American Journal of Obstetrics and Gynecology (2006) **194**, 369–76

ELSEVIER

American Journal of Obstetrics & Gynecology

www.ajog.org

A prospective study of the effects of female and male marijuana use on in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) outcomes

Hillary S. Klonoff-Cohen, PhD,[a] Loki Natarajan, PhD,[a] Rosa Victoria Chen, MD[b]

Department of Family and Preventive Medicine, University of California, San Diego,[a] La Jolla, CA; New York and Presbyterian Hospital,[b] New York, NY

Received for publication March 30, 2005; revised August 8, 2005; accepted August 8, 2005

KEY WORDS
Gamete intrafallopian transfer
In vitro fertilization
Live birth delivery
Marijuana
Pregnancy

Objective: This study was undertaken to examine whether marijuana use affects in vitro fertilization and gamete intrafallopian transfer (IVF/GIFT).
Study design: Prospective study of 221 IVF/GIFT couples.
Results: Amount of lifetime heavy marijuana use adversely affected IVF/GIFT. Women smoking more than 90 times in their lifetime had 27% fewer oocytes retrieved ($P = .03$) and 1 fewer embryo transferred ($P < .05$). Women smoking marijuana more than 10 times in their lifetime had infants 17% ($P = .01$) smaller at birth. If men smoked marijuana 11 to 90 times in their lifetime, there was a 15% decrease in infant birth weight ($P = .03$); if this increased to more than 90 times, there was a 23% decrease ($P = .01$). Timing also played a role. Women smoking marijuana 1 year before IVF/GIFT had 25% fewer oocytes retrieved ($P = .03$), whereas couples had 28% ($P = .04$) fewer oocytes fertilized. Women and men who smoked in the past 15 years, had 12%($P = .04$) and 16% ($P = .03$) smaller infants, respectively.
Conclusion: Both timing and amount of marijuana use negatively affected IVF/GIFT.
© 2006 Mosby, Inc. All rights reserved.

Marijuana is the most widely used illegal drug among women and men of reproductive age.[1,2] According to the Substance Abuse and Mental Health Services Administration's 2003 National Survey on Drug Use and Health, there are 3.1 million persons 12 years or older who used marijuana daily.[3]

The advent of human assisted reproductive technology (ART) has engendered much legal and ethical debate.[4] The "sine qua non" for patients and clinicians is to determine what factors negatively and/or positively affects success rates of ART. To date, there are no published studies regarding the effect of marijuana on in vitro fertilization and gamete intrafallopian transfer (IVF/GIFT) outcomes.

Hypothesis

Maternal and paternal marijuana use (ie, classified as lifetime, 1 year before the IVF/GIFT attempt, at the period of conception, throughout the pregnancy by trimesters) will have an adverse effect on live birth

Supported by grant number 4RT0032 from the University of California, Office of the President, Tobacco-Related Disease Research Program, Oakland, CA.
Reprints not available from the author.

0002-9378/$ - see front matter © 2006 Mosby, Inc. All rights reserved.
doi:10.1016/j.ajog.2005.08.020

delivery (primary outcome), as well as on secondary outcome measures, including oocyte retrieval, fertilization, embryo transfer, pregnancy, and neonatal characteristics. This is a secondary analysis; the primary hypothesis investigated the effects of passive tobacco smoke on IVF/GIFT.

Material and methods

Study design

This prospective study consisted of 221 couples undergoing IVF or GIFT at 7 fertility centers located in San Diego, Orange, and Los Angeles counties in California, who were recruited between 1993 and 1997. These centers were chosen because of the physicians' expertise and uniformly high success rates with ART as reported by SART.[5]

Subject recruitment

The inclusion criteria were as follows: age 20 years or older; all races; diagnosed with primary or secondary female infertility caused by tubal disease, endometriosis, immunologic causes, or unexplained infertility; undergoing only 1 treatment cycle; and in a marital or cohabitating relationship.[6] Couples were required to have undergone all forms of conventional therapy. Each patient evaluation consisted of a minimum of laparoscopy, hysteroscopy, and hysterosalpingography for the women, and a semen analysis and sperm penetration assays for the men.

