European Society of Human Reproduction and Embryology

COURSE 6

What is new? Where are we going?

Special Interest Group Psychology and Counselling

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Course 6 - Pre-congress course organised by the Special Interest Group Psychology and Counselling

"What's new? Where are we going?"

PROGRAM

Course coordinators: J. Boivin (UK) and J. Bitzer (CH)

Course description: The integration of psychology into reproductive medicine is a continuing process, and in recent years important research and clinical studies as well as guidelines for best practice have been published promoting this integration. In light of this constantly evolving process, the aim of the present course is to update current knowledge in key areas and provide future directions for clinical services and research activities.

Update 1: Why does stress make a difference to conception?

09.00 - 10.00 How do psychosocial factors impact IVF/GIFT success rates? **H. Klonoff-Cohen (USA)**
10.00 - 10.30 Discussion

10.30 - 11.00 Coffee break

Update 2: Managing psychosocial services in fertility clinics

11.00 - 11.45 Psychosocial interventions in infertility: What works and what doesn't? - **T. Wischmann (D)**

11.45 - 12.15 How do we assess our [own] effectiveness as practitioners? – **J. Boivin (UK)**
12.15 - 12.30 Discussion

12.30 - 13.30 Lunch

Update 3: Follow-up of people using fertility services

13.30 - 14.15 Follow-up of children conceived with fertility treatment – **F. Rice (UK)**
14.15 - 14.30 Discussion

14.30 - 15.15 Transition to biological childlessness - **J. Daniluk (CND)**
15.15 - 15.30 Discussion

15.30 - 16.15 Outcomes for families using donated gametes in the current context of greater openness - **P. Thorn (D)**
16.15 - 16.30 Discussion

16.30 - 17.00 General discussion and future directions

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

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There is no greater tribute to the importance and efficacy of IVF than the fact that $>1 \times 10^6$ 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, $\sim 1 \times 10^6$ 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.

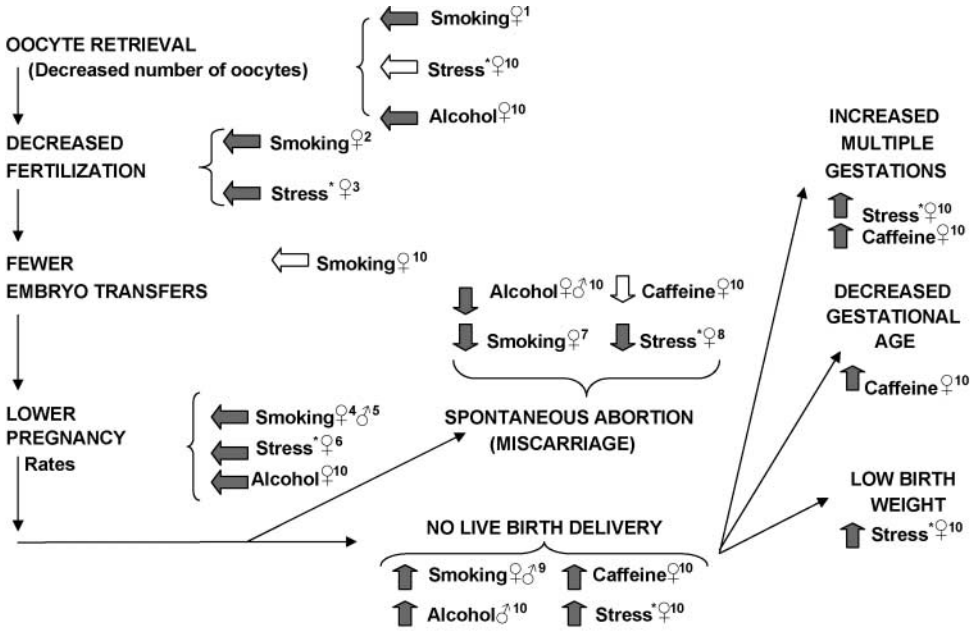
Stress and IVF

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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References

Aitken RJ, Best F, Richardson DW, Schats R and Simm G (1983) Influence of caffeine on movement characteristics, fertilizing capacity, ability to penetrate cervical mucus of human spermatozoa. J Reprod Fertil 67,19–27.

Augood C, Duckitt K and Templeton A (1998) Smoking and female infertility: review and meta-analysis. Hum Reprod 13,1532–1539.

Baluch B, Manyande A, Aghssa MM and Jafari R (1993) Failing to conceive with in vitro fertilization. Psychol Rep 72,1107–1110.

