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Female and male lifestyle habits and IVF: what is known and unknown

H.Klonoff-Cohen

Department of Family and Preventive Medicine, University of California, San Diego, 9500 Gilman Drive, Dept. 0607, La Jolla, CA 92093–0607, USA

E-mail: hklonoffcohen@ucsd.edu

There is no greater tribute to the importance and efficacy of IVF than the fact that >1 × 10^6 babies have been born to infertile couples since its clinical introduction in 1978. Despite enormous advances regarding the technical aspects of the IVF procedure, the parents' contribution has virtually been ignored when considering aspects that influence success rates. This systematic review focuses on the effects of female and male lifestyle habits (specifically: smoking, alcohol and caffeine use, and psychological stress) on the reproductive endpoints of IVF (i.e. oocyte aspiration, fertilization, embryo transfer, achievement of a pregnancy, live birth delivery, and perinatal outcomes, e.g. low birthweight, multiple gestations). What is currently known in the field of lifestyle habits and IVF? There is compelling evidence that smoking has a negative influence on IVF outcomes, whereas for stress, the evidence is suggestive but insufficient due to the heterogeneity of studies. The evidence for the effects of alcohol and caffeine on IVF is inadequate, and therefore unknown, due to the scarcity of studies.

Key words: alcohol/caffeine/IVF/smoking/stress

Introduction

A woman is born with all the oocytes she will ever have, with estimates varying from 400 000 to 2 × 10^6 (Edwards and Brody, 1995). Of these, only ~400 will be subject to ovulation during an average female's reproductive life. Contrary to this, with 1% of the supply of sperm created within a man each day, the entire stock of some billions of sperm can be replaced in <4 months (Edwards and Brody, 1995). When conditions are optimal, the maximum chance of a clinically recognized pregnancy occurring in a menstrual cycle is 30–40% (Macklon *et al.*, 2002).

There are ~5.0 to 6.3 × 10^6 women in the USA who are infertile, and by 2025, this will increase to 5.4 to 7.76 × 10^6 (Grainger and Tjaden, 2000). Among these, there is a subgroup of infertile couples who have exhausted all forms of conventional therapy for infertility and require assisted reproductive techniques such as IVF. Assisted reproductive treatment has been life-transforming for couples with longstanding female factor or male factor infertility. As assisted reproduction's perceived safety and success rates grow, so does its demand (Schultz and Williams, 2002).

IVF is used in the treatment of various forms of infertility including endometriosis, ovulatory dysfunction, pelvic adhesions, cervical factor, tubal disease, luteal defects, immunological causes, male factor, and unexplained infertility. It involves the collection of ripe oocytes from the woman's body in order to achieve fertilization outside of the body, followed by transfer into the woman's womb. A couple's chance of success with IVF is linked to the IVF clinic, causes of infertility, and a woman's age.

The universal experience of IVF success rates indicates that the live birth delivery rate/retrieval in North America is ~30% (National Center, 2003). In the USA, assisted reproductive techniques accounted for ~1 out of every 150 children born in 1999 (National Center, 2001; Schultz and Williams, 2002) and since 1978, ~1 × 10^6 children have been born as a result of assisted reproductive treatment (Schultz and Williams, 2002).

Although major advances have occurred in the field of assisted reproductive techniques during the past 25 years, researchers and clinicians are still grappling to identify additional factors other than female age, number of embryos transferred, quality of sperm, and response to hormonal stimulation (Craft and Brinsden, 1989), which negatively and positively affect success rates of IVF/gamete intra-Fallopian transfer (GIFT) (particularly healthy live birth deliveries).

The American Society for Reproductive Medicine currently has guidelines to limit the number of embryos implanted. However, there are no recommendations from reproductive endocrinologists regarding the modification of lifestyle habits, which could possibly affect assisted reproductive treatment success rates.

This paper is a systematic review of the short- and long-term effects of male and female smoking, alcohol and caffeine use, and psychological stress on the endpoints of IVF [i.e. oocyte

aspiration, fertilization, embryo transfer, spontaneous abortion, achievement of a pregnancy, live birth delivery, and perinatal outcomes (e.g. decreased infant gestational age, low birthweight, increased multiple gestations)].

Materials and methods

An intensive computerized search of the published literature was conducted on a total of eight databases (inclusive dates), specifically, PubMED (MEDLINE) (1953 to October 2004), Biosis previews (1969 to October 2004), Web of Science (1975 to October 2004), PsycINFO (1840 to October 2004), LexisNexis Academic (1981 to October 2004), Expanded Academic ASAP (1980 to October 2004), Sociological abstracts (1963 to October 2004), and Ovid Medline (1966 to October 2004). Retrieved articles were reviewed for content and their references were used to identify other relevant articles.

All languages were reviewed in the abstracts for the following key words: smoking, stress, caffeine, alcohol, *in vitro* fertilization, IVF, assisted reproductive technologies, and ART. The endpoints consisted of oocyte aspiration, fertilization, embryo transfer, achievement of a pregnancy, live birth delivery, and perinatal outcomes (e.g. birthweight, gestational age, multiple gestations).

Criteria for inclusion consisted of human studies, retrospective and case–control studies, and prospective studies, with detailed methods and statistical analysis sections. General exclusion criteria consisted of case reports, meeting abstracts, expert opinions, newspaper articles, magazines, and comments, all of which had insufficient information or no details on the lifestyle habit and/or IVF endpoints, which prohibited careful estimation of the accuracy and reproducibility of the study. Articles written in German, Chinese and Czech were excluded.

Intervention studies were considered premature and beyond the scope of this review. The objective was to determine whether a lifestyle habit had an impact on the biological/reproductive endpoints of IVF (i.e. success rates), not to determine the effectiveness of counselling, social support groups or cognitive behaviour treatments on IVF.

Among the studies identified, those not involving IVF (e.g. general infertility, animal studies, GIFT, and ICSI) were discarded. Frozen embryos and oocyte donation studies were omitted because of the inability to determine the effect of lifestyle habits on IVF outcomes.

In order to generate the strategy for assessing manuscripts, a PubMed search was conducted on 'criteria for reviewing literature' and 'criteria for reviewing literature in reproductive medicine', as well as an examination of all 'review' papers from *Human Reproduction Update* dating from 2000 to October 2004. All of the studies evaluated and approved for this manuscript were based on specific criteria adapted from Sackett *et al.* (1991), Peipert and Bracken (1997), Pelinck *et al.* (2002) and Tarlatzis *et al.* (2003).

The criteria consisted of: (i) an appropriate study design, (ii) description of the selection and characteristics of subjects and comparison group with a sample size of >25, (iii) the existence of standardized IVF outcome measures, (iv) the use of standardized instruments and/or laboratory samples to verify lifestyle habits, and (v) the existence of multivariate analysis. For each lifestyle habit, all studies were compared and contrasted using these five criteria.

Two other independent reviewers selected and reviewed the publications to be included in accordance with the above-mentioned criteria. If there was discordance, a discussion resolved the issue, leading to a uniform decision.

It was speculated that differences in study results could arise from seven sources: different hypotheses, different types (and sources) of patients, different methods (e.g. study design, different rigor and sample size), different ways of verifying exposures (e.g. lifestyle histories), different reproductive outcomes, different statistical methods, and different conclusions (supported by the data).

The hypothesis, study sample, study design, characteristics of the lifestyle habit, measurement for each lifestyle (e.g. instrument, laboratory samples), IVF outcomes, results, and conclusions are presented in Tables I–IV. The final association between a lifestyle habit and IVF was based on the Institute of Medicine criteria (i.e. evidence sufficient, evidence suggestive but insufficient, evidence inadequate, and evidence suggestive of no association) (Field and Lohr, 1990).

Smoking and IVF

Female and male smoking and natural reproduction

Tobacco smoke contains several hundred substances including nicotine, carbon monoxide and mutagens (e.g. radioactive polonine, benzo[a]pyrene, naphthalene and methylnaphthalene) (Stillman *et al.*, 1986).

There is strong evidence that smoking negatively impacts virtually all facets of fertility (Bolumar *et al.*, 1996; Buck *et al.*, 1997; Feichtinger *et al.*, 1997; Augood *et al.*, 1998), including follicle development/ovulation, oocyte retrieval from the ovary and its transport down the Fallopian tubes, and fertilization and early embryo development. Studies have illustrated that when a pregnant woman smokes, the future fertility of the fetus (male or female) is also put in jeopardy (Sharpe and Franks, 2002).

There is also evidence that smoking induces DNA damage in sperm (Rubes *et al.*, 1998; Zenzes *et al.*, 1999). According to Sharpe and Franks (2002), 'men's smoking can be associated with minor reductions in sperm count/morphology, but this is inconsistent and not usually associated with altered fertility' (Hughes and Brennan, 1996; Vine, 1996), although effects have been reported with IVF outcome (Joesbury *et al.*, 1998). Currently, it is generally accepted that smoking cessation should be an integral part of infertility treatment (Sharpe and Franks, 2002).

Female and male smoking and IVF

A total of 82 abstracts were retrieved from the eight databases, and 59 abstracts were excluded based on eligibility criteria (e.g. meeting abstracts, comments, review articles, newspapers, magazines, animal studies, GIFT, ICSI, infertility, interovarian differences, hyperandrogenism, and delayed conception as endpoints, semen quality as an endpoint, did not address primary question). This resulted in 23 articles being reviewed, with a further one article being excluded because it was in German. A total of 22 articles were included for the final review.

Table I. Studies investigating smoking and IVF

Reference	Study sample (no., source of sample, type of infertility, age, race); laboratory sample	Study design and analysis	Objectives	Lifestyle habits[a]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Augood *et al.* (1998), UK	12 studies on smoking and infertility from MEDLINE (1966–1997) and EMBASE (1974–1997) No laboratory sample	Meta-analysis (univariate)	Determine whether there is an association between smoking and risk of infertility in women of reproductive age, and assess the size of this effect	Meta-analysis (d) Cigarette (e) Current, former and non-smokers (g) Female	(1) Fertilization (2) Pregnancies/-number of IVF cycles	None	Random effects (1) Subfertile women undergoing IVF had reduction in fecundity among women smokers (OR for infertility = 1.60 [95% CI = 1.34–1.91] in smokers vs non-smokers) (2) OR = 0.66 (95% CI = 0.49–0.88) for pregnancies/number of IVF cycles in smokers vs non-smokers	Results point toward a significant association between smoking and infertility, with a 60% increase in risk of infertility among cigarette smokers
Crha *et al.* (2001), Czech Republic	159 infertile patients from the Centre for Assisted Reproduction No difference in age, and profession, but lower education in smoking patients Urine cotinine	Cross-sectional (univariate)	Outcome of IVF in smoking and non-smoking women	(a) Questionnaire (d) Cigarette (g) Female	(1) Basal hormone before treatment (2) Ovarian stimulation (3) Number of oocytes (4) Fertilization (5) Pregnancy	None	(1) Lower number of oocytes aspirated (7.3 vs 10.9, NS) (2) Number of fertilized oocytes lower in smoking women (68 vs 47.82, $P < 0.01$) (3) Fewer embryos in smoking vs non-smoking women (3.3 vs 4.7, NS) (4) 35 women became pregnant (22%) of which 29% were non-smokers, 12.5% were occasional smokers, 0% were regular smokers (5) OR for pregnancy in non-smokers was 1.48 ($P < 0.05$), while the OR in smokers was 0.57 ($P < 0.05$)	There is a negative influence of smoking on IVF outcome
Elenbogen *et al.* (1991), Israel	41 women < 37 years old undergoing IVF treatment at Chaim Sheba Medical Centre Mechanical infertility (tubal); 20 smoking women and 21 non-smoking women No laboratory sample	Prospective (univariate)	Influence of cigarette smoking on IVF outcome	(a) Questionnaire (c) Administered on the day of hormonal stimulation (d) Cigarette (e) Samples were divided into non-smokers and smokers of > 15 cigarettes per day (g) Female	(1) Fertilization (2) Pregnancy (3) Live births (4) Estradiol follicular fluid levels	None	(1) Follicular phase was longer in smokers than non-smokers ($P < 0.05$) (2) Required more hMG ampoules (MGA) for stimulation in smokers ($P < 0.05$) (3) Follicular fluid levels of estradiol lower in smoking vs non-smoking women (657 ± 367 vs 1077 ± 786 mg/ml, $P < 0.01$) (4) Fertilization rates lower in smoking vs non-smoking women (40.9 vs 61.7, $P < 0.05$) (5) Four pregnancies in non-smoking women (6) One ectopic pregnancy in smoking woman	Cigarette smoking had detrimental effects on IVF outcome
El-Nemr *et al.* (1998), UK	173 women undergoing IVF at the Royal Hospitals Trust Fertility Centre (108 smokers, 65 non-smokers) No laboratory sample	Retrospective (univariate)	Effect of cigarette smoking on ovarian reserve	(a) Interview (b) Identified smokers or non-smokers (c) At the first IVF consultation (d) Cigarette (e) Number of cigarettes smoked daily (g) Female	(1) Ovarian simulation (2) Number of oocytes (3) Fertilization (4) Pregnancy (5) Serum basal FSH concentrations (6) LH concentrations	None	(1) Smokers had higher serum FSH and required higher dosage of gonadotrophins than non-smokers (48.1 ± 15.6 vs 38.9 ± 13.6; $P < 0.0001$) (2) Smokers had lower mean number of oocytes than non-smokers (6.2 ± 3.4 vs 11.1 ± 6.3; $P < 0.0001$) (3) Higher rate of abandoned cycles in smokers (13.9 vs 4.6%, not statistically significant) (4) Higher rate of total fertilization failure in smokers (18.5 vs 8.3%, NS)	Cigarette smoking in women significantly reduces ovarian reserve and leads to poor response to ovarian stimulation at an earlier age
Feichtinger *et al.* (1997), Austria	799 patients (607 non-smokers and 192 smokers) in seven publications from MEDLINE 1982–1996 No laboratory sample	Meta-analysis (univariate)	Determine the influence of the status of female smokers on the clinical pregnancy rate after the first attempt at IVF	(a) Excel-Smoker data bank (d) Cigarette (g) Female	Pregnancy	None	(1) Almost twice as many IVF cycles were needed for smokers as for non-smokers to become pregnant ($P < 0.05$) (2) The success quotient of the probability of IVF success for non-smokers versus smokers was 1.79 (95% CI = 1.24–2.59) (3) Higher pregnancy rates in non-smokers compared to smokers (21 vs 14%, $P < 0.01$)	There is a significant negative effect on the chances of success for smokers to become pregnant compared to non-smokers