Only 1 attempt or cycle was included during the study period; hence, no subsequent cycles were included in the analysis. Women were excluded if they had preexisting illnesses requiring medical management during pregnancy (ie, high blood pressure, heart disease, diabetes, thyroid, or renal disease), or used donor spermatozoa, oocytes, and surrogate uteri, because the personal lifestyle habits and reproductive/medical history was unknown. Patients undergoing frozen embryo transfers were also excluded from the study.

The study sample was representative of the age, race, and education level of couples enrolling in IVF/GIFT programs in the United States.[7]

Data collection

All couples consented in English or Spanish for participation in the study. The women received 3 questionnaires: during the first clinic visit, during the procedure, and at the pregnancy outcome. The men received a baseline questionnaire during the first clinic visit and a final one during sperm collection. All questionnaires were pilot tested, and medical records were used to validate self-reported reproductive and medical histories (agreement rate $>90\%$), as well as sperm number, motility, and morphology.

The Institutional Review Board for the University of California, San Diego, as well as for the other participating infertility sites approved this study.

Definition of marijuana use

Participants provided detailed information about the type, timing, and amount of marijuana used during the various periods. For both men and women, the first questionnaire assessed lifetime marijuana use, whereas the second questionnaire addressed marijuana use at the time of the procedure for women, and during the time of sperm collection for men. The third questionnaire elicited information on pregnancy and pregnancy outcomes.

Statistical analysis

Descriptive characteristics of the men and women undergoing IVF were calculated. Exploratory tools, including box plots and scatter plots, guided the choice of appropriate statistical models.

Lifetime marijuana use was first characterized as a binary variable (eg, ever vs never). In addition, the amount of marijuana use was also estimated as follows. Subjects reported lifetime frequency of marijuana use by checking 1 of the following categories in the questionnaire: never, 1 to 2 times total in lifetime, up to 10 times in lifetime, every 3 months, every 6 months, monthly, weekly, or daily.

The frequency of marijuana use and the number of years of exposure were combined to yield a single variable estimating the "amount" of lifetime exposure. For example, a subject who reported smoking marijuana every 3 months for 6 years was estimated to have 24 (6×4) times of marijuana exposure.

To account for the possibility that timing of marijuana use might impact success of the procedure, the association between the age at which a woman stopped smoking marijuana and the reproductive outcomes was also assessed.

Finally, a composite variable combining both amount and timing as a combined score was derived as follows: a woman's amount category assignment (0, 1, 2, or 3) was appropriately weighted to reflect the time interval since she last smoked marijuana. This weight was defined as w = age at which marijuana use was terminated/current age. Thus, a subject who never smoked marijuana would receive a weight of 0, whereas one who was currently smoking marijuana would receive a weight of 1. If a 40-year-old person quit when she/he was 20 years, she/he would receive a weight of 0.50; if she/he quit at 30 years, the weight assigned would be 0.75 (Tables I and II). Each of the variables described previously was also derived for male partners.