Baram E, Tourtelot E and Muechler KE (1988) Psychosocial adjustment following unsuccessful in vitro fertilization. J Psychosom Obstet Gynaecol 9,181–190.

Barkay J, Zuckerman H, Sklan D and Gordon S (1977) Effect of caffeine on increasing the motility of frozen human sperm. Fertil Steril 28,175–177.

Beutel M, Kupfer J, Kirchmeyer P, Kehde S, Kohn FM, Schroeder-Printzen I, Gips H, Herrero HJ and Weidner W (1999) Treatment-related stresses and depression in couples undergoing assisted reproductive treatment by IVF or ICSI. Andrologia 31,27–35.

Boivin J and Takefman JE (1995) Stress level across stages of in vitro fertilization in subsequently pregnant and nonpregnant women. Fertil Steril 64,802–810.

Boivin J and Takefman JE (1996) Impact of the in vitro fertilization process on emotional, physical, and relational variables. Hum Reprod 11,903–907.

Boivin J, Andersson L, Skoog-Svanberg A, Hjelmstedt A, Collins A and Bergh T (1998) Psychological reactions during in-vitro fertilization: similar response pattern in husbands and wives. Hum Reprod 13,3262–3267.

Bolumar F, Olsen J and Boldsen J (1996) Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. The European study group on infertility and subfecundity. Am J Epidemiol 143,578–587.

Bolumar F, Olsen J, Rebagliato M and Bisanti L (1997) Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. Am J Epidemiol 145,324–334.

Bringhenti F, Martinelli F, Ardenti R and La Sala GB (1997) Psychological adjustment of infertile women entering IVF treatment: differentiating aspects and influencing factors. Acta Obstet Gynecol Scand 76,431–437.

Buck GM, Sever LE, Batt RE and Mendola P (1997) Life-style factors and female infertility. Epidemiology 8,435–441.

Callan VJ and Hennessey JF (1988) Emotional aspects of in in-vitro fertilization and embryo transfer. J In Vitro Fertil Embryo Transfer 5, 290–295.

Callan J, Kloske B, Kashima Y and Hennessey JF (1988) Towards understanding women's decisions to continue or stop in-vitro fertilization: the role of social, psychological, and background factors. J In Vitro Fertil Embryo Transfer 5,363–369.

Casas M, Ferrer S, Calaf J, Rodriguez-Espinosa J, Jane F, Herrera-Marschitz M and Ungerstedt U (1989) Dopaminergic mechanism for caffeine-induced decrease in fertility? Lancet 1,731.

Chan YF, O'hoy KF, Wong A, So WK and Ho PC (1989) Psychosocial evaluation in an IVF/GIFT program in Hong Kong. J Reprod Infant Psychol 7,67–77.

Field MJ and Lohr KN (1990) Clinical Practice Guidelines: Directions for New Programs Institute of Medicine. National Academy Press, Washington, DC.

Collins A, Freeman EW, Boxer AS and Tureck R (1992) Perception of infertility and treatment stress in females as compared with males entering in vitro fertilization treatment. Fertil Steril 57,350–356.

Connolly KJ, Edelmann RJ, Bartlett H, Cooke ID, Lenton E and Pike S (1993) An evaluation of counselling for couples undergoing treatment for in-vitro fertilization. Hum Reprod 8,1332–1338.

Craft I and Brinsden P (1989) Alternatives to IVF: the outcome of 1071 first GIFT procedures. Hum Reprod 4,29–36.

Crha I, Hruba D, Fiala J, Ventruba P, Zakova J and Petrenko M (2001) The outcome of infertility treatment by in-vitro fertilization in smoking and non-smoking women. Cent Eur J Publ Hlth 9,64–68.

Csemiczky G, Landgren BM and Collins A (2000) The influence of stress and state anxiety on the outcome of IVF-treatment: psychological and endocrinological assessment of Swedish women entering IVF-treatment. Acta Obstet Gynecol Scand 79,113–118.

Demyttenaere K, Bonte L, Gheldof M, Vervaeke M, Meuleman C, Vanderschuerem D, Demyttenaere K, Nijs P, Evers-Kiebooms G and Koninckx PR (1991) Coping, ineffectiveness of coping, and the psychoendocrinological stress responses during in-vitro fertilization. J Psychosom Res 35,231–243.

Demyttenaere K, Bonte L, Gheldof M, Vervaeke M, Meuleman C, Vanderschuerem D *et al.* (1998) Coping style and depression level influence outcome in in vitro fertilization. Fertil Steril 69, 1026–1033.

Demyttenaere K, Nijs P, Evers-Kiebooms G and Koninckx PR (1992) Coping and the ineffectiveness of coping influence the outcome of in vitro fertilization through stress responses. Psychoneuroendocrinology 17,655–665.