Table I. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race); laboratory sample	Study design and analysis	Objectives	Lifestyle habits[a]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Harrison *et al.* (1990), Australia	650 patients (108 smokers) being treated for IVF or gamete intrafallopian transfer in hospital No laboratory sample	Prospective (univariate)	Explore the effects of smoking on the endpoints of IVF	(a) Questionnaire (c) Patient admission to hospital (d) Cigarette (f) Stable for at least one month preceding treatment and throughout ovulation induction (g) Female	(1) Oocyte retrieval (2) Ovulation (3) Fertilization (4) Implantation (5) Pregnancy (6) Miscarriage	None	(1) Smokers produced fewer oocytes than non-smokers (NS) (2) Smokers had a lower pregnancy rate and a higher miscarriage rate than non-smokers ($P < 0.05$)	Smoking has an effect on the endpoints of IVF, especially number of oocytes and miscarriage
Hughes *et al.* (1992), Canada	222 couples undergoing 297 cycles of IVF at Chedoke-McMaster Hospitals No laboratory sample	Prospective (univariate)	Evaluate the impact of cigarette smoking on IVF for males and females	(a) Questionnaire (d) Cigarette (e) Non-smokers and Smokers (1–14 cigarettes/day and ≥15 cigarettes/day) (g) Male and female independently	(1) Ovarian stimulation (2) Fertilization (3) Embryo transfer	None	(1) No difference in the response to ovarian stimulation (2) The fertilization rate was higher in heavy smokers than in non-smokers (79.3 vs 61.3%, $P = 0.007$) (3) In smokers of 1–14 cigarettes/day, the likelihood of transferring an embryo was 0.87 (95% CI = 0.56–1 (4) versus 0.52 (95% CI = 0.31–0.88) in smokers of ≥15 cigarettes/day	Female smoking has no influence on outcome of ovarian stimulation, fertilization, and the clinical outcome following embryo transfer
Hughes *et al.* (1994), Canada	462 couples undergoing IVF at Chedoke-McMaster Hospitals Serum cotinine	Prospective (multivariate)	Assess whether cigarette smoking in women or men affect the outcomes of IVF and determine what functional levels of smoking is 'active'	(a) Questionnaire (c) At the onset of consecutive treatment cycles and at the time of embryo transfer (d) Cigarette (g) Male and female independently	(1) Fertilization (2) Pregnancy (3) Spontaneous abortion	Number of cigarettes smoked, female age and estradiol production	(1) No difference in fertilization, pregnancy and abortion rates (2) Multivariate analyses showed negative correlation between female age ($P = 0.04$), but no such effect was seen with female or male smoking (3) Sperm concentration was significantly reduced in male smokers, although fertilization rate was unaffected (66 vs 62%, $P < 0.001$)	Neither female nor male smoking has a measurable deleterious effect on conception rate among couples undergoing IVF
Hughes and Brennan (1996), Canada	27 comparative studies (cohort or case–control) with clinical pregnancy or live birth reported among smokers and non-smokers No laboratory sample	Review (univariate)	Determine if smoking affects natural and assisted fecundity	Review article (b) Current smoker/ex smoker (d) Cigarette (e) Number of cigarettes smoked/day (g) Male and female independently	(1) Time to conceive (2) Conceptions per subject and per cycle (2) Spontaneous abortion	None	(1) All but one of 13 natural conception studies showed negative association between smoking and fecundity (OR for conception or live birth in smokers vs non-smokers = 0.33–1.0) (2) Conception common OR for seven IVF–GIFT studies = 0.57 (0.42–0.78) (3) Small increased risk of spontaneous abortion among smokers vs non-smokers in seven studies (OR = 0.83–1.8) (4) No significant findings for male sperm quality or fertility in 25 studies	Small detrimental effect of female smoking on time to conception and spontaneous abortion risk, but effect of male smoking on fecundity less significant
Joesbury *et al.* (1998), Australia	498 consecutive IVF treatment cycles from clinical outcome records and files of 385 couples at clinic. Mean age female smokers = 33.1 and mean age female non-smokers = 34.6. Mean age male smokers = 36.2 and mean age male non-smokers = 36.5 No laboratory sample	Retrospective cohort (multivariate)	Determine whether smoking will affect the collective quality of embryos selected for uterine transfer as well as the likelihood of achieving ongoing pregnancy at 12 weeks	(a) Medical records (c) At the first consultation (d) Cigarette (g) Male and female independently	(1) Pregnancy at 12 weeks (2) Modified cumulative embryo score (mCES) (3) Ovarian reserve size	mCES, female age, male age, IVF or ICSI, tubal infertility, estradiol levels on day of hCG, vascular grade of endometrium, endometrial thickness, and male and female smoking	Multiple linear regression and multiple logistic regression (1) Female smokers had better quality embryos ($P < 0.05$) (2) Male smokers had 2.4% decreases in likelihood of achieving 12 week pregnancy with every 1 year increase in age ($P = 0.02$)	Male smoking has deleterious effect on pregnancy outcome among IVF patients

Table I. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race); laboratory sample	Study design and analysis	Objectives	Lifestyle habits[a]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Klonoff-Cohen *et al.* (2001), USA	221 couples > 20 years old Caucasian, Black, Asian or Hispanic races from 7 infertility clinics in southern California No laboratory sample	Prospective (multivariate)	To investigate the influence of cigarette smoking by the wife, husband or couple at various time points (lifetime, week prior or during the procedure)	(a) Five questionnaires (3 for females, 2 for males) (c) Before, during, and after the procedure (d) Cigarette, cigar and chewing tobacco (e) Number smoked/week (f) Lifetime, 1 year, 1 month, 1 week, and 1 day prior to procedure (g) Couple	(1) Oocytes aspirated and fertilized (2) Number embryos transferred (3) Achieved pregnancy (4) Live birth delivery (5) Birth outcomes (low birthweight, multiple gestations)	Female age, female race, female education, parity, type of procedure, number of attempts, and female alcohol, marijuana or recreational drugs for corresponding time periods	Linear regression and logistic regression (1) Couples who had ever smoked compared to non-smokers had adjusted RR = 2.41 (95% CI = 1.07–5.45) of not achieving pregnancy, and 3.76 (95% CI = 1.40–10.03) of not having live birth delivery (2) Couples who smoked >5 years, adjusted RR = 4.27 (95% CI = 1.53–11.97) of not achieving pregnancy (3) Number oocytes retrieved decreased by 40% for couples and by 46% for men who smoked during week of IVF visit ($P < 0.05$)	Couples should be made aware that smoking years before undergoing IVF or GIFT can impact treatment outcome
Maximovich and Beyler (1995), USA	340 consecutive questionnaires from 253 patients in the William Beaumont Fertility Center IVF programme with cycles resulting in embryo transfer after transvaginal ultrasound directed ovum retrieval Mean age smokers = 36.3 and mean age non-smokers = 35.5 No laboratory sample	Retrospective (univariate)	Determine whether smoking affects pregnancy outcome	(a) Questionnaire (c) Time of IVF programme entry (d) Cigarette (e) Packs smoked/day (g) Female	(1) Embryo transfer (2) Pregnancy (3) Spontaneous abortion (4) Live birth	None	χ^2 and Fisher's exact tests (1) No difference in pregnancy rate per embryo transfer between smokers and non-smokers (2) Smokers had higher abortion rate (73 vs 24%, $P < 0.001$)	Pre-entry IVF cigarette smoking has adverse affect on potential pregnancy outcome by increasing spontaneous abortion rates
Pattinson *et al.* (1991), Canada	447 IVF couples from Foothills Hospital In 124 couples, female smoked cigarettes, and in 236 couples, no smoking history	Retrospective (univariate)	Evaluate the effects of cigarette smoking by either partner on events preceding and during oocyte recovery, fertilization, implantation, and early pregnancy in a group of patients undergoing IVF	(a) Interview (b) Smoke: Yes/No (c) In the cycle before treatment (d) Cigarette (e) Number of cigarettes/day (g) Male and female independently	(1) Ovarian response (2) Oocyte recovery (3) Fertilization (4) Implantation (5) Pregnancy (6) Spontaneous abortion (7) Delivery rate	None	(1) 50 pregnancies in non-smokers compared to 19 in smokers (21.2 vs 15.3% per cycle, not statistically significant) (2) No significant differences in cycles between the two groups in peak estradiol level achieved, the number of oocytes retrieved, fertilization rate, or implantation rate (3) Spontaneous abortion was higher in smokers than in non-smokers (42.1 vs 18.9%, NS) (4) Delivery rate per cycle of IVF was significantly lower in smokers than non-smokers (9.6 vs 17.0%, $P < 0.01$) (5) No effect when only the husband was a smoker	Smoking appears to significantly reduce the chances of successful pregnancy after IVF treatment
Rosevear *et al.* (1992), UK	45 women undergoing IVF 24 with tubal and 21 with unexplained infertility Age range from 22 to 40 years old. Duration of infertility range from 2 to 17 years Cotinine in ovarian follicular fluid collected at the time of oocyte recovery	Prospective (univariate)	Examine possible mechanisms for the association between cigarette smoking and reduced infertility	(a) Cotinine only	(1) Number of oocytes (2) Fertilization	None	(1) 116 oocytes were collected in women with no cotinine detected (limit of 20 ng/ml), and 84 became fertilized (74%) (2) 20 out of 45 collected oocytes from women with cotinine concentration > 20 ng/ml became fertilized (44%, $P < 0.001$) (3) Median fertilization rated for individuals (range 1–8 oocytes each) in the high and low cotinine groups were 57 and 75%, respectively ($P < 0.05$)	Smoking has an negative impact on fertilization rates among women undergoing IVF
Sterzik *et al.* (1996), Germany	197 infertile (tubal factor), and healthy women who entered IVF programme for first time at Women's University Hospital Mean age non-smokers = 32.5 years, mean age passive smokers = 32.7 years and mean age active smokers = 32.4 years Follicular fluid cotinine	Prospective (univariate)	Determine whether smoking affects fertilization and pregnancy rates in IVF program	(c) Current smoking (active, passive, and non-smokers) (d) Cigarette (g) Female	(1) Fertilization (2) Pregnancy	None	χ^2 (1) No differences in fertilization or pregnancy rates between groups (2) Smokers had decreased estradiol serum levels ($P < 0.03$) (3) Negative correlation between cotinine and estradiol levels ($r = -0.65$, $P < 0.01$)	No impairment of fertilization due to female smoking

Table I. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race); laboratory sample	Study design and analysis	Objectives	Lifestyle habits[a]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Trapp *et al.* (1986), Germany	114 patients undergoing IVF and 65 patients with primary sterility at the Institute for Hormone and Fertility Disorders from 1984 to 1985 No laboratory sample	Prospective (univariate)	Determine if smoking affects IVF	(a) Questionnaire (d) Cigarette (e) Light smokers ($n = 19$, few cigarettes) and heavy smokers ($n = 19$, > 1 pack/day) (g) Female	(1) Fertilization (2) Pregnancy (3) SCN concentration (rhodanide) in serum and follicular fluid	None	(1) No significant difference between fertilization and pregnancy rates between smokers and non-smokers (2) SCN concentrations were increased in smokers ($P < 0.05$)	Smoking had no effect on fertilization and pregnancy rates on women undergoing IVF
Van Voorhis *et al.* (1996), USA	18 smokers and 36 non-smokers from University of Iowa Assisted Reproductive Techniques Program Two non-smokers matched to each smoker for age, weight and history of ovarian surgery No laboratory sample	Retrospective cohort (univariate)	Determine the effects of smoking on ovulation induction for ART	(a) Questionnaire (c) Sent to women after IVF if had procedure between January 1, 1989 and July 1, 1994 (d) Cigarette (e) and (f) Pack-years (g) Female	(1) Follicle retrieval (2) Oocyte retrieval (3) Embryo retrieval (4) Serum estradiol level (5) Implantation rate	None	(1) Lower serum estradiol levels (1728 vs 2297 pg/ml, $P = 0.03$) in smokers than in non-smokers (2) Fewer follicles in smokers than in non-smokers (NS) (3) Fewer oocytes retrieved (NS) (4) Fewer embryos per cycle in smokers than in non-smokers (NS) (5) Lower implantation rate in smokers than in non-smokers (6.7 vs 16.4%, $P = 0.04$)	Smoking adversely affects ovulation induction parameters and alters the follicular fluid hormonal milieu
Weigert *et al.* (1999), Austria	834 women undergoing IVF treatment at the University of Vienna Group I (332 patients): combined stimulation, group II (433 patients): ultra-short flare-up protocol, and group III (73 patients): long down-regulation protocol No laboratory sample	Retrospective (univariate)	Investigate the influence of smoking on different parameters such as oocyte count, embryo score, and basal hormone values within the scope of IVF	(a) Questionnaires (d) Cigarette (e) Light (1–9 cigarettes per day), medium (10–20 cigarettes per day) and heavy (more than 20 cigarettes per day) (g) Female	(1) Oocyte retrieval (2) Embryo retrieval (3) Fertilization (4) Pregnancy	None	(1) Smokers in Group I showed a significantly lower embryo score ($P = 0.0072$) and produced fewer oocytes ($P = 0.0113$) than non-smokers in group I, with fewer of them fertilized ($P = 0.0072$) and transferred ($P = 0.0067$) (2) Not significant for groups II or III	Study found significantly altered hormonal parameters and negatively influenced oocyte parameters in smokers, particularly after clomiphene stimulation. Might consider using only GnRH agonist protocols for smoking patients
Weiss and Eckert (1989), Australia	11 women undergoing IVF at Flinders Medical Centre Cotinine levels in follicular fluid and serum	Cross-sectional (univariate)	Investigate the concentration of cotinine in follicular fluid of women participating IVF	(a) Cotinine only (d) Cigarette (g) Female	(1) Follicle size	None	(1) Cotinine was not detectable in non-smokers, but detectable in smokers (2) Cotinine levels not related to follicle size	The presence of cotinine in follicular fluid of women smokers provides evidence for access of at least one component of cigarette smoke to the developing gamete and the cells of the follicle
Zenzes *et al.* (1996), Canada	111 women undergoing IVF at Toronto Hospital Cotinine levels in follicular fluid	Controlled clinical trial (univariate)	Determine if cotinine is detectable in follicular fluid of passive smokers in IVF	(a) Not stated (d) Cigarette (e) 44 active smokers, 17 passive smokers and 50 non-smokers (g) Male and female independently	No IVF outcomes	None	Strong correlation between number of cigarettes smoked and follicular fluid cotinine levels (active smokers = 710.4 ± 128.2 ng/ml, passive smokers = 76.3 ± 56.5 ng/ml, non-smokers = 4.2 ± 2 ng/ml, $P < 0.0001$)	Cotinine was detectable in a dose–response manner in active and passive smokers. It was detected in all active smokers and in a majority of passive smokers
Zenzes and Reed (1997), Canada	234 women undergoing IVF at Toronto Hospital Cotinine in follicular fluid	Cross-sectional (univariate)	Determine effects of cigarette smoking and age on oocyte maturation	(a) Not stated (self-report) (c) Prior to IVF (d) Cigarette (e) Non-smokers, passive, and current (g) Male and female independently	(1) Oocyte maturity (2) Fertilization	None	(1) Greater cotinine concentration accompanied greater oocyte maturity ($P = 0.0005$) and fertilization ($P = 0.007$) (2) Cotinine effect was positive in younger women (NS) and negative in older women (>40 years) ($P = 0.002$)	Negative effects of smoking were detectable in older women