Table I Association between marijuana use and outcomes of IVF/GIFT*

Measure of drug use	Female reproductive outcome	Male reproductive outcome	Couple reproductive outcome
LIFETIME MARIJUANA USE YES/NO			**Number of oocytes retrieved** (both partners) (19% less oocytes retrieved) Reg coeff = −0.21, 95% CI [−0.40 to −0,01], P = .04
LIFETIME AMOUNT CATEGORIZED	**Number of oocytes retrieved** Nonusers: Reference group Mild use (1-10 times): Not significant Moderate use (11-90 times): Not significant Heavy use (>90 times): 27% fewer oocytes retrieved Reg coeff = −0.31, 95% CI [−0.58 to −0.03], P = .03 **Number of embryos transferred** Nonusers: Reference group Mild use (1-10 times): 1 less embryo transferred Reg coeff = −0.55, 95% CI [−1.05 to −0.05], P = .03 Moderate use (11-90 times): Not significant Heavy use (>90 times): 1 less embryo transferred Reg coeff = −0.67, 95% CI [−1.33 to −0.01], P < .05		
TIMING			
1 Y BEFORE THE PROCEDURE (YES/NO)	**Number of oocytes retrieved** (25% fewer oocytes retrieved) Reg coeff = −0.29, 95% CI [−0.57 to −0.02], P = .03 **Number of embryos transferred** (1 less embryos transferred) Reg coeff = −0.85, 95% CI [−1.51 to −0.20], P = .01	**Number of embryos transferred**† (1 less embryos transferred) Reg coeff = −0.63, 95% CI [−1.25 to −0.02], P = .04	**Number of oocytes fertilized** (either)‡§ (28% fewer oocytes fertilized) Reg coeff = −0.33, 95% CI [−0.64 to −0.03], P = .04 **Number of embryos transferred** (either)§ (1 less embryo transferred) Reg coeff = 0.67, 95% CI [−1.19 to −0.15], P = .01
EACH YEAR TOWARD TIME OF PROCEDURE	**Number of oocytes retrieved** (1 % decrease) Reg coeff = −0.009, 95% CI [−0.017 to −0,001], P = .02		
PAST 15 Y (COMPARED WITH NONMARIJUANA SMOKERS)	**Number of oocytes retrieved** (23% fewer oocytes) Reg coeff = −0.27, 95% CI [−0.48 to −0.06], P = .01		
COMPOSITE			
EACH UNIT INCREASE IN SCORE	**Number of oocytes retrieved** (12% fewer oocytes) Reg coeff = −0.13, 95% CI [−0.24 to −0.01], P = .04		

* All the analyses were adjusted for female age, female education, female race, parity, attempt number, type of procedure, type of infertility, and female alcohol use.

† All the analyses were adjusted for the above-mentioned list of confounders, except male cigarette smoking was used rather than female smoking.

‡ No associations were found between marijuana use and pregnancy or live birth delivery. Only IVF included, n = 139 couples (GIFT/ZIFT excluded).

§ All the analyses were adjusted for the above-mentioned list of confounders except that couples' cigarette smoking was used rather than female cigarette smoking.

The relationship between marijuana use by women, men, and couples on each biologic endpoint was assessed in independent multivariate regression models. Logistic regression was used for each dichotomous variable (pregnancy, successful live-birth delivery) and linear regression was used for each continuous variable (number of oocytes retrieved, oocytes fertilized, and embryos transferred).

Table II Association between birth weight (log) and marijuana use*

Measure of drug use	Women	Men	Couple
LIFETIME MARIJUANA USE YES/NO	**13% decrease in infant birth weight** Reg coeff = −0.14, 95% CI [−0.25 to −0.04], *P* = .01		**16% decrease in infant birth weight** Reg coeff = −0.17, 95% CI [−0.26 to −0.07], *P* = .001
LIFETIME AMOUNT			
CATEGORIZED	Nonusers: Reference Group Mild use (1-10 times): Not significant Moderate use (>10 times): **17% decrease in infant birth weight** reg. coeff. = −0.18, 95% CI: [−0.32,−0.04], p = 0.01	Non Users: Reference Group Mild Use (1-10 times): Not significant Moderate Use (11-90 times): **15% decrease in infant birth weight** reg. coeff. = −0.16, 95% CI: [−0.31,−0.01], p = 0.03 Heavy Use (>90 times): **23 % decrease in infant birth weight** reg. coeff. = −0.27, 95% CI: [−0.46, −0.07], p = 0.01	
TIMING			
AGE STOPPED SMOKING	**1% decrease in infant birth weight** reg. coeff. = −0.006, 95% CI: [−0.01, −0.0004], p = 0.03	**1% decrease in infant birth weight** reg. coeff. = −0.007, 95% CI: [−0.01, −0.0006], p = 0.03	
TOTAL YEARS OF USE		**1.5% decrease in infant birth weight for each year of additional use** reg. coeff. = −0.02, 95% CI: [−0.03, −0.006], p = 0.002	**3% decrease in infant birth weight for each year of additional use**† reg. coeff. = −0.03, 95% CI: [−0.05, −0.01], p = 0.003
PAST 15 YRS	**12% decrease in infant birth weight** reg. coeff. = −0.13, 95% CI: [−0.25, −0.01], p = 0.04	**16% decrease in infant birth weight** reg. coeff. = −0.17, 95% CI: [−0.33, −0.02], p = 0.03	
COMPOSITE SCORE			
EACH UNIT INCREASE	**13% decrease in infant birth weight**‡ reg. coeff. = −0.14, 95% CI: [−0.23, −0.04], p = 0.01	**11% decrease in infant birth weight**§ reg. coeff. = −0.11, 95% CI: [−0.18, −0.04], p = 0.002	