Demyttenaere K, Nijs P, Evers-Kiebooms G and Koninckx PR (1994) Personality characteristics, psychoendocrinological stress and outcome of IVF depend upon the etiology of infertility. Gynecol Endocrinol 8,233–240.

Edelmann RJ (1990) Emotional aspects of in vitro fertilization procedures: review. J Reprod Infertil Psychol 8,161–173.

Edwards RG and Brody SA (1995) Principles and Practice of Assisted Human Reproduction. WB Saunders Company, Philadelphia, PA.

Elenbogen A, Lipitz S, Mashiach S, Dor J, Lebran D and Ben-Rafael Z (1991) The effect of smoking on the outcome of in-vitro fertilization-embryo transfer. Hum Reprod 6,242–244.

El-Nemr A, Shawaf T, Sabatini L, Wilson C, Lower AM and Grudzinskas JG (1998) Effect of smoking on ovarian reserve and ovarian stimulation in in-vitro fertilization and embryo transfer. Hum Reprod 13, 2192–2198.

Facchinetti F, Matteo ML, Artini GP, Volpe A and Genazzani AR (1997) An increased vulnerability to stress is associated with a poor outcome of in vitro fertilization-embryo transfer treatment. Fertil Steril 68,384–385.

Fazakas-Todea I (1995) The effect of ethanol upon early development in mice and rats. XX. The effect of chronic biparental beer intake in mice upon early implantation events. Rom J Morphol Embryol 41,7–12.

Feichtinger W, Papalambrou K, Poehl M, Krischker U and Neumann K (1997) Smoking and in vitro fertilization: a meta-analysis. J Assist Reprod Genet 14,596–599.

Freeman EW, Boxer AS, Rickels K, Tureck R and Mastroianni L, Jr (1985) Psychological evaluation and support in a program of in vitro fertilization and embryo transfer. Fertil Steril 43,48–53.

Gallinelli A, Roncaglia R, Matteo ML, Ciaccio I, Volpe A and Facchinetti F (2001) Immunological changes and stress are associated with different implantation rates in patients undergoing in vitro fertilization-embryo transfer. Fertil Steril 76,85–91.

Grainger DA and Tjaden BL (2000) Assisted reproductive technologies. In Goldman MB and Hatch MC (eds) Women and Health. Academic Press, San Diego, CA.

Hammarberg K, Astbury J and Baker HWG (2001) Women's experience of IVF: a follow-up study. Hum Reprod 16,374–383.

Hammitt DG, Bedja E, Rogers PR, Syrop CH, Donovan JF and Williamson RA (1989) Comparison of motility stimulants for cryopreserved human semen. Fertil Steril 52,495–502.

Harlow CR, Fahy UM, Talbot WM, Wardle PG and Hull MGR (1996) Stress and stress-related hormones during in-vitro fertilization treatment. Hum Reprod 11,274–279.

Harrison KL, Callan VJ and Hennessey JF (1987) Stress and semen quality in an in-vitro fertilization program. Fertil Steril 48,633–636.

Harrison KL, Breen TM and Hennessey JF (1990) The effect of patient smoking habit on the outcome of IVF and GIFT treatment. NZ J Obstet Gynaecol 30,340–342.

Harrison RF (1978) Insemination of husband's semen with and without the addition of caffeine. Fertil Steril 52,495–502.

Hatch EE and Bracken MB (1993) Association of delayed conception with caffeine consumption. Am J Epidemiol 138,1082–1092.

Hjelmstedt A, Widstrom AM, Wramsby H, Hatthiesen AS and Collins A (2003) Personality factors and emotional responses to pregnancy among IVF couples in early pregnancy: a comparative study. Acta Obstet Gynecol Scand 82,151–161.

Hsu YL and Kuo BJ (2002) Evaluations of emotional reactions and coping behaviors as well as correlated factors for infertile couples receiving assisted reproductive technologies. J Nurs Res 10, 291–302.

Hughes E and Brennan B (1996) Does cigarette smoking impair natural or assisted fecundity? Fertil Steril 66,679–689.

Hughes E, Young Lai E and Ward S (1992) Cigarette smoking and outcomes of in-vitro fertilization and embryo transfer: a prospective cohort study. Hum Reprod 7,358–361.

Hughes E, Yeo J, Claman P, Younglai EV, Sagle MA, Daya S and Collins JA (1994) Cigarette smoking and the outcomes of in vitro fertilization: measurement of effect size and levels of action. Fertil Steril 62, 807–814.