Table I. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race); laboratory sample	Study design and analysis	Objectives	Lifestyle habits[a]	IVF outcomes	Confounders	**Results (type of analyses)**	**Conclusions**
Zitzman *et al.* (2003), Germany	301 couples at University Reproductive and Andrology Unit Total of 153 ICSI and 148 IVF patients (415 treatment cycles) 139 habitual smokers (ICSI: 71 men, 41 women; IVF: 68 men and 36 women) No laboratory sample	Retrospective cohort (multivariate)	Determine whether male smokers have decreased success rates for IVF and ICSI	(a) Standardized interview (c) During first visit (d) Cigarette (e) > 5 cigarettes/day for ≥ 2 years (g) Male and female independently	(1) Number of embryos transferred (2) Oocyte retrieval (3) Fertilization (4) Pregnancy	Female and male age, male smoking habits, number embryos transferred, sperm motility and morphology, and repetitions of treatment	Multiple nominal regression (1) Male smokers' success rates for IVF lower than non-smokers' success rates for IVF (18 vs 32%, $P < 0.01$) (2) Clinical pregnancy after IVF was dependent on male age (negative association, $P = 0.01$), male smoking (negative association, $P = 0.003$), number of embryos transferred (positive association, $P = 0.001$), and sperm motility (positive association, $P = 0.04$) (3) Female smoking influenced number of oocytes retrieved (negative association, $P = 0.01$) and fertilization rates for IVF (negative association, $P = 0.02$)	Male smoking decreases IVF success rates

(a) Questionnaire, interview, medical record, data bank, or cotinine only; (b) smoking status: yes/no; (c) timing prior to or during IVF procedure; (d) type of smoking; (e) amount and/or frequency of smoking; (f) duration of smoking; (g) male smoking only, female smoking only, male and female independently, and couple smoking.
OR = odds ratio; CI = confidence interval; RR = relative risk; NS = not significant.

Appropriate study design

Six retrospective studies (Pattinson *et al.*, 1991; Maximovich and Beyler, 1995; Van Voorhis *et al.*, 1996; El-Nemr *et al.*, 1998; Joesbury *et al.*, 1998; Weigert *et al.*, 1999), 10 prospective studies (Trapp *et al.*, 1986; Harrison *et al.*, 1990; Elenbogen *et al.*, 1991; Hughes *et al.*, 1992; Rosevear *et al.*, 1992, Hughes *et al.*, 1994; Sterzik *et al.*, 1996; Crha *et al.*, 2001; Klonoff-Cohen *et al.*, 2001a), two meta-analyses (Feichtinger *et al.*, 1997; Augood *et al.*, 1998) and one systematic review (Hughes and Brennan, 1996) have investigated the effect of smoking on the biological and reproductive endpoints of IVF and GIFT (Table I).

Sample size and method of selection and description of subjects and comparison group

The size of the study sample (not including meta-analyses) varied from 41 patients (Elenbogen *et al.*, 1991) to 650 patients (Harrison *et al.*, 1990). The source of patients was derived entirely from infertility clinics, and all studies had groups of smokers and non-smokers. One race was represented in every study, except one, which contained Whites, Asians, African-Americans, and Hispanics (Klonoff-Cohen *et al.*, 2001b).

Existence of standardized IVF outcomes

Maternal smoking resulted in decreased fertilization rates [Elenbogen *et al.*, 1991; Rosevear *et al.*, 1992; Zenzes and Reed, 1997; Weigert *et al.*, 1999 (in clomiphene citrate/hMG-stimulated women); El-Nemr *et al.*, 1998; Crha *et al.*, 2001; Zitzmann *et al.*, 2003], decreased numbers of oocytes (Harrison *et al.*, 1990; El-Nemr *et al.*, 1998; Weigert *et al.*, 1999; Crha *et al.*, 2001; Klonoff-Cohen *et al.*, 2001; Zitzmann *et al.*, 2003), decreased embryos (Van Voorhis *et al.*, 1996), decreased embryo transfer rates (Klonoff-Cohen *et al.*, 2001), decreased pregnancy rates (Harrison *et al.*, 1990; Pattinson *et al.*, 1991; Feichtinger *et al.*, 1997; Augood *et al.*, 1998; Klonoff-Cohen *et al.*, 2001), increased miscarriage rates (Harrison *et al.*, 1990; Pattinson *et al.*, 1991; Maximovich and Beyler 1995; Hughes and Brennan 1996), and lower live birth delivery rates (Pattinson *et al.*, 1991; Klonoff-Cohen *et al.*, 2001) (Figure 1 and Table I).

In contrast, several studies determined that there was no effect of smoking on fertilization rates [Trapp *et al.*, 1986; Harrison *et al.*, 1990; Pattinson *et al.*, 1991; Hughes *et al.*, 1992, 1994; Sterzik *et al.*, 1996; Zenzes and Reed, 1997 (in the younger group); Weigert *et al.*, 1999], implantation rates (Harrison *et al.*, 1990; Pattinson *et al.*, 1991), and pregnancy rates (Hughes *et al.*, 1992, 1994; Maximovich and Beyler, 1995; Hughes and Brennan, 1996; Sterzik *et al.*, 1996; El-Nemr *et al.*, 1998; Weigert *et al.*, 1999). Only one study considered multiple endpoints of IVF, including live birth delivery and neonatal characteristics (low birth, multiple gestations) (Klonoff-Cohen *et al.*, 2001).

Use of standardized instruments and/or laboratory samples to verify lifestyle habits

Methodological limitations for obtaining smoking history may have contributed to the contradictory findings. Smoking history was ascertained by questionnaire (Trapp *et al.*, 1986; Elenbogen *et al.*, 1991; Hughes, 1994; Weigert *et al.*, 1999; Klonoff-Cohen *et al.*, 2001a), follicular fluid cotinine concentrations (Rosevear *et al.*, 1992; Hughes *et al.*, 1994; Zenzes *et al.*, 1996; Zenzes and Reed, 1997) or both (Crha *et al.*, 2001). The definition of smoking history in these studies was insufficient, failing to differentiate the amount, frequency, type (e.g. cigarettes, cigars, and pipes), and timing of smoking. Some classified smokers as current or former smokers (Augood *et al.*, 1998; Sterzik *et al.*, 1996) or as active, passive and non-smokers (Zenzes *et al.*, 1996; Zenzes and Reed, 1997), whereas others used only two

Table II. Studies investigating stress and IVF

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Baluch *et al.* (1993), England	42 Iranian women: Group A: 14 infertile women (mean age = 37 years) with unsuccessful or multiple IVF treatments Group B: 14 infertile women (mean age = 35 years) without any IVF treatment Group C: 14 fertile women (mean age = 36 years)	Cross-sectional (univariate)	Determine psychological aspects of failing to conceive with IVF	(a) Psychological distress and discomfort (b) Once (c) Psychological distress in daily activities	4-point scale	None stated (treatment)	None	Infertile women without any IVF treatment showed more distress than infertile women with unsuccessful or multiple IVF treatments and fertile women ($P < 0.001$)	Psychological discomfort associated with infertility, yet unsuccessful treatment cycles did not create more infertility
Beutel *et al.* (1999), Germany	56 women and men undergoing IVF or ICSI (28 women and 28 men)	Retrospective (1 year) (univariate)	Compare treatment-related stress for couples undergoing IVF or ICSI (ejaculated, epididymal, testicular) and to identify male and female differences in stress	(a) Treatment-related stress and depression (b) Once (c) Two types: (1) Depression (2) Self-esteem	(1) von Zerssen Depression Scale (2) German version of Rosenberg Self-esteem Scale	None stated (treatment)	None	Treatment-related distress was higher for females than males ($P < 0.001$)	Future studies on emotional reactions of women and men undergoing assisted reproductive treatment should take the specific treatments and related diagnoses into account, since both the clinical background and psychological impact are likely to differ
Boivin and Takefman (1995), Canada	40 women (72 invited to join) Mid-30s Most had primary infertility and had been infertile for 4 years	Prospective (multivariate)	Determine whether stress levels differ in different ovulatory phases and treatment phases (on the effect of achieving a pregnancy with IVF)	(a) Stress during treatment and 3 days after the pregnancy test (b) Daily (c) Three types: (1) Marital satisfaction (2) Anxiety (3) Coping	(1) Marital Adjustment Scale (2) STAI (3) Social Desirability Scale (4) Miller Behavioral Style Scale (5) Daily Record Keeping (DRK) Sheet on emotional, physical, and behavioural reactions	(1) Embryo transfer (2) Pregnancy	Age, years living together, years infertile, years in treatment, occupation	(1) No significant group differences on marital adjustment, anxiety, coping style, social desirability, infertility-related stress, or preparation for IVF and expectations about its success (2) Less stress during luteal phase: high stress during ovulatory phase (3) Higher stress in non-pregnant group during oocyte retrieval ($P < 0.05$), embryo transfer ($P < 0.05$) and pregnancy test ($P < 0.001$) (4) Poorer biological variable values were associated with greater stress: number of oocyte retrieved with stress during oocyte retrieval (NS) and number of embryo transferred with stress during transfer (NS) (5) Non-pregnant group reported more stress (0.092 ± 0.58: mean $\pm$ SD) than the pregnant group (-0.654 ± 0.55)	(1) There are reliable differences in daily emotional reactions between those who eventually achieve a pregnancy with IVF and those who do not (2) The timing of assessments (prospective, retrospective) will determine the conclusions made about emotional reactions to IVF, because patients' recall of treatment is not consistent with their ongoing experience of it
Boivin *et al.* (1998), UK	40 couples undergoing IVF or ICSI at a private infertility clinic (husbands' mean age = 34.8; wives' mean age = 32.1 years)	Prospective (multivariate)	Examine difference in daily emotional, physiological, and social reactions in husbands and wives undergoing IVF	(a) Baseline and daily procedural stress (b) Daily (c) Five types: (1) Optimism (2) Physical discomfort (3) Marital relationship (4) Social relationship (5) Fatigue	(1) Interview (2) Daily Record Keeping (DRK) Chart	(1) Oocytes aspirated (2) Fertilization (3) Embryo transfer (4) Pregnancy	Female age, years of infertility	(1) Men and women had similar responses to oocyte retrieval, fertilization, embryo transfer and the pregnancy test	Most important psychological determinant of reactions during IVF was uncertainty of treatment

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Bringhenti *et al.* (1997), Italy	122 infertile women entering IVF at Sterility Center at University and 57 mothers attending routine care on the same site from 1994 to 1995	Cross-sectional (multivariate)	Study psychological aspects of women entering IVF	(a) Baseline stress (b) Once Infertile group: during an ultrasound examination. Fertile group: at the end of the routine examination (c) Six types: (1) Anxiety (2) Emotional instability (3) Conditions of stress (4) Depression (5) Self-esteem (6) Job and marital satisfaction	(1) STAI (2) Eysenck Personality Questionnaire (EPQ) (3) Psychophysiological Questionnaire (4) Questionnaire for depression (5) Rosenberg's Self-esteem Scale (6) Kansas Marital Satisfaction Scale (KMSS)	None stated (treatment)	Duration of infertility, number of attempts, employment, education, personality (extraversion, neuroticism)	(1) Infertile group higher than mothers with respect to satisfaction of relationship and their husband's perception of care and state-anxiety (2) Emotional scores of infertile women influenced by number of cycles, job satisfaction, personality dimension	Infertile women entering IVF treatment do not show signs of psychological maladjustment
Callan *et al.* (1988), Australia	254 infertile couples who complete ≥ 1 IVF cycle in the same IVF programme (women's mean age = 33 years; men's mean age = 35 years)	Cross-sectional (multivariate)	Understand women's decisions to continue or stop IVF	(a) Belief about the outcomes of continuing on IVF (b) Once (c) Two types: (1) Coping (2) Optimism	(1) Questionnaire on background information and beliefs about the outcomes of continuing an IVF programme (2) Questionnaire to assess their coping methods (3) 6-point Likert scales to assess optimism	None stated (continue/stop IVF)	Age, education, number of children, years of infertility, initial wait for IVF, number of pregnancies prior to IVF, number of IVF pregnancies, number of IVF treatments, having children, having an IVF pregnancy	(1) Women not continuing IVF had older husbands (2) Women's intentions about IVF were best predicted about their attitudes towards another attempt and perceptions of social pressure (3) Discontinuers of IVF were less optimistic about another attempt (4) Both groups of women felt that an IVF attempt involved some stress, disappointment, and financial strain (5) Discontinuers felt their husbands, doctors, family and friends did not think that they should not have another IVF attempt	IVF teams should continually seek the perceptions of their patients about the demands of treatment and better prepare couples for a demanding procedure
Callan and Hennessey (1988), Australia	254 infertile couples, ≥ 1 IVF cycle out of 423; 182 continued vs 72 discontinue IVF procedure in the same IVF programme (wife's mean age = 32 years; husbands' mean age = 36 years)	Cross-sectional (univariate)	Investigate the emotional demands on women in an IVF programme	(a) Procedural stress (b) Once questionnaire administration followed by 2 h semi-structured interview. (c) Three types: (1) Perception of emotional demands of IVF (2) Explanations for failed attempts (3) Coping strategies and sources of emotional support	(1) Questionnaire on background information and beliefs about the outcomes of continuing on an IVF programme (2) Questionnaire to assess their coping methods (3) 6-point Likert scales to assess optimism	None stated (number of attempts)	None	(1) Two most difficult stages were waiting for possible pregnancy and blood test and injections (2) Women were overly optimistic after first attempt (70% being moderately or highly optimistic) (3) Optimism declined after first attempts (half of the women stopped at 4 cycles, all stopped at 6 cycles) (4) Lack of success attributed to low success rate, being anxious or stressed, bad luck, problems associated with their condition (5) Major coping strategy might be successful in the long term (6) Other coping strategies: keeping busy, staying calm, seeking support	(1) Majority felt less fulfilled if they did not have a child through IVF (2) Continued infertility not detrimental to quality of marriage
Chan *et al.* (1989), China	112 couples (women's mean age = 33 years, men's mean age = 38 years) enrolled in IVF programme in Hong Kong	Cross-sectional (univariate)	Evaluate psychosocial stress in couples enrolled in IVF	(a) Baseline stress Feelings about infertility, perception of IVF/GIFT procedure: Pre-treatment questionnaires and interview (about attitude towards infertility and IVF/GIFT, future plan, and social support) (b) Once (c) Three types: (1) Anxiety (2) Personality (3) Depression	(1) STAI (2) Eysenck Personality Questionnaire (3) Leeds Scale for self-assessment of anxiety and depression (4) General Health Questionnaire	None stated (during treatment)	None	(1) Several higher scores for anxiety in women than men (2) Half of the couples did not disclose their treatment to other people (3) Only half of the couples had social support	This study had its emphasis on the dissemination of adequate information and the assessment of emotional and attitudinal factors before commencement of treatment so that couples were psychologically prepared for the procedures that followed