* The birth-weight analyses were adjusted for multiple births and cigarette smoking status. Age and socioeconomic status (number of years of schooling) did not change the adjusted OR.

† Adjusted for multiple births and couples cigarette smoking.

‡ Adjusted for multiple births and female cigarette smoking.

§ Adjusted for multiple births and male cigarette smoking.

The logarithmic transformation was applied to the 2 continuous outcome variables: (1) number of oocytes retrieved, and (2) number of oocytes fertilized, to satisfy the normality assumptions of least squares regression models. Odds ratios for logistic models and regression coefficients for linear models and their 95% CIs were estimated.

Furthermore, to investigate the possibility that the effects of marijuana use could be modified by a factor (eg, age, number of IVF attempts), interaction terms were included in the multivariate models and tested for significance.

For the subset of couples who achieved a successful live-birth delivery, the association between marijuana and/or recreational drug use and each of infant birth weight (continuous), and multiple births (dichotomous) was assessed.

All the analyses were adjusted for female age, education, ethnicity/race, number of IVF attempts, parity, type of procedure, type of infertility, cigarette smoking (eg, ever smoked cigarettes, years of cigarette smoking), and alcohol use.

Results

Demographic and reproductive characteristics

The demographic and reproductive characteristics of the couples undergoing IVF in our study were previously reported.[6] Women's ages ranged from 26 to 49 years (mean = 36.42, SD = 4.26) and men's ages from 22 to 55 years (mean = 38.37, SD = 5.68). The majority (approximately 75%) of the participants were white, with black subjects, Asians, and Hispanics accounting for the remaining 20%. Greater than 75% of the women and men were college educated and employed.

The mean number of years of infertility among women was 4.18 years (SD = 3.05). Forty-nine percent of couples underwent IVF, 31% used GIFT, 17% used IVF/GIFT, and 3% used ZIFT. For 64% of the couples, this was their first IVF/GIFT attempt.

The mean number of embryos transferred per participant was 3.95 (median = 4). The overall pregnancy rate in the study was 32% (n = 71). There were 41 couples who had successful live births and of these 11 had multiple births. The average birth weight of the infants was 7.01 lbs (SD = 1.41 lbs). A total of 21 pregnant women had a spontaneous abortion.

Lifetime use of marijuana by men and women

Sixty-three percent of women, 59% of men, 44% of couples (in which both partners smoked), and 70% of couples (when either partner smoked) reported marijuana use in their lifetime (ie, continually since puberty). The duration of marijuana intake for women ranged from once to 25 years (mean years = 7.1, SD = 5.69), and for men from once to 27 years (mean years = 6.13, SD = 6.34).

Amount of marijuana use

The amount of marijuana ever smoked by female subjects ranged from 1 to 9125 times (median 8, mean 290). Because of the skewness apparent in the distribution, this variable was categorized into 4 classes, as never users (n = 76), occasional users (1-10 times, n = 70), moderate users (11-90 times, n = 31), and heavy users (>90 times, n = 29). These 4 categories were coded as 0, 1, 2, and 3. Among female marijuana smokers, the age at which marijuana use was discontinued ranged from 12 to 43 years (median 21 years, mean 22.16 years, SD = 5.92).

Among men, there were 56 never users, 64 who had used marijuana on 1 to 10 occasions, 25 on 11 to 90 occasions, and 40 who had smoked marijuana more than 90 times in their lifetime. The age at which men stopped using marijuana ranged from 8 to 45 years (mean = 23.85, SD = 7.02, median = 22).

