

Recent cigarette smoking and assisted reproductive technologies outcome

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Objective: To assess the association between recent cigarette smoking (CS) in female and male partners and assisted reproduction technology (ART) outcomes.

Design: Cohort prospective study.

Setting: University ART program in Chile.

Patient(s): One hundred sixty-six couples seeking pregnancy through ART.

Intervention(s): Follicular fluid (FF) and serum cotinine concentrations were measured in female partners. Self-reported CS data were collected through personal interviews.

Main Outcome Measure(s): The association between female recent smoking, assessed by FF and serum cotinine concentrations, and ART outcomes, such as number of ova retrieved and implantation rates, and the association between self-reported male recent smoking and live birth rates.

Result(s): A significant age-adjusted association between increased FF cotinine level and decreased number of ova retrieved was found. The male partner's smoking habit significantly decreased the live birth rate from 21.1% to 7.8%. Serum cotinine concentrations paralleled those of FF.

Conclusion(s): The hypothesis of a detrimental effect of recent female smoking over implantation rates is rejected. However, recent male smoking is associated with significantly decreased live birth rates even after adjusting for confounders. Female recent smoking was significantly associated with decreased number of retrieved ova. (Fertil Steril® 2010;93:89–95. ©2010 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, cigarette smoking, number of retrieved ova, male recent smoking

Cigarette smoking (CS) is widely recognized as hazardous to health and is a major cause of preventable mortality. Many epidemiologic studies show that smoking in women of reproductive age present with increased time to conception and decreased fecundity. There is a strong association between CS and both reduced fertility and earlier mean age of menopause. Overall, the literature supports a small but significant negative impact of female CS on time to conception in spontaneous menstrual cycles. This is especially true among heavy smokers, although the subject remains controversial; several authors who postulate that CS has no effect on spontaneous fertility (1–4).

Despite being different from natural conception, in vitro fertilization (IVF) represents an interesting model in which

to evaluate the precise effect of CS on fertility. Female CS has been associated with lower fertilization rates (5, 6), decreased numbers of ova retrieved (7), lower clinical and term pregnancy rates (8–11), and increased rates of spontaneous abortion. It has been suggested that the negative effect of CS on IVF outcomes is mediated by a decrease in oocyte number and quality, possibly resulting in a high frequency of spontaneous abortion (12, 13).

Conflicting results have been reported in studies that have evaluated the effect of female CS on couples undergoing ART. A recent study demonstrated no measurable effect of past female CS on ART outcome (14). On the other hand, most of the studies are based on self-reported smoking status with almost no research accounting for cigarette exposure during the cycle days of the ART procedure. Keeping this in mind, we performed a prospective cohort study to evaluate the effect of recent cigarette exposure (active or passive), as established by cotinine levels in the follicular fluid, on ART outcome measures. Our hypothesis was that female recent smoking would be associated with a decreased number of ova available for fertilization and a poor implantation rate.

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METHODS

Patients

A cohort of 166 patients undergoing a first cycle of IVF or intracytoplasmic sperm injection (ICSI) treatment were selected at our center between July 2004 and April 2005. Patients undergoing their first attempt at ART were defined to be in the first cycle. The criteria of selection included only those women who had reached the follicular aspiration step. Owing to the experimental question, treatment cycles involving ovarian hyperstimulation syndrome and oocyte donation were excluded from analysis. Follicular fluid and serum were collected on the same day as follicular aspiration and then frozen until cotinine concentrations were determined for each female patient. The study was previously approved by the Ethics Board of the San Borja-Arriarán Hospital in Santiago.

The CS data were collected by conducting personal interviews on the day of hospitalization for oocyte retrieval. The questionnaire given by a midwife also included information about the quantity of alcohol and caffeine imbibed. The serum cotinine concentrations were not determined in male partners.

CS Status

There were two groups formed according to the concentrations of cotinine measured in the follicular fluid: 1) recent smoker women (RSW), who had cotinine concentrations >10 ng/mL in the follicular fluid; and 2) nonsmoking women (NSW) who denied smoking during the ART cycle and showed undetectable levels of cotinine in their follicular fluid. The CS status of male participants was determined only through their questionnaire answers.

Ovarian Stimulation

Every woman participating in this study underwent gonadotropin suppression with the GnRH agonist leuprolide at a dose of 1 mg/day SC starting during the luteal phase of the last menstrual cycle before ART. On day 3 of the subsequent cycle, ovulation induction was accomplished using a daily administration of 150–300 IU recombinant FSH. Human menopausal gonadotropin (hMG) dose (150–225 IU) was adjusted according to the E_2 production and follicular development. The final stage of follicular maturation was initiated by injection of 10,000 IU of hCG when at least three follicles reached a diameter of 18 mm on ultrasound examination.

Follicular Aspiration

Follicles were monitored by transvaginal ultrasound. All follicles were aspirated 36 h after hCG administration using transvaginal ultrasound guidance and regional anesthesia. All follicular fluid samples used for the cotinine assay were the first aspirate and were collected in sterile centrifuge tubes to avoid contamination by medium and blood. Follicular fluid samples were centrifuged at 400g for 10 min. The supernatants were collected in 1-mL polystyrene cryovials and frozen at -20°C .

Percentage of High-Quality Embryos

Embryo quality was assessed on the same day as embryo transfer (3 days after follicular aspiration). The percentage of high-quality embryos was calculated for RSW and NSW by dividing the number of embryos of optimum quality by the total number of embryos in each group. The characteristics of a top-quality embryo were the absence of multinucleated blastomeres, a count of six to eight blastomeres, and a level of fragmentation $<14\%$ (of the embryo volume), thereby allowing an adequate spatial relationship between the blastomeres within an embryo.

Cotinine Assay

The cotinine concentrations were established by a competitive chemiluminescent immunoassay in a solid phase (Immulite LKNM1; DPC, Los Angeles, CA). Concentrations of cotinine were expressed as ng/mL. The sensitivity of the assay (lowest detectable value) was 0.25 ng/mL. Readings less than this were arbitrarily assigned the value of 0.10, following Zenzes et al. (15).

Statistical Analyses

Based on an implantation rate of 15% in our IVF program, the total sample size necessary to detect a 40% effect of smoking on implantation rates was 160 subjects, assuming $\alpha = .05$ and $(1 - \beta) = 80\%$.

The normal distribution of continuous variables was established through the Kolmogorov-Smirnov test. Relative risk and 95% confidence interval (CI) and t test were used where appropriate. Multiple regression analysis was used to test the relationship between cotinine concentrations in follicular fluid and the number of retrieved oocytes, age, body mass index (BMI), and coffee and alcohol consumption. Logistic regression was used to compare rates adjusting for confounders.

Fertilization rate was calculated as the number of ova fertilized divided by the number of ova inseminated. A positive pregnancy test was established with an elevated β -hCG 14 days after transfer and then was confirmed if this value was twofold higher 3 days later. Clinical pregnancy was confirmed with a positive fetal heartbeat by ultrasound 6.5 weeks after a positive pregnancy test (β -hCG). The number of fetal sacs with a positive heartbeat divided by the total number of embryos transferred was used to calculate implantation rate.

RESULTS

Population

The overall prevalence of history of CS (ever having smoked) among the 166 couples was close to 58% in male partners and 56% in female partners. According to cotinine levels in the follicular fluid samples, there were 33 (19%) RSW and 133 (80.1%) NSW. The age of RSW was significantly higher than that of NSW (35.12 ± 0.66 years vs. 33.17 ± 0.30 years, respectively, $P < .05$; Table 1). There were no differences in BMI and alcohol and coffee consumption between the two

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