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Collins *et al.* (1992), Sweden	200 couples in IVF programme from the hospital of the University of Pennsylvania between 1989 and 1990 (women's mean age = 34 years; men's mean age = 36 years)	Cross-sectional (multivariate)	Perceptions of treatment stress in women vs men for couples undergoing IVF	(a) Perceptions and feelings about infertility (b) Once	(1) Infertility Reaction Scale (2) Duration of infertility (3) Degree of social support (4) Effect of infertility on sexual relationship (5) Expected likelihood of achieving pregnancy (6) Anticipation of stress during treatment	None stated	Age, having children, years of infertility, years of marriage, medical diagnosis, psychosocial support	(1) Women anticipated more stress but greater social support during IVF than men (2) Both partners overestimated their successes (3) Factor analyses of infertility scale produced three factors that were similar to both sexes (i) Desire to have a child as a major focus of life with inadequacy of the male role (ii) Social functioning and work efficiency (iii) Pressure to have a child	The intense focus on having a child was the predominant factor in anticipated stress of IVF treatment for both males and females
Csemiczky *et al.* (2000), Sweden	22 women with tubal infertility entering IVF and 22 fertile women at the Reproductive Medicine Center from 1997 to 2000	Retrospective (univariate)	Comparing stress levels for IVF outcomes	(a) Pre-treatment Stress (b) Once (c) Five types: (1) Anxiety (2) Muscular tension (3) Impulsivity (4) Monotony avoidance (5) Aggression–hostility	(1) STAI (2) KSP (3) Emotional response to the pregnancy scale (3) Hormone measurement (serum prolactin cortisol, FSH levels)	Pregnancy	None	(1) Significant differences in estradiol and progesterone ($P < 0.01$) in luteal phase between pregnant and failed women (2) There was a trend toward higher STAI among women who did not become pregnant ($P < 0.06$)	Infertile women have different personality profiles: more suspicion, guilt and hostility compared to controls. In addition, prolactin and cortisol levels were also elevated in infertile women
Demyttenaere *et al.* (1991), Belgium	40 women respondents out of 80 individual women attending infertility clinic at University hospital for IVF (mean age = 32 years; mean infertility = 6 years)	Prospective (univariate)	Determine stress responses during IVF as a factor of 'coping and ineffectiveness of coping'	(a) Baseline stress (b) Immediately after the first visit to the clinic. Hormone measurement was conducted in the mid-follicular phase (c) Four types: (1) Anxiety (2) Coping (3) Depression (4) Personality	(1) STAI (2) ABV-B (3) UCL (4) Zung Depression Scale (5) Hormone measurement (prolactin and cortisol)	(1) Oocytes retrieval (2) Embryo transfer	None	(1) IVF women's Zung depression score, trait anxiety, and neuroticism were higher than in a general population ($P < 0.0001$, $P < 0.05$, and $P < 0.01$, respectively) (2) State anxiety levels were high in the follicular phase, high before oocyte retrieval and embryo transfer but low after oocyte retrieval and embryo transfer (3) Prolactin (PRL) concentrations were low in the early follicular phase but an anticipatory increase in PRL concentrations exists before OR (4) An anticipatory cortisol concentration increased in the early follicular phase, before oocyte retrieval and before embryo transfer	Stress responses are important for conception rates in stimulated and spontaneous cycles
Demyttenaere *et al.* (1992), Belgium	40 women attending the infertility clinic for IVF at the University Hospital in Gasthuisberg (mean age = 32.4 years; mean infertility = 6.1 years)	Prospective (univariate)	Investigate if coping style and stress responses to oocyte retrieval and embryo transfer are correlated with the quality of ovulation induction, with the oocyte number, fertilization rate, cleavage, quality of luteal phase and establishment of pregnancy	(a) Baseline stress (b) Immediately after the first visit to the clinic Hormone measurement was conducted during oocyte retrieval and embryo transfer (c) Four types: (1) Anxiety (2) Coping (3) Depression (4) Personality	(1) STAI (2) Zung depression score (3) ABV-B (4) UCL (5) Hormone Measurement (prolactin, cortisol, LH, FSH)	(1) Number of oocytes (2) Embryo transfer (3) Pregnancy (4) Miscarriage	Blood levels of prolactin and cortisol for stress	(1) Women with a higher Zung depression score, active coping score, avoiding score, and expression of emotion score had a lower pregnancy rate ($P = 0.02$) and a higher spontaneous abortion rate ($P = 0.01$) than women with a lower depression, coping, avoiding and emotion scores (2) State anxiety levels were higher in unsuccessful subjects (not pregnant) than in the successful subjects (pregnant) (3) Higher prolactin concentrations were correlated with pregnancy ($P = 0.04$) and during oocyte retrieval or embryo transfer (4) In successful women, cortisol concentrations were lower than the unsuccessful women, except after embryo transfer	The influence of prolactin stress concentrations is unclear: women with high prolactin concentrations seem to have more oocytes but lower fertilization rates

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Demyttenaere *et al.* (1994), Belgium	40 women (23 with subtle cycle disturbances and 17 with normal cycles) attending the infertility clinic for IVF at the University Hospital in Gasthuisberg (mean age = 32.4 years; mean infertility = 6.1 years	Prospective (univariate)	Women with subtle cycle disturbances will have a different% of pregnancy than women with normal cycles	(a) Baseline stress (b) Immediately after the first visit to the clinic Hormone measurement was conducted during oocyte retrieval and embryo transfer (c) Four types: (1) Anxiety (2) Coping (3) Depression (4) Personality	(1) Zung depression score (2) UCL (3) STAI (4) Hormone measurement (prolactin, cortisol, LH, FSH)	Pregnancy	Blood levels of prolactin and cortisol for stress	(1) 5/23 pregnancies in cycle disturbances group (22%) (2) 5/17 pregnancies in normal cycle group (29%) (3) No personality differences between groups (4) Higher state anxiety in those with cycle disturbances (5) Only slightly higher trait anxiety in those with cycle disturbances	The state anxiety level in the early follicular phase, which is correlated with a negative outcome in IVF, is higher in women with cycle disturbances
Demyttenaere *et al.* (1998), Belgium	98 women entering IVF at the Leuven University Fertility Center (mean age = 29.7 years; infertility = 4.1 years)	Prospective (univariate)	Examine the influence of depression levels and coping on IVF outcome in women, taking the cause of infertility into account	(a) Baseline stress (b) Immediately after the first visit to the clinic (c) Three types: (1) Anxiety (2) Depression (3) Coping	(1) Zung Depression Scale (Dutch version) (2) UCL	Pregnancy	None	(1) Higher palliative coping and decreased expression of negative emotions was found in women who became pregnant ($P = 0.03$) compared with those who did not ($P = 0.01$) (2) In the subgroup of female subfertility, a higher depression score ($P = 0.01$) and greater depressive coping score ($P = 0.003$) were associated with a lower pregnancy rate (3) In the subgroup with male subfertility, a higher depression score ($P = 0.009$), greater depressive coping score ($P = 0.01$) and palliative coping score ($P = 0.03$) were associated with higher pregnancy rates	Expression of negative emotions predicts depression levels and IVF outcome. The cause of infertility should be taken into account when investigating the relation between psychological functioning and IVF outcome
Facchinetti *et al.* (1997), Italy	49 women undergoing IVF at the Department of Obstetrics and Gynecology, University of Modena from 1993 to 1995 (mean age = 33.9 years)	Prospective (multivariate)	Cardiovascular stress is associated with poor IVF outcome	(a) Procedural stress (b) Stroop Color Word Test was conducted on the day of oocyte retrieval. STAI was conducted evening before the oocyte retrieval. (c) Four types: (1) Coping ability (2) Cognitive Dissonance (3) Psychological tension (4) Anxiety	(1) Stroop Color Word Test (2) STAI (3) Systolic and diastolic blood pressure and heart rate	Pregnancy	Age, years of education, employment status, years of infertility, number of IVF attempts	(1) Anxiety scores were higher in the failure group (48.6 ± 9.4; $n = 20$) than in the success group (41.0 ± 8.7; $n = 9$) ($P = 0.047$)	A negative correlation between stress susceptibility and IVF outcome gives further substantiation that programmes of psychological support for infertile couples would increase the success of assisted reproduction treatment
Freeman *et al.* (1985), USA	200 couples in IVF programme (seen at a pretreatment) from 1983 to 1984	Cross-sectional (univariate)	What are the attitudinal and emotional characteristics of the sample	(a) Baseline stress (b) Once during the initial IVF visit (c) Five types: (1) Distress (2) Personality (3) Ego strength (4) Anxiety (5) Coping skills	(1) MMPI (2) Non-standardized counsellor ratings of coping skills	None stated	None	(1) Half the women ($n = 100$) and 15% of the men reported that infertility was the most upsetting experience of their lives (2) 20% of men and women had one elevated scale score suggesting dysfunctional emotional distress or personality difficulties (3) Half of the sample had high scores on MMPI Ego Strength scale (i.e. effective functioning and ability to withstand stress)	It is important to provide patients with emotional support and to develop better understanding of the psychological components of IVF
Gallinelli *et al.* (2001), Italy	40 infertile women undergoing IVF at the university hospital (age range = 27–35 years)	Prospective (multivariate)	Evaluate whether immunological changes and stress are associated with different implantation rates in IVF	(a) Procedural stress (b) Stroop Color and Word Test was administered just before oocyte retrieval. STAI was administered evening before oocyte retrieval. (c) Four types: (1) Coping ability (2) Cognitive Dissonance (3) Psychological tension (4) Anxiety	(1) Stroop and Color Word Test (2) STAI (3) Blood sampling	Implantation	None (the two groups analysed were homogeneous for education, age, years of infertility, and parity)	Total number of T lymphocytes increased significantly during ovulation induction, resulting in significantly higher levels in subjects achieving embryo implantation than in those showing a failure of implantation ($P < 0.05$)	Prolonged stress is associated with a reduced implantation rate in women undergoing IVF

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Hammarberg *et al.* (2001), Australia	211 women who had their last contact with the clinic in 1994	Retrospective (univariate)	Increase understanding of how women feel about the experience of IVF 2–3 years after ceasing treatment	(a) Feelings toward IVF (b) Once (c) Four types	(1) Satisfaction With Life Scale (SWLS) (2) Golombok Rust Inventory of Martial Status (GRIMS) (3) GHQ-12 (4) 161 item questionnaire	None stated	None	(1) Women who did not have a baby were more critical about the clinic and more negative about the experience of treatment but did not regret having tried IVF (2) Women who did not have a baby had statistically significantly lower scores on SWLS but did not differ from those with babies on GRIMS and GHQ-12 scales	A few years after ending IVF treatment, emotional well-being and marital satisfaction are not affected by lack of success; however, life satisfaction is lower for women who are unsuccessful
Harlow *et al.* (1996), UK	170 women attending the Gynaecology and Reproductive Medicine clinics at St Michael's Hospital. Group 1: 24 control women Group 2: 25 unstimulated IVF women Group 3: 26 stimulated IVF women	Prospective (univariate)	Women undergoing IVF have a higher state anxiety and stress level than women not undergoing IVF	(a) Baseline and procedural stress: (b) In part 1, all three groups completed STAI at initial consultation. In part 2, only Group 3 (stimulated IVF) completed STAI on three occasions (baseline, a follicular phase, a day prior to the procedure) (c) Anxiety	(1) STAI (2) Hormones (cortisol and prolactin)	Pregnancy	None	(1) State anxiety was significantly higher ($P < 0.05$) in the stimulated vs unstimulated IVF all three times (2) Anxiety also increased during treatment in the IVF group (3) Median baseline and preoperative trait anxiety appeared to be higher in women who failed to become pregnant compared with those who became pregnant (not statistically significant)	Women undergoing IVF have significantly higher state anxiety and stress than women not undergoing IVF
Harrison *et al.* (1987), Australia	500 couples undergoing IVF from 1985 to 1986	Prospective (univariate)	Determine specific effects of stresses on quality of semen sample used at the fertilization stage in IVF	(a) Baseline (lower) and procedural (higher) stress (b) Measurement of semen quality at pre-IVF workshop and after ovum aspiration (c) None	No psychological instruments	Fertilization	None	(1) The incidence of total fertilization failure in the procedure dramatically increased for the 35 cases, revealing a deterioration, severe pathology in semen character	Stress affects semen quality and leads to fertilization failure
Hjelmstedt *et al.* (2003), Sweden	(1) IVF group: 57 pregnant women after IVF and their 55 male partners from the IVF units at university hospitals (2) Control group: 43 naturally conceived women and their 39 male partners at four antenatal clinics. Recruited from 1997 to 2000	Prospective (multivariate)	Compare couples who have conceived after IVF and couples who have conceived naturally regarding personality factors and emotional responses to pregnancy	(a) Baseline and procedural stress for IVF group Baseline and pregnancy stress for control group (b) A total of five assessments up to 6 months postpartum) (c) Five types: (1) Distress (2) Marital satisfaction (3) Personality (4) Anxiety (5) Emotional responses to pregnancy. Interviewed about sociodemographic background	(1) Infertility reaction scale (IRS) (2) Barnett scale (3) KSP (4) STAI (5) Emotional Responses to Pregnancy Scale (ERPS)	Pregnancy	IVF group/control group, anxiety proneness, age, previous miscarriages and ectopic pregnancies, years of cohabitation, and level of education	(1) IVF women had more muscular tension and were more anxious about losing the pregnancy than the control women ($P < 0.06$) (2) IVF women with high infertility distress were more anxious about losing the pregnancy than the control women ($P < 0.05$) (3) IVF men had more somatic anxiety, indirect aggression and guilt (4) IVF men with high infertility distress were more anxious about the baby not being normal ($P < 0.05$)	Women and men who had conceived after IVF differed on a number of personality dimensions and emotional responses to the pregnancy compared to women and men who had conceived naturally
Hsu and Kuo (2002), China	120 infertile couples attending the IUI or IVF at the medical clinic for infertility treatment from 1999 to 2000	Prospective (multivariate)	Explore the differences between wives and husbands in their emotional reactions and coping behaviours among infertile couples receiving infertility treatment	(a) Baseline and procedural stress (b) Before treatment, on the day of sonography test, and before IVF (c) Five types: (1) Anxiety (2) Coping (3) Depression (4) Mood (5) Anger	(1) POMS (2) Ways of Coping questionnaire (3) Tension–Anxiety (4) Depression–Dejection (5) Anger–Hostility (6) Fatigue–Inertia	None stated	Age, education, years of infertility, duration of receiving treatment, number of treatments received, number of existing children, infertility cause, current method of treatment	(1) Infertile wives experienced more emotional disturbance than husbands did (2) Wives adopted more coping behaviours to deal with infertility and treatment than husbands did	Wives demonstrated more emotional disturbance than husbands while they showed more coping behaviours to deal with their infertility than their husbands
Johnston *et al.* (1987), UK	Clinic sample: 26 women at IVF clinic Surgery sample: 23 surgical inpatients for IVF	Prospective (univariate)	Patients participating in IVF would overestimate the likelihood of success and underestimate the likelihood of an earlier stage in the procedure	(a) Baseline, procedural, after IVF distress (b) Three times (c) Three types: (1) Anxiety (2) Distress (3) Mood	(1) Visual analogue scales (VAS) (2) STAI (3) 7-point scales to assess confusion levels of the programme and importance of having a baby	(1) Oocyte retrieval (2) Embryo transfer (3) Fertilization	None	10 data on patients' distress showed high anxiety at points of uncertainty and failure ($P < 0.05$) (2) Women who failed to fertilize had significantly higher STAI scores than those who succeeded ($P < 0.005$)	These results suggest that models of stress and of making judgments under conditions of uncertainty are useful in predicting the responses of patients to clinical situations