Marijuana use around the time of the procedure

Among women, 10%, 5%, 3%, and 3%, reported smoking marijuana the year before, month before, week before, and day before the IVF procedure, respectively. For men, 10.5%, 4%, 3% and 0.5%, smoked marijuana the year before, month before, week before, and day before the IVF procedure, respectively. For all other periods (ie, month, week, and day before the attempt), the frequency of routine use for men and women was 2% or less.

The effect of female marijuana use on IVF/GIFT outcomes

Lifetime amount of marijuana use on IVF/GIFT

The amount of marijuana smoked in a woman's lifetime had negative effects on the number of oocytes retrieved and number of embryos transferred. Women who smoked from 1 to 10 times in their lifetime (mild use) had approximately 1 less embryo transferred (regression coefficient from linear regression [reg coeff] = −0.55, 95% CI [−1.05 to −0.05], P = .03) (Table I). Women who smoked more than 90 times in their lifetime (heavy use) had 27% fewer oocytes retrieved (reg coeff = −0.31, 95% CI [−0.58 to −0.03], P = .03) and 1 less embryo transferred (reg coeff = −0.67, 95% CI [−1.33 to −0.01], P < .05) (Table I).

Timing of marijuana use on IVF/GIFT

Women who reported smoking marijuana 1 year before the procedure had 25% fewer oocytes retrieved (reg coeff = −0.29, 95% CI [−0.57 to −0.02], P = .03), and approximately 1 fewer embryo transferred (reg coeff = −0.85, 95% CI [−1.51 to −0.20], P = .01) (Table I).

When the age that the women stopped smoking marijuana was subtracted from the age at the time of the IVF/GIFT procedure, for each year that the woman smoked closer to the time of the procedure, there was a 1% decrease in the number of oocytes retrieved (reg coeff = −0.009, 95% CI [−0.017 to −0.001], P = .02) (Table I). Women who smoked marijuana during the past 15 years had 23% fewer oocytes retrieved (reg coeff = −0.27, 95% CI [−0.48 to −0.06], P = .01) compared with nonsmokers (Table I).

Composite score of marijuana use on IVF/GIFT

Finally, a composite score was calculated that considered the amount and timing of marijuana use (amount × timing) together as a combined score. For each 1 point increase in this composite score, there was a 12% decrease (reg coeff = −0.13, 95% CI [−0.24 to −0.01], P = .04) in the number of oocytes retrieved (Table I).

The effect of male marijuana use on IVF/GIFT outcomes

Timing of marijuana on IVF/GIFT

Male marijuana smoking 1 year before the procedure was associated with approximately 1 fewer embryo transferred (reg coeff = −0.63, 95% CI [−1.25 to −0.02], P = .04), suggesting that passive smoking could have a deleterious effect on pregnancy (Table I).

The effect of couples' marijuana use on IVF/GIFT outcomes

Lifetime amount of marijuana use on IVF/GIFT

The initial findings confirmed that if both partners ever smoked marijuana in their lifetime, there was a 19% decrease in oocytes retrieved compared with those couples who never smoked marijuana (reg coeff = −0.21, 95% CI [−0.40 to −0.01], P = .04) (Table I).

Timing of marijuana use on IVF/GIFT

Among couples in which either partner smoked marijuana the year before the procedure, there were 28% fewer oocytes fertilized (reg coeff = −0.03, 95% CI [−0.64 to −0.03], P = .04), and approximately 1 fewer embryo transferred (reg coeff = −0.67, 95% CI [−1.19 to −0.15], P = .01) compared with couples who never smoked the year before (Table I).

There were no statistically significant associations between marijuana use by men, women, or both partners, and 3 pregnancy outcomes, "achieving a pregnancy," "having a spontaneous abortion," and "attaining a live-birth delivery."

No significant interactions were found between any of the marijuana measures and (1) female age (≤35 vs >35 years), (2) attempt number (1 vs >1), and (3) cigarette smoking.