Imoedemhe D, Sigue A, Pacpaco E and Olazo A (1992) The effect of caffeine on the ability of spermatozoa to fertilize mature human oocyte. J Assist Reprod Genet 9,155–160.

Joesbury K, Edirisinghe W, Phillips MR and Yovich JL (1998) Evidence that male smoking affects the likelihood of a pregnancy following IVF treatment: application of the modified cumulative embryo score. Hum Reprod 13,1506–1513.

Johnston M, Shaw R and Bird D (1987) Test-tube baby procedures: stress and judgments under uncertainty. Psychol Hlth 1,25–38.

Kaufman MH (1997) The teratogenic effects of alcohol following exposure during pregnancy, and its influence on the chromosome constitution of the pre-ovulatory egg. Alcohol 32,113–128.

Kee BS, Jung BJ and Lee SH (2000) A study on psychological strain in IVF patients. J Assist Reprod Genet 17,445–448.

Klonoff-Cohen H, Natarajan L, Marrs R and Yee B (2001a) Effects of female and male smoking on successs rates of IVF and gamete intra-Fallopian transfer. Hum Reprod 16,1382–1390.

Klonoff-Cohen H, Chu E, Natarajan L and Sieber W (2001b) A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. Fertil Steril 76, 675–687.

Klonoff-Cohen H, Bleha J and Lam-Kruglick P (2002) A prospective study of the effects of female and male caffeine consumption on the reproductive endpoints of IVF and gamete intra-Fallopian transfer. Hum Reprod 17,1746–1754.

Klonoff-Cohen H, Lam-Kruglick P and Gonzalez C (2003) Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. Fertil Steril 79,330–339.

Lee TY, Sun GH and Chao SC (2001) The effect of an infertility diagnosis on treatment-related stresses. Arch Androl 46,67–71.

Leiblum SR, Kemmann E and Lane MK (1987) The psychological concomitants of in-vitro fertilization. J Psychosom Obstet Gynecol 6,165–178.

Lovely LP, Meyer WR, Ekstrom RD and Golden RN (2003) Effect of stress on pregnancy outcome among women undergoing assisted reproduction procedures. South Med J 96,548–551.

Macklon NS, Geraedts JPM and Fauser BCJ (2002) Hum Repod Update 8,333–343.

Mahlstedt PP, Macduff S and Bernstein J (1987) Emotional factors and the in vitro fertilization and embryo transfer process. J In Vitro Fertil Embryo Transfer 4,232–236.

Maximovich A and Beyler S (1995) Cigarette smoking at time of in vitro fertilization initiation has negative effect on in vitro fertilization-embryo transfer success. J Assist Reprod Genet 12,75–77.

Merari D, Feldberg D, Elizur A, Goldman J and Modan B (1992) Psychological and hormonal changes in the course of in vitro fertilization. J Assist Reprod Genet 9,161–169.

Merari D, Chetrit A and Modan B (2002) Emotional reaction and attitudes prior to in vitro fertilization: an inter-spouse study. Psychol Hlth 17,629–640.

Milad M, Klock S, Moses S and Chatterton R (1998) Stress and anxiety do not result in pregnancy wastage. Hum Reprod 13,2296–2300.

Mori E, Nadaoka T, Morioka Y and Saito H (1997) Anxiety of infertile women undergoing IVF-ET: relation to the grief process. Gynecol Obstet Invest 44,157–162.

National Center for Chronic Disease Prevention and Health Promotion's 1991 Assisted reproductive technology success rates: national summary and fertility clinic reports (2001): available online at www.cdc.gov/nccdphp/drh/art.htm.

National Center for Chronic Disease Prevention and Health Promotion's 2001 Assisted Reproductive Technology Success Rates Reports (2003): available online at www.cdc.gov/nccdphp/drh/art.thm.

Newton CR, Hearn MT and Yuzpe AA (1990) Psychological assessment and follow-up after in-vitro fertilization: assessing the impact of failure. Fertil Steril 54,879–886.

Pattinson HA, Taylor PJ and Pattinson MH (1991) The effect of cigarette smoking on ovarian function and early pregnancy outcome of in vitro fertilization treatment. Fertil Steril 55,780–783.

Peipert JF and Bracken MB (1997) Systematic reviews of medical evidence: the use of meta-analysis in obstetrics and gynecology. Obstet Gynecol 89,628–633.

Pelinck MJ, Hoek A, Simons AHM and Heineman MJ (2002) Efficacy of natural cycle IVF: a review of the literature. Hum Reprod Update 8,129–139.