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Kee *et al.* (2000), South Korea	138 infertile women (mean age = 32.76 years) receiving medical treatment for infertility 78 control fertile women (mean age = 32.96 years) visiting the outpatient department at University hospital between 1997 and 1999	Cross-sectional (univariate)	Compare average stress levels in infertile women and fertile women and their chances of pregnancy	(a) Procedural stress for IVF patients (b) Once (c) Three types: (1) Perceived stress (2) Anxiety (3) Depression	(1) STAI (2) BDI	Pregnancy	None	(1) Infertile women showed significant increases in trait anxiety and depressive symptoms than fertile women (2) Anxiety and depression in the IVF-failed women were significantly higher than the IVF-success women (3) Levels of STAI and BDI were significantly lower in pregnant women than non-pregnant women ($P < 0.05$) after IVF treatment	We must pay attention to the infertile patient, especially from the initial infertility work-up
Klonoff-Cohen *et al.* (2001), USA	151 women (Caucasian, Asian, Hispanic, Black) attending seven IVF clinics in Southern California between 1993 and 1998	Prospective (multivariate)	Evaluate whether baseline or procedural stress during IVF or GIFT affects pregnancy or live birth delivery rates	(a) Baseline (acute and chronic) stress Procedural (acute) stress *All stress instruments were administered at initial clinic visit and before embryo transfer (b) Two times (c) Nine types: (1) Mood (2) Depression (3) Anxiety (4) Anger (5) Perception (6) Optimism (7) Social support (8) Perceived stress (9) Coping	(1) PANAS (2) POMS (3) Perceived Stress Scale (4) Self-rated Stress Scale (5) Infertility–Reaction Scale (6) Expected likelihood of achieving a Pregnancy Scale (7) Network Resource Scale (8) Ways of Coping Scale	(1) Oocyte aspiration (2) Fertilization (3) Embryo transfer (4) Pregnancy (5) Spontaneous abortion (6) Live birth	Female age, race, education, parity, type of procedure, no. of attempts, and alcohol, marijuana or recreational drugs during corresponding time periods	(1) Baseline PANAS negatively influenced number of oocytes retrieved and embryo transferred (2) At baseline, risk of no live birth was 93% lower for women who had highest positive-affect score compared to those with the lowest score (3) Infertility Reaction Scale scores negatively impacted live birth delivery, infant birthweight, and multiple births (4) Procedural PANAS and POMS were related to number of oocyte fertilized and embryo transferred; stress did not affect pregnancy or delivery	Baseline stress affected biological endpoints (i.e. number of oocytes retrieved and fertilized) as well as pregnancy, live birth delivery, birthweight, and multiple gestations. Procedural stress only influenced biological endpoints
Lee *et al.* (2001), Taiwan	100 infertile Chinese couples (female, male, and mixed infertility) at a medical centre (husbands' mean age = 34 years; wives' mean age = 32 years)	Cross- sectional (univariate)	Determine the effect of an infertility diagnosis on treatment-related stresses	(a) Procedural stress (b) Once (c) Coping	(1) Treatment-related Stress Scale (TSS) (2) Perceived Stress Scale (PSS) (3) 40-item Jalowiec Coping Scale	None stated (treatment)	Marital duration, time in treatment, number of IVF procedures	(1) Women experience significantly more stress from infertility tests and treatment than men (2) Men with mixed or idiopathic infertility experienced less stress to infertility than men with only male or only female infertility (3) Women with mixed or idiopathic infertility experienced less stress to infertility than women with only female infertility	Infertility tests and treatments created a stressful experience for couples, with wives experiencing more stress than their husbands. Stress decreased the likelihood of conception and further affected the outcome of the infertility treatment
Leiblum *et al.* (1987), USA	59 infertile couples who completed ≥ 1 cycle of IVF who were refereed to the IVF programme at UMDNJ–Robert Wood Johnson Medical School from 1983 to 1985 (wives' mean age = 33 years; husbands' mean age = 34 years)	Prospective (univariate)	Determine psychological and physical associations with IVF and assess reactions to IVF from men and women	(a) Baseline and procedural stress (b) twice (pre- and post-IVF) (c) Four types: (1) Sadness (2) Anger (3) Depression (4) Marital Satisfaction	(1) The short form of the Locke–Wallace Martial Adjustment Test (MAT) (2) POMS (3) The Rotter Internal–External Control of reinforcement Scale	None stated (treatment)	Administered questionnaires both pre- and post-IVF treatment	(1) Couples overly optimistic about likelihood of achieving pregnancy via IVF (2) Most rated IVF as moderately stressful with one-third rating IVF as very stressful (3) Common reactions to unsuccessful IVF were sadness, anger and depression and were more pronounced in men than women (4) Most couples reported satisfaction with IVF despite failure to conceive (5) Women with previous children able to cope better with unsuccessful IVF than women without children	IVF tends to be an intense, emotional experience for both husbands and wives

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Lovely *et al.* (2003), USA	42 women who underwent assisted reproduction treatment (40 IVF, one gamete intra-Fallopian transfer, one zygote intra-Fallopian transfer in 18 month period and 10 oocyte donor controls) at the university hospital from 1995 to 1997	Prospective (univariate)	Examined the effect of stress on pregnancy outcome in women who underwent assisted reproduction treatment	(a) Procedural stress (b) The day after administration of hCG, subjects completed STAI and 24 h urine specimen hormone measurement (c) Anxiety	(1) STAI (2) Hormone measurement [cortisol and 6-sulphatoxy-melatonin (6-SM)]	Pregnancy	Used biochemical measures for stress	Analysis of covariance, χ^2 and Fisher's exact test (1) Self-ratings of acute anxiety not associated with pregnancy outcome (2) Total daily 6-SM value not associated with pregnancy outcome (3) Cortisol levels not associated with pregnancy outcome	Neither biochemical markers nor subjective measures supported deleterious effect of stress on pregnancy in assisted rproduction treatment
Mahlstedt *et al.* (1987), USA	94 women attended three IVF programmes at universities from 1984 to 1985 (women's median age = 34 years)	Retrospective (univariate)	Describe emotional state and experience of patients when undergoing IVF	(1) Procedural stress (b) Once (c) Focusing on the experience of infertility, IVF process, and social support	The brief, retrospective, self-report questionnaire	None stated	Collected data from three different programmes	(1) 77% reported infertility still painful concern at time of IVF (2) Loss of control is patients' most stressful dimension (3) Emotional strain major consideration influencing decision whether or not to repeat IVF	For many, IVF procedures are like emotional roller coaster on which women experience a wide range of emotions in a short period of time
Merari *et al.* (1992), USA	113 couples with mechanical and unexplained infertility applying for IVF treatment at the Hasharon Hospital	Prospective (multivariate)	Investigate concurrently the psychological and hormonal changes at three critical points during IVF treatment	(a) Baseline and procedural stress (b) DACL and STAI were administered at four different times along with hormone measurement. Personal Background Questionnaire was only employed during the first session (c) Two types: (1) Anxiety (2) Depression	(1) Personal Background Questionnaire (2) Lubin's Depression Adjective Check List (DACL) (3) STAI (4) Hormone measurement (cortisol and prolactin)	(1) Pregnancy	None	(1) Patients' anxiety and depression scores were significantly higher than the population norm ($P < 0.0001$, $P < 0.002$ respectively) (2) Psychological test scores and hormonal levels showed a similar pattern of change: increasing on oocyte retrieval day, decreasing on embryo transfer day, and rising again on pregnancy test day (3) During oocyte retrieval, conceiving women had higher depression scores than non-conceiving women (4) During embryo transfer, there was a reduction in anxiety and depression in both conceiving and non-concieving women	Success in IVF treatment may depend, in part, on differential modes of coping with anxiety and depression, involving hormonal or endorphin mediation
Merari *et al.* (2002), USA	113 childless couples who suffered from infertility of unknown or mechanical cause and who had been referred to the IVF unit at Hasharon Hospital	Cross-sectional (multivariate)	Examine spouse's emotional responses and attitudes to IVF treatment	(a) Procedural stress: emotional responses and attitude (b) Once (c) Two types: (1) Depression (2) Anxiety	(1) Personal Background Questionnaire (2) Lubin's Depression Adjective Checklist (DACL) (3) STAI (4) Olson's Family Adaptability and Cohesion Evaluation Scales (FACES)	(1) Oocytes aspirated (2) Embryo transfer (3) Pregnancy	Age, religion, adoption, cohesiveness, emotional reaction	(1) Women had significantly higher state and trait anxiety and depression than normative levels, irrespective of whether they were successful in conceiving (2) Husbands' of conceiving women scored higher on depression than husbands of non-conceiving women (3) High emotional responses to the treatment were positively associated with treatment success in women (OR 3.32, 95% CI 1.28–8.58, $P = 0.05$) and men (OR 7.15, 95% CI 1.87–27.4, $P = 0.03$)	Women showed higher state and trait anxiety and depression regardless of their treatment outcomes, whereas high emotional responses to the treatment were positively related with treatment success especially in men
Milad *et al.* (1998), USA	40 patients (all had positive pregnancy test) at the IVF programme in Northwestern Medical Faculty Foundation	Prospective (univariate)	Compare stress levels and hormonal samples in groups of patients undergoing IVF	(a) Procedural stress (b) Questionnaires and salivary sample collections were employed at 13 days, 27 subjects at 20 days and 13 subjects at 27 days after embryo transfer, and followed through delivery (c) Anxiety	(1) STAI (2) Pregnancy Anxiety Scale (PAS) (3) Perception of miscarriage scale (4) Physio-logical measurement (amylase, cortisol, progesterone, allopregnanolone, hCG, prolactin)	(1) Pregnancy (2) Miscarriage (adverse outcomes)	(1) Blood and saliva to measure stress and anxiety	(1) PAS scores were not significantly related to outcome and had a low correlation with STAI scores (2) A moderately high correlation was found between the subjects' estimation of the average chances of miscarriage and their own chances ($P < 0.001$)	It does not appear that high levels of anxiety and stress result in an adverse pregnancy outcome

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Mori *et al.* (1997), Japan	102 infertile women undergoing IVF at the University hospital from 1991 to 1993 (mean age = 34 years)	Cross-sectional (univariate)	Investigate psychological characteristics of women undergoing IVF	(a) Procedural stress (b) Once (scales and semi-structured interview) (c) Two types: (1) Anxiety (2) Process of accepting infertile and attitudes towards treatment	(1) STAI (2) Manifest anxiety scale (MAS)	None stated (treatment)	None	(1) The mean score of state anxiety for IVF women was 50, which was considerably higher than the standard score of 42 in Japanese females (2) Women undergoing IVF with higher levels of anxiety remained in the introversive stage of the grief process, had a more positive attitude toward treatment, and a pessimistic outlook on the possibility of successful pregnancy	Women with higher levels of anxiety have a pessimistic outlook on the possibility of successful pregnancy
Newton *et al.* (1990), Canada	947 women and 899 male partners consecutively admitted to an IVF programme in a university teaching hospital from 1984 to 1989 (1) Pre-IVF: 995 patients returned first two questionnaires (2) Post-IVF: 213 women and 184 men returned the last two questionnaires	Prospective (multivariate)	Assess immediate psychological impact of failed IVF	(a) Baseline and procedural stress Pre-IVF: (b) Questionnaires were mailed 3 months before the treatment, and a structured interview was conducted on assessment day. Post-IVF: Questionnaires were completed during the final hospital visit (3 weeks after the first IVF attempt) (c) Three types: (1) Anxiety (2) Appraisal (3) Depression	(1) Family Environment Scale (FES) (2) STAI (3) BDI (4) Life Appraisal Inventory (5) Life Satisfaction Questionnaire	None stated	Fertility history, a series of four two-factor (male vs female, child vs no child), sex, marital relationship	(1) After failed first cycle, both men and women showed increase in anxiety and depression ($P = 0.034$ for women, $P < 0.001$ for men) (2) Prevalence of both mild and moderate depression increased substantially in women (3) Women without children were a subgroup particularly vulnerable to the stress of failure	Predisposition towards anxiety, pre-IVF depressive symptoms, and fertility history were the most important predictors of emotional response
Phromyothi and Virutamasen (2003), Thailand	60 infertile couples at the infertile clinic in 2000 (age range 36–40 years)	Cross-sectional (univariate)	What are determinant factors and anxiety levels of infertile couples during IVF treatment?	(a) Procedural stress (b) Once (while waiting for treatment) (c) Two types: (1) Emotional disturbance (2) Anxiety	(1) Personal and Health Data Questionnaire (2) Cornell Medical Index (3) Determinant Factors of Anxiety	Treatment outcome and success	None	(1) Women had slightly higher anxiety than men (2) Determinants of anxiety: side-effects of infertility treatment, inadequate time to consult with the physician/-nurse, outcome of the infertility treatment, possibility of not succeeding	Study results serve as a guideline for improving better services and understanding between the physician and the patient
Reading *et al.* (1989), USA	37 women undergoing IVF (assessed at start of IVF cycle and following treatment) (mean age = 35.8 years)	Prospective (univariate)	Examine whether psychological state and coping styles affect IVF	(a) Baseline and procedural stress (b) Three times (at the start of their treatment cycle, treatment day 8, following outcome) (c) Six types: (1) Stress and arousal (2) Pleasantness/unpleasantness (3) Grief (4) Coping (5) Depression (6) Confusion	(1) GHQ (2) POMS (3) Scale to measure hassles and uplifts (4) Scale to assess subjective reactions to outcome	Treatment outcome	None	(1) No difference in psychological states according to treatment outcome ($P < 0.005$). (3) On the GHQ, 18% of manifested signs of clinical depression (4) POMS and stress measures increased over time	Extended follow-up on coping in women undergoing IVF is necessary, because women scoring higher in distress in the short term may have better long-term adjustment. At post-treatment, the IVF women show significantly higher scores on tension ($P < 0.05$), depression ($P < 0.005$), fatigue ($P < 0.005$), and confusion ($P < 0.005$)