The effect of female marijuana use on infant birth weight

Lifetime amount of marijuana use on infant birth weight

There were striking effects of marijuana use on infant birth weight, among women who used IVF/GIFT. In the subsample (n = 41) of couples who delivered an infant, women who ever smoked marijuana in their lifetime compared with women who never smoked marijuana delivered infants with a 13% lower birth weight (reg coeff = −0.14, 95% CI [−0.25 to −0.04], P = .01) (Table II), adjusted for multiple births and cigarette smoking.

The amount of lifetime marijuana use revealed that women who smoked marijuana for 1 to 10 times in their lifetime had no effect on birth weight (P = .08), whereas women who smoked for more than 10 days in their lifetime had infants who were 17% smaller in birth weight (reg coeff = −0.18, 95% CI [−0.32 to −0.04], P = .01) (Table II).

Timing of marijuana use on infant birth weight

Timing of female marijuana use was also associated with infant birth weight. When the age that women stopped using marijuana was subtracted from the age at the time of the ART procedure, for each additional year that the woman smoked nearer to the procedure, there was a 1% drop in infant birth weight (reg coeff = −0.006, 95% CI [−0.01 to −0.0004], P = .03) (Table II). Women who smoked in the past 15 years had 12% smaller infants (reg coeff = −0.13, 95% CI [−0.25 to −0.01], P = .04) compared with those who were nonsmokers (Table II).

Composite score of marijuana on infant birth weight

Finally, when the amount and timing of marijuana use were incorporated into a composite score, for each unit increase in the marijuana composite score, there was a 13% decrease in infant birth weight (reg coeff = −0.14, 95% CI [−0.23 to −0.04], P = .01) (Table II).

All birth weight analyses were adjusted for multiple births and female cigarette smoking. In addition, when maternal age and socioeconomic status (ie, number of years of schooling, mean = 16.81 years) were added to the above models, the adjusted odds ratios remained unchanged. There was no information available on parent body weight or previous infant's birth weight.

The effect of male marijuana use on infant birth weight

Lifetime amount of marijuana use on infant birth weight

The amount of lifetime marijuana use revealed a dose-response effect, whereby the mild group was not

statistically significant; however, if men smoked marijuana 11 to 90 times, there was a 15% decrease in birth weight (reg coeff = −0.16, 95% CI [−0.31 to −0.01], P = .03), and if this increased to more than 90 times in their lifetime, there was a 23% decrease in infant birth weight (reg coeff = −0.27, 95% CI [−0.46 to −0.07], P = .01) (Table II).

Timing of marijuana use on infant birth weight

If the age that men stopped smoking marijuana was subtracted from the age at the time of the procedure, for each year that the man smoked marijuana nearer to the time of the procedure, there was a 1% decrease in infant birth weight (reg coeff = −0.007, 95% CI [−0.01 to −0.0006], P = .03) (Table II). Each additional year that a man smoked marijuana was associated with a 1.5% (reg coeff = −0.02, 95% CI [−0.03 to −0.006], P = .002) decrease in birth weight (Table II). Finally, men who smoked in the past 15 years had infants who were 16% less birth weight compared with nonsmokers (reg coeff = −0.17, 95% CI [−0.33 to −0.02], P = .03) (Table II).

Composite score of marijuana use on infant birth weight

Finally, when amount and timing of male marijuana use were incorporated into a composite score, the male marijuana users had infants who were 11% smaller (reg coeff = −0.11, 95% CI [−0.18 to −0.04], P = .002) in birth weight for each unit increase in the composite score (Table II). Hence, lifetime male marijuana use has a powerful effect on infant birth. All birth weight analyses were adjusted for multiple births and male cigarette smoking. Adjusting for age and socioeconomic status (ie, number of years of schooling) did not substantially change the adjusted odds ratios.

The effect of couples' marijuana use on infant birth weight

Lifetime amount of marijuana use on infant birth weight

Marijuana use by both partners was associated with a 16% decrease in birth weight (reg coeff = −0.17, 95% CI [−0.26 to −0.07], P = .001) (Table II).

Timing of marijuana use on infant birth weight

Each additional year of couples' smoking marijuana was associated with a 3% decrease in birth weight (reg coeff = −0.03, 95% CI [−0.05 to −0.01], P = .003) (Table II).

