadotropin treatment, all the women underwent hysterosalpingography (HSG). Only those with normal transfer and spill from at least one fallopian tube were included in the study. All the male partners underwent semen analysis that was handled and interpreted according to the WHO Manual and Standards [17]. Women with male partners with less than 5 million total motile sperms after sperm washing or swim-up, were excluded.

Because the possibility of bias could not be eliminated, for purposes of the present study, we included only patients treated with COH using gonadotropin and IUI who were considered to have a favorable prognosis *a priori*, i.e., patients ≤35 years undergoing from their first and up to their forth COH and IUI cycle attempts. Patients were assigned to gonadotropin stimulation according to the following criteria: anovulatory infertility following failure to respond or conceived with clomiphene citrate; partial mechanical infertility; unexplained infertility; and male factor infertility.

The same COH and IUI procedure was used in all cases, as previously described [18]. Briefly, the first treatment cycle consisted of an initial dose of 112.5 IU of either recombinant FSH or urinary gonadotropins, starting on day 5 of the menstrual cycle. The daily dose of gonadotropin was adjusted according to follicular growth and serum E2 levels. Human chorionic gonadotropin (hCG) was administered when the leading follicle reached a diameter of >17 mm, and was followed by two intrauterine inseminations 24 h and 48 h later.

Data on patient age, smoking habits, and variable related to infertility-treatment were collected from the files. Ovarian stimulation characteristics, including the duration of stimulation, the total dose of gonadotropin administered, serum E2 levels, and vaginal ultrasound measurements of follicular diameter and endometrial thickness on the day of hCG administration were recorded. Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound.

The results are presented as means ± standard deviations. Differences in mean values between the groups were statistically analysed with the nonparametric Wilcoxon signed rank test, Student's t-test, and chi-square test, as appropriate. A p value of less than 0.05 was considered significant.

Results

A total of 2,318 cases were evaluated: 1,803 in nonsmoking patients (n=679) and 515 in smokers (n=206). Mean patient age during the study period was 27.1±3.6 years. Causes of infertility in the smoker and non-smoker groups, respectively, were as follows: unexplained −30.6% and 23.8%; oligo-anovulatory −18.4% and 21.4%; male factor −24.8% and 26.4%; mechanical −4.8% and 3.8%; none of these differences reached statistical significance.

While assessing the smoking status of the male partners in the two study groups, the prevalence of smokers among the male partners in the smoking group was significantly higher as compared to the non-smoking group (62.6% vs 26.8, respectively; p<0.000).

Pregnancy was achieved in 286 nonsmokers (pregnancy rate, 15.8% per cycle) and 84 smokers (pregnancy rate, 16.3% per cycle); the difference between the groups was not statistically significant. Moreover, no significant differences were observed between the two groups in abortion rate or in the prevalence of ectopic pregnancy.

The clinical characteristics of the COH cycles by smoking status are shown in Table 1.The smokers used significantly more gonadotropin ampoules and gained a thinner endometrium on the day of hCG administration than the nonsmokers (p<0.016 for both). There were no between-groups differences in patient age, duration of gonadotropin stimulation, number of follicle >14 mm in diameter, or E2 levels on the day of hCG administration.

Table 1 Infertility treatment variables and patients characteristics of smokers and non-smokers undergoing COH and IUI for infertility treatment