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Sanders *et al.* (1999), Australia	90 women undergoing IVF at Concept fertility centre from 1990 to 1993 (age range from 23 to 43 years)	Cross-sectional (multivariate)	Women with different hostility scores will have different pregnancy success rates	(a) Baseline stress (b) Once (1–3 months prior to the treatment) (c) Two types: (1) Mood states (2) Anxiety	(1) POMS (2) STAI	Pregnancy	Age, prior pregnancy, body mass index, education, work, socioeconomic status, smoker, alcohol, coffee, tea, POMS scales	(1) Lower scores on the POMS agreeable–hostile scale, indicating greater hostility, were associated with a decreased risk of pregnancy (2) Neither state scale (POMS and STAI) appeared to have any association with pregnancy rates	The findings that full-time work and more hostile mood states are associated with reduced pregnancy rates conform to the original hypothesis that psychosocial stress reduces successful treatment outcomes. The findings that trait anxiety and depression are also related to treatment outcome further emphasize the importance of psychosocial factors but indicate that these relationships are complex
Smeenk *et al.* (2001), Netherlands	291 women who went to the university hospital and private hospitals for the first cycle of a new IVF/ICSI treatment from 1999 to 2000	Prospective (multivariate)	Clarify the role of anxiety and depression on assisted reproduction treatment outcomes	(a) Pre-existing (baseline) stress (b) Once (before the stimulation cycle) (c) (1) Anxiety (2) Depression:	(1) STAI (2) BDI	(1) Number of follicles (2) Number of embryos (3) Pregnancy	Age, number of previous pregnancies and State Anxiety	(1) A significant relationship was shown between baseline psychological factors and the probability of becoming pregnant after IVF/ICSI treatment, controlling for other factors (2) State anxiety had a slightly stronger correlation ($P = 0.001$) with treatment outcome than depression ($P = 0.03$)	Pre-existing psychological factors are independently related to treatment outcome in IVF/ICSI, and should therefore be taken into account in patient counselling
Stoleru *et al.* (1997), France	48 women and 32 spouses treated by IVF in a private infertility clinic	Prospective (multivariate)	Determine whether psychological factors have an influence on the outcome of the fertilization of IVF	(a) Baseline and procedural stress (b) STAI was consecutively completed starting 2 days before the day of oocyte retrieval and ending 2 days after embryo transfer. CPQ and Ways of Coping Checklist were employed the day before oocyte retrieval (c) Two types: (1) Anxiety (2) Coping	(1) Child Project Questionnaire (CPQ) (2) Ways of Coping Checklist (3) STAI	Fertilization	Women's age, number of previous IVF trials, type of infertility, type of ovarian stimulation, and length of treatment	(1) There was a significant overall time effect on STAI scores ($P < 0.01$): women had higher state anxiety scores after the feedback than before (2) Normal sperm, tubal lesions or occlusion, women's factor II of the CPQ (i.e. Perception of Marital Harmony in the Project to Conceive a Child) were found to be statistically significant predictors of fertilization ($P < 0.05$)	Women's perception of marital harmony in the Project to Conceive Child is a statistically significant predictor of the success of fertilization during IVF
Tarabusi *et al.* (2000), Italy	45 couples from the Assisted Reproduction Unit at a university hospital from 1993 to 1995. The couples were classed into 'success' or 'failure' group (patients' mean age = 36.1 years)	Cross-sectional (multivariate)	Evaluate the association between vulnerability to stress and treatment outcome in male partners of couples submitted to IVF	(a) Procedural stress (b) Scale was administered on the day of oocyte retrieval. Physiological measurements for baseline and after the testing (c) Three types: (1) Coping ability (2) Cognitive Dissonance (3) Psychological tension	(1) Stroop Color Word Conflict (2) Physiological measurement [systolic and diastolic blood pressure Heart rate (HR)]	Pregnancy	None	(1) The failure group showed a higher value for heart rate (50.6 ± 36.7 of percentage total change) than the success group (31.8 ± 16.9; $P = 0.006$) (2) No significant differences were found in the performance score of the Stroop Color Word in male partners of women becoming pregnant (success) or not (failure)	The study suggests that psychosocial interventions need to be focused on the couple, because both males and females might benefit from the psychosocial support and improve the probability of success of having a child

Table II. *Continued*

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Stress scales[b]	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Van Balen *et al.* (1996), Netherlands	Infertile couples from the IVF clinic of a university hospital (1) 45 IVF couples (mean age of women = 33.3 years, men = 34.5 years) (2) 35 formerly infertile couples without IVF (mean age of women = 31.6 years, mean age of men = 34.6 years) (3) 35 fertile control couples from neighborhood hospitals (mean age of women = 27.6 years, men = 30.9 years)	Cross-sectional (univariate)	Compared the experience of pregnancy and delivery among IVF parents	(a) Procedural stress: Psychological burden of fertility treatment (b) Once (c) Three types: (1) Physical burden (2) Psychological burden (3) Personal experience (enjoyment, exceptionality, stress)	(1) 5-point scale (2) Two 3-point scales	Treatment outcome	Two comparison groups	(1) Pregnancy complications were more frequently reported by IVF mothers and infertile mothers than fertile mothers. After controlling for age (IVF and infertile groups) there was no difference (3) IVF parents and infertile couples evaluated pregnancy as more stressful than fertile parents ($P < 0.05$). (4) IVF mothers experienced their delivery as more exceptional, while fathers thought that the pregnancy was more exceptional ($P < 0.05$)	IVF and infertile parents feel more stressful about their pregnancies than fertile parents, albeit they experienced delivery as more exceptional than fertile couples
Verhaak *et al.* (2001), Netherlands	207 women on first IVF or ICSI cycle from fertility department at a university and a regional hospital	Prospective (multivariate)	Determine differences in emotional status (anxiety and depression) and marital satisfaction in pregnant and non-pregnant women before and after their first cycle of IVF and ICSI	(a) Baseline and procedural stress (b) Twice (3–12 days before first treatment cycle and repeated 3 weeks after the pregnancy test) (c) Four types: (1) Anxiety (2) Depression (3) Mood (4) Marital satisfaction	(1) STAI (2) BDI (3) POMS (4) Maudsley Marital Questionnaire	Pregnancy	None	(1) At pretreatment, the women who became pregnant showed lower levels of depression than those who did not (2) It might be possible to identify a trend toward higher levels of state anxiety among women who did not become pregnant, compared with those who became pregnant (3) Higher levels of depression in non-pregnant women were due to a higher score on cognitive aspects of depression	Differences in emotional status between pregnant and non-pregnant women occurred before treatment and became more apparent after the first IVF and ICSI cycle
Yong *et al.* (2000), UK	37 women undergoing IVF at the Edinburgh Assisted Conception Unit in 1999	Prospective (univariate)	Identify the stages of IVF treatment where men are most vulnerable to psychological stress	(a) Baseline and procedural stress (b) Three times (before treatment, embryo transfer, and pregnancy test) (c) Five types: (1) Sensation seeking (2) Positive affect (3) Hostility (4) Depression (5) Anxiety	Mean Affect Adjective Check List (MAACL)	(1) Embryo transfer (2) Pregnancy	None	The hostility, depression, and state anxiety scores for visit 3 (before pregnancy) were higher than the corresponding scores for visits 1 and 2 (before treatment and embryo transfer) ($P < 0.001$) (2) No significant differences in the psychological stress experienced by the pregnant group vs the non-pregnant group	Psychological counselling should be targeted at women after embryo transfer and leading up to the pregnancy test

(a) timing of stress; (b) frequency; (c) type of stress.
STAI = State-Trait Anxiety Inventory; GHQ = General Health Questionnaire; KSP = Karolinska Scales of Personality; ABV = Amsterdamse Biografische Vragenlijst; UCL = Utrechtse Coping Vragenlijst; MMPI = Minnesota Multiphasic Personality Inventory; POMS = Bipolar Profile of Mood Status; BDI = Beck Depression Inventory; PANAS = Positive and Negative Affect Scale.

categories, smokers and non-smokers (Elenbogen *et al.*, 1991; Hughes *et al.*, 1992). The number of cigarettes was quantified per day (with number of years not specified) (Pattinson *et al.*, 1991; Hughes *et al.*, 1996; El-Nemr *et al.*, 1998; Klonoff-Cohen *et al.*, 2001a), as well as packs/day (Trapp *et al.*, 1986; Maximovich and Beyler, 1995), and pack-years (Van Voorhis *et al.*, 1996). Zitzmann *et al.* (2003) quantified smoking as cigarettes/day for ≥2 years, while Klonoff-Cohen *et al.* (2001a) ascertained number of cigarettes or cigars smoked per week during the subject's lifetime, as well as 1 year, 1 week, 1 day prior to and during the IVF procedure (Table I).

Smoking was only classified once at study entry (Harrison *et al.*, 1990; Maximovich and Beyler, 1995; El-Nemr *et al.*, 1998; Joesbury *et al.*, 1998; Zitzmann *et al.*, 2003) or after IVF treatment (Van Voorhis *et al.*, 1996) and not throughout the procedure, when habits could change markedly, resulting in misclassification of smokers and quitters. One additional study administered questionnaires twice (Hughes *et al.*, 1994), while Klonoff-Cohen *et al.* (2001a) administered questionnaires at three different time-points, specifically, at the initial clinic visit, during embryo transfer for women and sperm collection for the men, and after pregnancy outcome.

Table III. Studies investigating alcohol and IVF

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Questionnaires	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Klonoff-Cohen *et al.* (2003), USA	221 infertile couples undergoing IVF	Prospective multicentre study (multivariate)	To determine whether the amount and timing of female and male alcohol use during IVF and GIFT affect reproductive endpoints	(1) Type (mixed drinks, wine, beer, liquor) (2) Amount (drinking/days or week) (3) Time period (1 year, 1 month, 1 week, 1 day before and during week 1 of attempt)	Five self-administered questionnaires: (1) Women completed three questionnaires. During week 1 of the attempt, the week of the procedure, and at the pregnancy outcome (2) Men completed two questionnaires during week 1 of the attempt and at the time of sperm collection	(1) Live birth (2) Sperm (motility, morphology, count) (3) Oocyte retrieval (4) Fertilization (5) Pregnancy (6) Miscarriage (7) Multiple gestations	Female or male tobacco smokers, age, race, years of schooling, parity, types of infertility, types of assisted reproduction procedure, and number of assisted reproduction attempts	Alcohol was associated with: (1) 13% decrease in number of oocytes aspirated for 1 additional drink per day, 1 year before the IVF or GIFT attempt (CI 0.77–0.98, $P = 0.02$) (2) 2.86 times the risk of not achieving a pregnancy for 1 month before the attempt (CI 0.99–8.24, $P = 0.05$) (3) 2.21 times increased risk of miscarriage for 1 week before the procedure (CI 1.09–4.49, $P = 0.03$) Males: (1) 1 additional drink/-day increased the risk of not achieving a live birth by 2.28 (CI 1.08–4.80, $P = 0.03$) to 8.32 (CI 1.82–37.97, $P < 0.01$) times, depending on the time-period (2) Beer affected live births (OR 5.49 − 45.64)	This is the first study to report an association between both female and male alcohol consumption and IVF outcomes (oocytes aspirated, pregnancy, miscarriage, live births)

(a) Male and female caffeine intake was converted to exact amount in milligrams.
GIFT = gamete intra-Fallopian transfer; OR = odds ratio; CI = confidence interval.

Furthermore, the contribution of the male partner's smoking history, although included in four studies (Hughes and Brennan, 1996; Joesbury *et al.*, 1998; Klonoff-Cohen *et al.*, 2001a; Zitzmann *et al.*, 2003), was entirely omitted in the majority of studies (Trapp *et al.*, 1986; Weiss and Eckert, 1989; Harrison *et al.*, 1990; Elenbogen *et al.*, 1991; Rosevear *et al.*, 1992; Sterzik *et al.*, 1996; Weigert *et al.*, 1999; Crha *et al.*, 2001).

Existence of multivariate analyses

Potential confounders such as age, race, education, type of assisted reproduction procedure, parity, type of infertility, and number of IVF attempts, estradiol levels, endometrial thickness, and sperm parameters were not usually adjusted for in any of the studies, apart from four (Hughes *et al.*, 1994; Joesbury *et al.*, 1998; Klonoff-Cohen *et al.*, 2001a; Zitzmann *et al.*, 2003), and only one study (Klonoff-Cohen *et al.*, 2001a) adjusted for other lifestyle habits (e.g. marijuana and recreational drug use, and alcohol consumption) (Table I).

Body of evidence for effect of smoking on IVF

In summary, despite the variations between studies, there was compelling evidence that smoking had a negative influence on IVF outcome (Harrison *et al.*, 1990; Elenbogen *et al.*, 1991; Pattinson *et al.*, 1991; Rosevear *et al.*, 1992; Van Voorhis *et al.*, 1996; Maximovich and Beyler, 1995; Feichtinger *et al.*, 1997; Augood *et al.*, 1998; El-Nemr *et al.*, 1998; Joesbury *et al.*, 1998; Crha *et al.*, 2001; Klonoff-Cohen *et al.*, 2001a; Zitzmann *et al.*, 2003).

Mechanism

It has been noted that the zona pellucida of oocytes and embryos of active and passive smokers were significantly thicker than those of non-smokers, and did not become thinner after 48 h in culture (Shiloh *et al.*, 2004). Smoking may be one of the factors that interfere with fertility (Shiloh *et al.*, 2004).