The birth weight analyses were adjusted for multiple births and couples' smoking status. Adjusting for age and socioeconomic status (ie, number of years of schooling) did not substantially affect the adjusted odds ratios.

Comment

For women, lifetime amount of marijuana (categorized), timing (ie, 1 year before, each year towards the time of the procedure, and past 15 years) and composite score (timing and amount) negatively affected the number of oocytes retrieved and the number of embryos transferred (Table II). For men, marijuana use 1 year before the IVF/GIFT procedure (timing) negatively impacted embryo transfer (Table II).

Marijuana was not associated with maintaining a pregnancy or having a successful live birth delivery. This could imply that the marijuana group had higher implantation rates compared with nonusers. A sensitivity analysis was conducted on implantation rates, and there was no difference between marijuana users and nonusers for both lifetime use (ever vs never, 11% vs 13%, P = .93) and use during the past year before the procedure (users vs nonusers, 10% vs 12%, P = .70).

Marijuana use has resulted in a decrease in sperm density and motility as well as an increase in the number of abnormal sperm.[8-10] In our study, there was no statistically significant association between sperm parameters and any IVF/GIFT outcome, possibly because of the small sample size (ie, information on sperm motility was available for only 91 men).

Sperm motility and morphology assessments are subjective by nature, have intertechnician and interlaboratory variability,[11-15] and are not fully standardized (despite the existence of the World Health Organization guidelines[16,17]), which may explain our negative findings for sperm parameters and marijuana.

Marijuana has been implicated with low birth weight, although the results are inconsistent.[18-23] Our findings are consistent with a growing body of evidence based on natural conceptions that suggest that infants of cannabis users, and particularly heavy or regular users, are more likely to be at an increased risk of reduced birth weight. In our study, the birth weight reduction in fathers of children who smoked marijuana was demonstrated in years of marijuana use, amount of lifetime use (with a dose-response effect), timing of marijuana use, and with the composite score. Our findings require replication in larger prospective studies.

It is possible that there was underreporting of true marijuana intake in our study sample. No women reported marijuana use during their pregnancy. It has been reported that pregnant women are more likely to underreport or provide dishonest answers about their use of marijuana,[24] thereby obscuring the real effects; however, in another study on pregnant women, only 5.72% tested positive among those reporting never using marijuana.[25] Two studies[26,27] made important contributions toward establishing the veracity of self-report as a method of data collection compared with radioimmunoassay of blood and urine specimens for cannabinoids,

reporting no positive tests among those denying marijuana use. Therefore, our results, in combination with blood and urine marijuana samples, would have provided stronger evidence of the negative effects of marijuana use on IVF endpoints.

Because of the relatively long recruitment period (5 years), stimulation protocols, and number of embryos transferred may have changed, which could have affected ART outcomes. In our study, the average number of embryos transferred was 3 to 4 (median = 4). The technical aspects of the procedure (ie, protocol, technique, culture media) were standardized across study centers; hence, these factors would not confound the relationship between marijuana and success rates.

In summary, this study determined that lifetime as well as marijuana use 1 year before the procedure by men and women played a vital role on the endpoints of IVF/GIFT.

Acknowledgment

We thank Dr Richard Marrs, Dr Bill Yee, and Dr Snunit Ben-Ozer, for their assistance with patient recruitment. In addition, we also thank Ms Tomomi Lager for her editorial expertise.