	Nonsmoking	Smoking	P
No. patients	679	206	
No. cycles	1803	515	
Age (years)	27.1±3.6	27.6±3.7	ns
Smoking/day(Packs)	0	0.8±0.3	
Primary infertility (%)	448 (66%)	125 (61%)	ns
Number of male partner smokers	182 (26.8%)	129 (62.6%)	0.000
Duration of infertility (yrs)	1.4±1.0	1.5±1.1	ns
Day 3 FSH (IU/L)	6.3±3.4	6.6±2.7	ns
Mean no. cycles/patient	2.2±1.4	2.1±1.3	0.08
Duration of Gn stimulation	8.5±3.2	8.5±3.4	ns
Mean Gn per cycle (IU)	949±526	1016±556	0.016
No. of follicles ≥14 mm on hCG day	2.4±1.9	2.5±1.8	ns
E2 level on hCG day (pmol/L)	2379±1867	2347±1970	ns
Endometrial thickness on hCG day (mm)	9.3±2.0	8.9±2.1	0.016
Clinical pregnancies (n)	286	84	
Pregnancy rate/cycle	15.8%	16.3%	ns
Early abortions (<12wk) (% of clinical pregnancies)	39 (13.6%)	10 (11.9%)	ns
EUP (% of clinical pregnancies)	5(1.7%)	1 (1.2%)	ns

Gn-gonadotropin

EUP-extra uterine pregnancy

Discussion

The present study of subfertile patients with a favorable prognosis—a priori—for ART, clearly showed that smokers undergoing COH with IUI required significantly more gonadotropin ampoules than nonsmokers in order to achieve a comparable pregnancy rate. There were no significant differences in the other COH treatment variables.

This observation is in accordance with other studies showing an association between smoking and an increased gonadotropin requirement during COH for IVF [15, 19, 20]. However, the lower peak E2 levels [21, 22] and recruitment of fewer follicles and oocytes [7, 13, 15, 21, 23, 24] in smokers that were reported in earlier studies were not observed in our population, in which milder and less vigorous stimulation was required.

The lack of a difference in clinical pregnancy rate between smokers and nonsmokers in the present study contradicts most earlier studies of the effect of smoking on IVF outcome, which demonstrated lower implantation and pregnancy rates in smokers [cited in a recent meta-analysis by Waylen [5]. Nevertheless, a recently published meta-analysis failed to note any difference in live birth rate between smokers and nonsmokers. It may therefore be speculated that while the effect of smoking on treatment outcome is more profound during IVF, which requires a more vigorous stimulation is required, it can be overcome during COH and IUI, in which milder stimulation is needed.

The comparable abortion rate between smokers and non-smokers in our study is in agreement with a recently published meta-analysis [5]. Although we did not observe any difference in the prevalence of ectopic pregnancy, it should be noted that the higher prevalence of ectopic pregnancy among smokers, reported by Waylen [5] was based on the analysis of two small studies of only 28 pregnancies, 6 in smokers and 22 in nonsmokers.

In the present study, smokers gained a thinner endometrium on the day of hCG administration than nonsmokers. Our findings disagree with the report of Hughes et al [20] who noted a similar endometrial thickness and morphology in smokers and nonsmokers undergoing IVF. At the same time, it is in accordance with the observed detrimental effect of smoking on endometrial receptivity [6, 25]. It is noteworthy that in both our groups, endometrial thickness was above the suggested lower limit, which may explain this negative effect [26].

While sperm concentrations, motility, morphology and sperm function were all shown to be detrimentally affected by smoking, the effect of smoking on male fertility remains inconclusive [2]. In the present study, the prevalence of male partner smokers in the smoking group was found to be higher than in the non-smoking group, however, no in-between groups differences were observed in pregnancy or abortion rates. These observations may be explained by the exclusion of couples with severe male factor infertility, i.e. male partners with less than 5 million total motile sperms after sperm washing or swim-up. Moreover, the male smoking status is not expected to affect the increased in

female gonadotropin requirement during COH, as observed in the present study.

In the present study of patients undergoing COH with IUI for the treatment of subfertility, the detrimental effect of smoking on treatment outcome could be overcome by increasing the dose of gonadotropin. We therefore suggest, that when individualizing the initial daily dose of gonadotropin in patients undergoing COH, as recently published in the CONSORT study [27], the clinician should direct attention to the patient's smoking habit, which may necessitate an increase in the daily dose of gonadotropin.

Further large studies are required to assess the effect of smoking on COH variables and treatment outcome. These studies may help fertility specialists to individualize and carefully tailor COH protocols, to optimize success in smoking patients.

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