Table IV. Studies investigating caffeine and IVF

Reference	Study sample (no., source of sample, type of infertility, age, race)	Study design	Objectives	Lifestyle habits[a]	Questionnaires	IVF outcomes	Confounders	Results (type of analyses)	Conclusions
Klonoff-Cohen *et al.* (2002), USA	221 infertile couples undergoing IVF	Prospective multicentre study (multivariate)	To investigate the effect of caffeine consumption by men on success rates of IVF	(1) Type (caffeinated or decaffeinated coffee, tea, soft drinks, cocoa drinks, milk chocolate, and dark chocolate) (2) Amount (number of cups, glasses or ounces/day and/or week) of caffeine during various time periods (3) Timing (usual lifetime caffeine intake, week of initial clinic visit, week before IVF procedure, and week of the IVF procedure)	Five self-administered questionnaires: (1) Women completed three questionnaires. During week 1 of the attempt, the week of the procedure, and at the pregnancy outcome (2) Men completed two questionnaires during week 1 of the attempt and at the time of sperm collection	(1) Sperm profile (2) Oocytes retrieval (3) Fertilization (4) Embryo transfer (5) Pregnancy (6) Multiple gestations (7) Miscarriage (8) Live birth delivery (9) Infant gestational age (10) Infant birthweight	Smoking and alcohol use, age, race, years of school, parity, types of infertility, types of procedure, and number of good quality embryos transferred	Female: (1) Usual caffeine intake of >2–50 and 50 mg/day vs 0–2 mg/day yielded OR for miscarriage of 19.8 (CI 1.3–300.9) and 10.5 (CI 0.9–125.3) respectively (2) Usual caffeine intake of >50 mg/day during week of initial visit decreased infant gestational age by 3.8 (CI −6.0 to −0.7) or 3.5 (−6.7 to −0.3) weeks. Men: (1) Usual caffeine intake or intake "usually" or during week of initial clinic visit by an extra 100 mg/day increased risk of multiple gestations by 2.2 (CI 0.9–5.0, $P = 0.02$) and 3.0 (CI 1.2–7.4, $P = 0.02$) respectively	This is the first study to report any effect of caffeine on live births, gestational age, and multiple gestations

(a) Male and female caffeine intake was converted to exact amount in milligrams.
OR = odds ratio; CI = confidence interval.

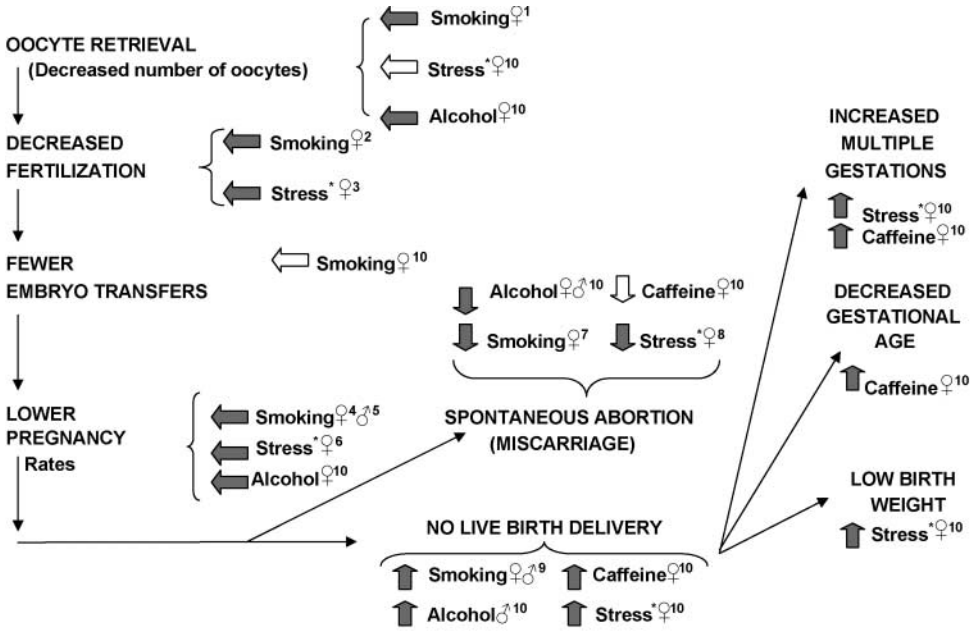
Stress and IVF

Infertility is often described as the most stressful event in the lives of most couples (Freeman *et al.*, 1985). The IVF procedure is stressful because of daily hormone injections, blood samples, laparoscopic surgery, and the possibility of pregnancy failure; however, the most traumatic aspects are waiting to see if fertilization was successful, undergoing oocyte retrieval (Demyttenaere *et al.*, 1991) and embryo transfer (Johnston *et al.*, 1987; Siebel and Levine, 1987; Baram *et al.*, 1988; Callan and Hennessey, 1988; Demyttenaere *et al.*, 1991; Connolly *et al.*, 1993), and not achieving a pregnancy after a prolonged treatment (Baram *et al.*, 1988; Connolly *et al.*, 1993).

A total of 344 abstracts was retrieved from the eight databases, and 302 abstracts were excluded based on eligibility criteria (e.g. meeting abstracts, book chapters, dissertation abstracts, review articles, animal studies, GIFT and infertility as endpoints, oxidative, sperm, and heat stress, psychoendocrinology, interventions and intervention counselling, support groups, ethical issues, and did not address primary question). This resulted in 48 articles being reviewed, with a further three articles being excluded because they were written in German, Chinese and Czech, and two articles being excluded because the sample sizes were <25. A total of 43 articles was included for the final review.

Appropriate study design

There was a total of four retrospective studies (Mahlstedt *et al.*, 1987; Leiblum *et al.*, 1987; Beutel *et al.*, 1999; Csemiczky *et al.*, 2000; Hammarberg *et al.*, 2001), 24 prospective studies (Johnston *et al.*, 1987; Harrison *et al.*, 1987; Reading *et al.*, 1989; Newton *et al.*, 1990; Demyttenaere *et al.*, 1991, 1992, 1994, 1998; Merari *et al.*, 1992; Boivin and Takefman, 1995; Harlow *et al.*, 1996; Facchinetti *et al.*, 1997; Stoleru *et al.*, 1997; Boivin *et al.*, 1998; Milad *et al.*, 1998; Yong *et al.*, 2000; Gallinelli *et al.*, 2001; Klonoff-Cohen *et al.*, 2001b; Smeenk *et al.*, 2001; Verhaak *et al.*, 2001; Hsu and Kuo, 2002; Hjelmstedt *et al.*, 2003; Lovely *et al.*, 2003), and 15 cross-sectional studies (Freeman *et al.*, 1985; Callan *et al.*, 1988; Callan and Hennessey, 1988; Chan *et al.*, 1989; Collins *et al.*, 1992; Baluch *et al.*, 1993; Van Balen *et al.*, 1996; Bringhenti *et al.*, 1997; Mori *et al.*, 1997; Sanders and Bruce, 1999; Kee *et al.*, 2000; Tarabusi *et al.*, 2000; Lee *et al.*, 2001; Merari *et al.*, 2002; Phromyothi and Virutamasen, 2003) on stress and IVF (Table II).



KEY: = females, =males; ⇦ : Findings are statistically significant.

*Stress (Speilberger State-Trait Anxiety Inventory, Infertility Reaction Scale, Positive Affect Negative Affect, Expectation of Pregnancy, Profile of Mood States, Zung Depression Scale, Back Depression Inventory)

[1]El-Nemar *et al.*, 1998; Weigert *et al.*, 1999; Klonoff-Cohen *et al.*, 2001; Zitzman *et al.*, 2003.

[2]Elenbogen *et al.*, 1991; Rosevear *et al.*, 1992; Zenzes *et al.*, 1997 (only older); Weigert *et al.*, 1999; Crha *et al.*, 2001; Zitzman *et al.*, 2003.

[3]Harrison *et al.*, 1987; Johnston *et al.*, 1987; Stoleru *et al.*, 1997; Klonoff-Cohen *et al.*, 2001.

[4]Harrison *et al.*, 1990; Feichtinger *et al.*, 1997; Augood *et al.*, 1998; Klonoff-Cohen *et al.*, 2001.

[5]Joesbury *et al.*, 1998; Zitzman *et al.*, 2003.

[6]Demyttenaere *et al.*, 1994; Boivin and Takefman., 1995; Facchinettie *et al.*, 1997; Demyttenaere *et al.*, 1998; Sanders *et al.*, 1999; Csemiczky *et al.*, 2000; Kee *et al.*, 2000; Klonoff-Cohen *et al.*, 2001; Smeenk *et al.*, 2001.

[7]Harrison *et al.*, 1990; Pattinson *et al.*, 1991; Maximovich and Beyler, 1995; Hughes and Brennan, 1996.

[8]Demyttenaere *et al.*, 1992.

[9]Pattinson *et al.*, 1991; Klonoff-Cohen *et al.*, 2001.

[10]Klonoff-Cohen *et al.*, 2001, 2002, 2003.

Figure 1. Female and male lifestyle habits and in vitro fertilization.

Sample size and method of selection and description of subjects and comparison group

The sample size ranged from a total of 37 patients (Reading *et al.*, 1989; Yong *et al.*, 2000) to 500 subjects (Harrison *et al.*, 1987). All studies recruited women attending IVF clinics at university-affiliated or private clinics. A total of seven studies used fertile women as the comparison group (Baluch *et al.*, 1993; Harlow *et al.*, 1996; Van Balen *et al.*, 1996; Bringhenti *et al.*, 1997; Csemiczky *et al.*, 2000; Kee *et al.*, 2000; Hjelmstedt *et al.*, 2003), while the remainder had no control group (Table II).

Existence of standardized IVF outcomes

The majority of studies on stress and IVF explored one or two IVF outcomes, and the majority concentrated on achieving a pregnancy (Demyttenaere *et al.*, 1992, 1994, 1998; Merari *et al.*, 1992, 2002;, Boivin and Takefman, 1995; Harlow *et al.*, 1996; Facchinetti *et al.*, 1997; Boivin *et al.*, 1998; Milad *et al.*, 1998; Sanders *et al.*, 1999; Csemiczky *et al.*, 2000; Kee *et al.*, 2000; Tarabusi *et al.*, 2000; Yong *et al.*, 2000; Smeenk *et al.*, 2001; Verhaak *et al.*, 2001; Hjelmstedt *et al.*, 2003; Lovely *et al.*, 2003). The remaining studies investigated the effects of stress on the number of oocytes aspirated (Demyttenaere *et al.*, 1991; Merari *et al.*, 1992; Boivin *et al.*, 1998), fertilization (Harrison *et al.*, 1987; Johnston *et al.*, 1987; Smeenk *et al.*, 2001; Stoleru *et al.*, 1997; Boivin *et al.*, 1998), embryo transfer (Johnston *et al.*, 1987; Demyttenaere *et al.*, 1991; Merari *et al.*, 1992; Boivin and Takefman, 1995; Boivin *et al.*, 1998; Yong *et al.*, 2000), implantation rates (Gallinelli *et al.*, 2001), spontaneous abortion rates (Demyttenaere *et al.*, 1991), and number of positive pregnancy outcomes (Milad *et al.*, 1998). One other study (Klonoff-Cohen *et al.*, 2001b) examined the effect of stress on six IVF outcomes, including the number of oocytes aspirated, fertilization, embryo transfer, achievement of a pregnancy, spontaneous abortion, and live birth delivery, as well as neonatal characteristics (e.g. low birthweight, gestational age, and multiple gestations) (Table II).

A total of 19 studies indicated no specific IVF endpoints, other than treatment-related (Leiblum *et al.*, 1987; Chan *et al.*, 1989; Baluch *et al.*, 1993; Bringhenti *et al.*, 1997; Mori *et al.*, 1997; Beutel *et al.*, 1999; Lee *et al.*, 2001), IVF treatment outcomes (Reading *et al.*, 1989; Van Balen *et al.*, 1996; Phromyothi and Virutamasen, 2003), continued or stopped IVF (Callan *et al.*, 1988), number of attempts (Callan and Hennessey, 1988), pre-

and post-IVF (Newton *et al.*, 1990), and nothing stated in the articles (Freeman *et al.*, 1985; Mahlstedt *et al.*, 1987; Collins *et al.*, 1992; Kee *et al.*, 2000; Hammarberg *et al.*, 2001; Hsu and Kuo, 2002) (Table II).

Use of standardized instruments and/or laboratory samples to verify lifestyle habits

The most common stress instrument utilized in the literature on stress and IVF was Spielberger State-Trait Anxiety Inventory (STAI). To date, 15 international studies and four studies in the USA have utilized the STAI to examine the effects of anxiety on oocyte retrieval and embryo transfer (Johnston *et al.*, 1987; Demyttenaere *et al.*, 1991; Merari *et al.*, 1992; Boivin and Takefman, 1995; Merari *et al.*, 2002), achievement of implantation (Gallinelli *et al.*, 2001), fertilization (Johnston *et al.*, 1987; Stoleru *et al.*, 1997; Smeenk *et al.*, 2001), pregnancy (Chan *et al.*, 1989; Demyttenaere *et al.*, 1992, 1994; Merari *et al.*, 1992, 2002; Boivin and Takefman, 1995; Harlow *et al.*, 1996; Facchinetti *et al.*, 1997; Milad *et al.*, 1998; Sanders and Bruce, 1999; Csemiczky *et al.*, 2000; Kee *et al.*, 2000; Smeenk *et al.*, 2001; Verhaak *et al.*, 2001; Hjelmstedt *et al.*, 2003; Lovely *et al.*, 2003), spontaneous abortions (Demyttenaere *et al.*, 1992), and adverse outcomes (Milad *et al.*, 1998) with IVF (Figure 1 and Table II).

Contradictory results were reported among studies examining state anxiety and IVF. Anxiety apparently increased during both oocyte retrieval and embryo transfer (Demyttenaere *et al.*, 1991) in one study, yet decreased during embryo transfer day and rose again on pregnancy test day in another study (Merari *et al.*, 1992). Women undergoing IVF had significantly higher state anxiety than those not undergoing treatment (Harlow *et al.*, 1996), whereas another study found that anxiety did not influence the chance of pregnancy (Harlow *et al.*, 1996; Milad *et al.*, 1998) or miscarriage rates (up to <20 weeks) (Milad *et al.*, 1998).

The other 27 studies investigated depression [11 international (Chan *et al.*, 1989; Demyttenaere *et al.*, 1991, 1992, 1994, 1998; Beutel *et al.*, 1995; Bringhenti *et al.*, 1997; Kee *et al.*, 2000; Smeenk *et al.*, 2001; Verhaak *et al.*, 2001; Hsu and Kuo, 2002), four in the USA (Leiblum *et al.*, 1987; Reading *et al.*, 1989; Merari *et al.*, 1992, 2002)], marital status [six international (Newton *et al.*, 1990; Boivin and Takefman, 1995; Bringhenti *et al.*, 1997; Hammarberg *et al.*, 2001; Verhaak *et al.*, 2001; Hjelmstedt *et al.*, 2003), one in the USA (Leiblum *et al.*, 1987)], coping styles [nine international (Callan *et al.*, 1988; Callan and Hennessey, 1988; Demyttenaere *et al.*, 1991, 1992, 1994, 1998; Stoleru *et al.*, 1997; Lee *et al.*, 2001; Hsu and Kuo, 2002), three in the USA (Freeman *et al.*, 1985; Reading *et al.*, 1989; Klonoff-Cohen *et al.*, 2001] (Table II).