References

1. Greenfield SF, O'Leary G. Sex differences in marijuana use in the United States. Harv Rev Psychiatry 1999;6:297-303.
2. Fried PA, Smith AM. A literature review of the consequences of prenatal marihuana exposure: an emerging theme of a deficiency in aspects of executive function. Neurotoxicol Teratol 2001;23: 1-11.
3. Substance Abuse and Mental Health Services Administration. 2003 National Survey on Drug Use and Health, 2004. Available at http://oas.samhsa.gov/2k4/dailyMJ/dailyMJ.cfm. Accessed August 7, 2005.
4. Chang WY, DeCherney AH. History of regulation of assisted reproductive technology (ART) in the USA: a work in progress. Hum Fertil (Camb) 2003;6:64-70.
5. American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology Registry. Assisted reproductive technology in the United States: 1997 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 2000; 74:641-53.
6. Klonoff-Cohen H, Natarajan L, Marrs R, Yee B. Effects of female and male smoking on success rates of IVF and gamete intrafallopian transfer. Hum Reprod 2001;16:1382-90.
7. Stephen EH, Chandra A. Use of infertility services in the United States, 1995. Fam Plann Perspect 2000;32:132-7.
8. Huang HF, Nahas G, Hembree W. Morphological changes of spermatozoa during marijuana induced depression of human spermatogenesis. Federal Proceedings 1978;37:739.
9. Hembree W 3rd, Nahas G, Zeidenberg P, Huang H. Changes in human spermatozoa associated with high dose marijuana smoking. In: Nahas GG, Paton WDM, editors. Marijuana: biological effects. New York: Pergamon Press; 1979. p. 429-39.
10. Vescovi P, Pedrazzoni M, Michelini M, Maninetti L, Bernardeli F, Passeri M. Chronic effects of marijuana smoking on luteinizing hormone, follicle-stimulating hormone and prolactin levels in human males. Drug Alcohol Depend 1992;30:59-63.
11. Neuwinger J, Behre HM, Nieschlag E. External quality control in the andrology laboratory: an experimental multicenter trial. Fertil Stertil 1990;54:308-14.
12. Cooper TG, Neuwinger J, Bahrs S, Nieschlag E. Internal quality control of semen analysis. Fertil Steril 1992;58:172-8.
13. Matson PL. External quality assessment for semen analysis and sperm antibody detection: results of a pilot scheme. Hum Reprod 1995;10:620-5.
14. Ombelet W, Bosmans E, Janssen M, Cox A, Maes M, Punjabi U, et al. Multicenter study on reproducibility of sperm morphology assessments. Arch Androl 1998;41:103-14.
15. Auger J, Eustache F, Ducot B, Blandin T, Daudin M, Diaz I, et al. Intra- and inter-individual variability in human sperm concentration, motility and vitality assessment during a woodshop involving ten laboratories. Hum Reprod 2000;15:2360-8.
16. WHO. World Health Organization laboratory manual for the examination of human semen and sperm-cervical mucus interaction, 3rd ed. Cambridge: Cambridge University Press; 1992.
17. WHO. World Health Organization laboratory manual for the examination of human semen and sperm-cervical mucus interaction, 4th ed. Cambridge: Cambridge University Press; 1999.
18. Zuckerman B, Frank D, Hingson R. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989;320:762-8.
19. Fergusson DM, Horwood LJ, Northstone K, ALSPAC Study Team. Avon longitudinal study of pregnancy and childhood: maternal use of cannabis and pregnancy outcome. BJOG 2002;109: 21-7.
20. Linn S, Schoenbaum S, Monson R, Rosner R, Stubblefield P, Ryan K. The association of marijuana use with outcome of pregnancy. Am J Public Health 1983;73:1161-4.
21. Shiono PH, Klebanoff MA, Nugent RP, Cotch MF, Wilkins DG, Rollins DE, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. Am J Obstet Gynecol 1995;172:19-27.
22. English DR, Hulse GK, Milne E, Holman CD, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. Addiction 1997;92:1553-60.
23. Balle J, Olofsson MJ, Hilden J. Cannabis and pregnancy [in Danish] Ugeskr Laeger 1999;161:5024-8.
24. Hingson R, Zuckerman B, Amaro H. Maternal marijuana use and neonatal outcome: uncertainty posed by self-reports. Am J Public Health 1986;76:667-9.
25. Markovic N, Ness RB, Cefilli D, Grisso JA, Stahmer S, Shaw LM. Substance use measures among women in early pregnancy. Am J Obstet Gynecol 2000;183:627-32.
26. Greenland S, Staisch K, Brown N, Gross S. The effects of marijuana use during the pregnancy—I: a preminary epidemiologic study. Am J Obstet Gynecol 1982;143:408-13.
27. Fried P. Marijuana use by pregnant women: neurobehavioral effects in neonates. Drug Alcohol Depend 1980;6:415-24.