Eight studies measured stress hormones in conjunction with psychological scales (Demyttenaere *et al.*, 1991, 1992, 1994; Harlow *et al.*, 1996; Merari *et al.*, 1992; Milad *et al.*, 1998; Csemiczky *et al.*, 2000; Lovely *et al.*, 2003), whereas one study did not employ any psychological scales (Harrison *et al.*, 1987). A total of two studies (Klonoff-Cohen *et al.*, 2001b; Lee *et al.*, 2001) used the Perceived Stress Scale; however, only one study administered it before and after hormone use (Klonoff-Cohen *et al.*, 2001b). Furthermore, five studies employed the Bipolar Profile of Mood Status (POMS) (Leiblum *et al.*, 1987; Reading *et al.*, 1989; Sanders *et al.*, 1999; Klonoff-Cohen *et al.*, 2001b; Hsu and Kuo, 2002), and three utilized the Infertility Reaction Scale (Collins *et al.*, 1992; Klonoff-Cohen *et al.*, 2001b; Hjelmstedt *et al.*, 2003). Finally, the Network Resource Scale, the Positive Negative Affect Scale (PANAS), and Expected Likelihood of Achieving a Pregnancy Scale were used in only one study in conjunction with five other scales (Klonoff-Cohen *et al.*, 2001b) (Table II).

Existence of multivariate analyses

A total of 13 studies employed multivariate analyses and adjusted for potential confounders (Callan *et al.*, 1988; Newton *et al.*, 1990; Collins *et al.*, 1992; Boivin and Takefman, 1995; Facchinetti *et al.*, 1997; Bringhenti *et al.*, 1997; Stoleru *et al.*, 1997; Boivin *et al.*, 1998; Sanders *et al.*, 1999; Klonoff-Cohen *et al.*, 2001b; Hsu and Kuo, 2002; Merari *et al.*, 2002; Hjelmstedt *et al.*, 2003) (Table II). Only two studies adjusted for other lifestyle habits, specifically smoking, alcohol, and caffeine (Sanders *et al.*, 1999; Klonoff-Cohen *et al.*, 2001b), and the latter study also adjusted for recreational drugs.

Limitations of studies investigating stress and IVF

Potential limitations of studies evaluating the effect of stress on IVF include: (i) not taking more than one psychological or psychosocial measure into account (Harrison *et al.*, 1987; Mahlstedt *et al.*, 1987; Baluch *et al.*, 1993; Yong *et al.*, 2000), (ii) not examining IVF endpoints beyond pregnancy, specifically live birth deliveries and neonatal outcomes (Freeman *et al.*, 1985; Harrison *et al.*, 1987; Johnston *et al.*, 1987; Leiblum *et al.*, 1987; Mahlstedt *et al.*, 1987; Callan *et al.*, 1988; Callan and Hennessey, 1988; Chan *et al.*, 1989; Reading *et al.*, 1989; Newton *et al.*, 1990; Demyttenaere *et al.*, 1991, 1992, 1994; Collins *et al.*, 1992; Baluch *et al.*, 1993; Boivin and Takefman, 1995; Harlow *et al.*, 1996; Van Balen *et al.*, 1996; Bringhenti *et al.*, 1997; Facchinetti *et al.*, 1997; Mori *et al.*, 1997; Stoleru *et al.*, 1997; Boivin *et al.*, 1998; Milad *et al.*, 1998; Beutel *et al.*, 1999; Sanders *et al.*, 1999; Csemiczky *et al.*, 2000; Kee *et al.*, 2000; Tarabusi *et al.*, 2000; Yong *et al.*, 2000; Gallinelli *et al.*, 2001; Hammarberg *et al.*, 2001; Lee *et al.*, 2001; Smeenk *et al.*, 2001; Verhaak *et al.*, 2001; Hsu and Kuo, 2002; Merari *et al.*, 2002; Hjelmstedt *et al.*, 2003; Lovely *et al.*, 2003; Phromyothi and Virutamasen, 2003), apart from one study (Klonoff-Cohen *et al.*, 2001b), (iii) not differentiating procedural stress versus lifetime stress in results, apart from seven studies (Johnston *et al.*, 1987; Newton *et al.*, 1990; Harlow *et al.*, 1996; Stoleru *et al.*, 1997; Yong *et al.*, 2000; Klonoff-Cohen *et al.*, 2001b; Verhaak *et al.*, 2001), (iv) having small sample sizes ($n = 40$) (Demyttenaere *et al.*, 1991, 1992; Boivin and Takefman, 1995; Gallinelli *et al.*, 2001), high drop-out rates, and retrospective or cross-sectional designs that measure stress at one time-point (Freeman *et al.*, 1985; Callan *et al.*, 1988; Callan and Hennessey, 1988; Chan *et al.*, 1989; Collins *et al.*, 1992; Baluch *et al.*, 1993; Van Balen *et al.*, 1996; Bringhenti *et al.*, 1997; Mori *et al.*, 1997; Sanders *et al.*, 1999; Kee *et al.*, 2000; Tarabusi *et al.*, 2000; Lee *et al.*, 2001; Merari *et al.*, 2002; Phromyothi and Virutamasen, 2003), (v) recruiting only one race, except for one study (Klonoff-Cohen *et al.*, 2001b), and (vi) not considering the independent effect of male stress on IVF

outcomes aside from three studies (Harrison *et al.*, 1987, Tarabusi *et al.*, 2000; Klonoff-Cohen *et al.*, 2001b).

Body of evidence for the effect of stress on IVF

The evidence that psychological stress during treatment was associated with negative IVF outcomes is suggestive but insufficient due to the heterogeneity of studies, particularly with reference to stress instruments and IVF endpoints (Harrison *et al.*, 1987; Johnston *et al.*, 1987; Leiblum *et al.*, 1987; Mahlstedt *et al.*, 1987; Callan *et al.*, 1988; Chan *et al.*, 1989; Newton *et al.*, 1990; Demyttenaere *et al.*, 1991, 1992, 1994; Harlow *et al.*, 1996; Van Balen *et al.*, 1996; Boivin *et al.*, 1998; Milad *et al.*, 1998; Kee *et al.*, 2000; Merari *et al.*, 1992, 2002; Yong *et al.*, 2000; Csemiczky *et al.*, 2000; Hammarberg *et al.*, 2001; Lee *et al.*, 2001; Verhaak *et al.*, 2001; Hjelmstedt *et al.*, 2003; Phromyothi and Virutamasen, 2003). In contrast, the emotional impact by IVF was not apparent during IVF treatment (Bringhenti *et al.*, 1997; Lovely *et al.*, 2003).

Mechanism

Psychological stress may diminish success rates, possibly by one of the following mechanisms: hypothalamic dysfunction either by neurotransmitting alterations, catecholamine depletion, or interference with hypothalamic receptors for neurotransmitters. The exact mechanism by which stress interferes with the hypothalamic–pituitary–gonadal axis is not clearly understood (Edelmann, 1990). Progesterone and cortisol, the neuroendocrine measures of stress, may provide potential pathways through which stress could affect IVF outcome (Boivin and Takefman, 1996). Future studies should measure plasma and follicular levels of stress hormones such as prolactin and cortisol to clarify the role of these hormonal mechanisms, and determine the neuroendocrine and physiological pathways that mediate an effect on IVF outcomes (Rubinow and Roca, 1995).

Alcohol and IVF

Female and male alcohol consumption and IVF

Although studies have evaluated the effect of tobacco on IVF, the effects of alcohol consumption have only been indirectly studied as a potential confounder of smoking (Hughes *et al.*, 1992).

A total of 324 abstracts was retrieved from the eight databases, and 323 abstracts were excluded based on eligibility criteria (e.g. meeting abstracts, case reports, comments, no human data, semen/oocyte donors or donations, female fecundity as an endpoint, alcohol in fertile medium, cryopreservation, did not address primary question, did not have any endpoints). This resulted in one article being reviewed.

Only one study has examined female and male alcohol consumption as a primary risk factor for IVF (Klonoff-Cohen *et al.*, 2003). Female alcohol consumption was associated with a decrease in oocyte retrieval (OR 0.87, CI 0.77–0.98, $P = 0.02$), pregnancy (OR 2.86, CI 0.99–8.24, $P = 0.05$), and increased risk of miscarriage (OR 2.2, CI 1.09–4.49, $P = 0.03$) (Figure 1 and Table III).

Men who drank ~1 drink during any time period increased the risk of experiencing spontaneous miscarriages, compared with men who did not drink 1 month before the IVF attempt (OR 2.7, CI 1.00–7.27, $P = 0.05$), or up to 1 week before sperm collection (OR 38.04, CI 3.30–438.56, $P = 0.01$) (Klonoff-Cohen *et al.*, 2003) (Figure 1 and Table III). In addition, for men, one additional can of beer per day decreased the risk of a live birth by 5.49 to 45 times (CI 1.11–27.18, $P = 0.04$), depending on the time of consumption (Klonoff-Cohen *et al.*, 2003) (Figure 1 and Table III).

Body of evidence for effect of alcohol on IVF

The findings of this one study require confirmation in future, multiple, prospective studies. The evidence for an association between alcohol and IVF is inadequate and unknown at this time due to the paucity of published articles.

Mechanism

In mice, exposure to alcohol had a similar action on the meiotic spindle apparatus during the estrous cycle before conception, and induced chromosome segregation errors in the ovulated oocyte. The successful fertilization of such oocytes consequently resulted in the production of aneuploid embryos, which had a very high chance of being spontaneously aborted during the first trimester of pregnancy (Kaufman, 1997).

A potential biological effect of alcohol on the male gamete was demonstrated in the mouse model. Chronic biparental beer intake had a noxious effect on implantation in mice, manifested by delayed attachment of blastocysts, absence of the decidual reaction, and resynchronization of the implantation process (Fazakas-Todea, 1995).

Caffeine and IVF

Female and male caffeine consumption and IVF

In assisted reproductive technique studies, caffeine was added in *in vitro* medium to stimulate hamster sperm motility. The results were inconsistent. The addition of caffeine to medium increased motility of cryopreserved sperm (Barkay *et al.*, 1977; Harrison, 1978; Aitken *et al.*, 1983; Hammitt *et al.*, 1989), reduced percentage of penetrated oocytes (Hammitt *et al.*, 1989), and decreased fertilizing ability and embryonic development (Imoedemhe *et al.*, 1992).

A total of 95 abstracts was retrieved from the databases, and 94 abstracts were excluded based on eligibility criteria (e.g. meeting abstracts, case reports, comments, animal data, caffeine in fertile medium, caffeine added to frozen–thawed, human semen as an endpoint, motility of preserved sperm as an endpoint, *in vitro* caffeine treatments, did not address primary question, did not have any IVF endpoints). This resulted in one article being included for review.

There is only one study to date that has investigated the effect of caffeine consumption by men and women on success rates of IVF (Klonoff-Cohen *et al.*, 2002). In this study, female caffeine intake had a profound effect on miscarriages [OR ranging from 19.8 (CI 1.3–300.9) to 6.2 (CI 0.9–40.8) depending on the amount and timing of consumption], not achieving a live birth [OR 2.9 (CI 1.1–7.5, $P = 0.01$) − 3.9 (CI 1.3–11.6, $P = 0.01$) depending on timing and amount of caffeine], and infant gestational age [OR decreases of 3.5 (CI − 6.7–0.3, $P = 0.10$) to 3.8 (CI − 6.9 to − 0.7, $P = 0.06$) weeks based on

timing] (Klonoff-Cohen *et al.*, 2002) (Figure 1 and Table IV). Male caffeine intake did not affect any sperm parameters, IVF endpoints, or neonatal characters (Klonoff-Cohen *et al.*, 2002).

Body of evidence for effect of caffeine on IVF

The findings of this one study require confirmation in several new prospective studies. The evidence for an association between caffeine and IVF is inadequate at present due to the scarcity of studies.

Mechanism

There are several biological pathways by which caffeine could affect female reproduction. It could affect ovulation through alterations in hormone levels. Caffeine consumption is inversely correlated with levels of estradiol in pregnant women (Hatch and Bracken, 1993) and positively correlated with levels of sex hormone-binding globulin (Hatch and Bracken, 1993). Caffeine decreases plasma levels of prolactin in non-pregnant, healthy women (Casas *et al.*, 1989), and may inhibit ovulation or corpus luteum function (Bolumar *et al.*, 1997).

What is known and unknown

Figure 1 shows what is currently known about female and male lifestyle habits and IVF. There is compelling evidence that smoking has a negative influence on IVF outcomes (i.e. oocyte retrieval, fertilization, embryo transfer, pregnancy, live births, and spontaneous abortion), whereas for stress, the evidence is suggestive of negative IVF outcomes (i.e. oocyte retrieval, fertilization, pregnancy, spontaneous abortion, live births, multiple gestation, low birthweight) but insufficient due to the heterogeneity of studies. The body of evidence for the effects of alcohol and caffeine on IVF is inadequate, and therefore unknown, due to the scarcity of studies. A final avenue of exploration will be to determine whether there is an indirect effect of lifestyle habits on infants as they progress to children, teenagers, and adults.

Future studies

There is a need for methodologically sound studies that: (i) investigate the most important IVF outcomes, specifically healthy live birth delivery and neonatal characteristics, (ii) consider lifetime versus procedural timing of the lifestyle habit, (iii) determine the quantity, frequency, and duration of the lifestyle habit, and which standardized instruments or samples are used, (iv) investigate the combination of two or more lifestyle habits, (v) separate the male versus female role, (vi) include a comparison group, (vii) address the lack of standardization of semen analyses and sperm processing methods, (viii) adjust for potential confounders (i.e. type of ovarian stimulation, use of fresh versus frozen–thawed embryos, and other lifestyle habits), (ix) collect multiple samples of cotinine, blood alcohol, cortisol and paraxanthine levels (primary metabolite of caffeine) throughout the procedure, (x) obtain an adequate sample size and good follow-up rates, (xi) employ a longitudinal design to follow patients at the initial clinic visit, throughout the IVF procedure, pregnancy and delivery, and (xii) identify underlying mechanisms attributable to each lifestyle habit and endpoint of IVF.

Summary

There are currently 19 237 articles cited in Index Medicus in October 2004 dealing with IVF; however, only a few of them have examined the effect of one specific lifestyle habit on IVF.

The imperative to constantly improve IVF success rates is the engine that drives the field of reproductive endocrinology (Van Blerkom and Gregory, 2004). Understanding the effects of lifestyle habits on IVF may help create guidelines for clinicians, increase success rates, and provide a forceful impetus for both men and women undergoing assisted reproductive techniques to modify or abstain from negative lifestyle habits. By integrating laboratory-related (i.e. technical) aspects of the procedure with patient characteristics (e.g. lifestyle habits, maternal age, aetiology and duration of infertility, and parity), one will obtain a more complete understanding of the importance and inter-relatedness of both factors on IVF.

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