Phromyothi V and Virutamasen P (2003) The determinant factors and the anxiety level of infertile couples during the treatment of in vitro fertilization and embryo transfer at Chulalongkorn Hospital. J Med Assoc Thai 86,425–429.

Reading AE, Chang LC and Kerin JF (1989) Psychological state and coping styles across an IVF treatment cycle. J Reprod Infant Psychol 7,95–103.

Rosevear S, Holt D, Lee T, Ford W, Wardle P and Hull M (1992) Smoking and decreased fertilization rates in vitro. Lancet 340,1195–1196.

Rubes J, Lowe X, Moore D, Perreault S, Slott V, Evenson D, Selevan SG and Wyrobek AJ (1998) Smoking cigarettes is associated with increased sperm disomy in teenage men. Fertil Steril 70,715–723.

Rubinow DR and Roca CA (1995) Infertility and depression. Psychosom Med 57,514–516.

Sackett DL, Haynes RB, Guyatt GH and Tugwell P (1991) Clinical Epidemiology: A Basic Science for Clinical Medicine, 2nd edn. Little, Brown and Company, Boston, USA.

Sanders KA and Bruce NQ (1999) Psychosocial stress and treatment outcome following assisted reproductive technology. Hum Reprod 14,1656–1662.

Schultz RM and Williams CJ (2002) The science of ART. Science 296,2188–2190.

Seibel MM and Levin S (1987) A new era in reproductive techonologies: the emotional stages of in vitro fertilization. J In Vitro Fert Embryo Transf 4,135–140.

Sharpe RM and Franks S (2002) Environment, lifestyle and infertility—an inter-generational issue. Nat Cell Biol 4,s33–s40.

Shiloh H, Lahav-Baratz S, Koifman M, Ishai D, Bidder D, Weiner-Meganzi Z and Drinfeld M (2004) The impact of cigarette smoking on zona pellucida thickness of oocytes and embryos prior to transfer into the uterine cavity. Hum Reprod 19,157–159.

Smeenk JM, Verhaak CM, Eugster A, van Minnen A, Zielhuis GA and Braat DD (2001) The effect of anxiety and depression on the outcome of in-vitro fertilization. Hum Reprod 16,1420–1423.

Sterzik K, Strehler E, De Santo M, Trumpp N, Abt M, Rosenbusch B and Schneider A (1996) Influence of smoking on fertility in women attending an in vitro fertilization program. Fertil Steril 65, 810–830.

Stillman RJ, Rosenberg MJ and Sacks BP (1986) Smoking and reproduction. Fertil Steril 46,545–566.

Stoleru S, Cornet D, Vaugeois P, Fermanian J, Magnin F, Zerah S and Spira A (1997) The influence of psychological factors on the outcome of the fertilization step of in vitro fertilization. J Psychosom Obstet Gynaecol 18,189–202.

Tarabusi M, Matteo ML, Volpe A and Faccinetti F (2000) Stress-response in male partners of women submitted to in vitro fertilization and embryo transfer. Psychother Psychosom 69,275–279.

Tarlatzis BC, Zepiridis L, Grimbizis G and Bontis J (2003) Clinical management of low ovarian response to stimulation for IVF: a systematic review. Hum Reprod Update 9,61–76.

Trapp M, Kemeter P and Feichtinger W (1986) Smoking and in-vitro fertilization. Hum Reprod 1,357–358.

Van Balen F, Naaktgeboren N and Trimbos-Kemper TCM (1996) In-vitro fertilization: the experience of treatment, pregnancy and delivery. Hum Reprod 11,95–98.

Van Blerkom GL (2004) In: Van Blerkom, J. and Gregory, L. (eds), Essential IVF: basic research and clinical applications. Boston: Kluwer Academic Press.

Van Voorhis B, Dawson J, Stovall D, Sparks AE and Syrop CH (1996) The effect of smoking on ovarian function and fertility during assisted reproduction. Obstet Gynecol 88,785–791.

Verhaak CM, Smeenk JM, Eugster A, van Minnen A, Kremer JA and Kraaimaat FW (2001) Stress and marital satisfaction among women before and after their first cycle of in vitro fertilization and intracytoplasmic sperm injection. Fertil Steril 76,525–531.

Vine MF (1996) Smoking and male reproduction: a review. Int J Androl 19,323–337.

Weigert M, Hofstetter G, Kaipl D, Gottlich H, Krischker U, Bichler K, Poehl M and Feichtinger W (1999) The effect of smoking on oocyte quality and hormonal parameters of patients undergoing in vitro fertilization-embryo transfer. J Assist Reprod Genet 16, 287–293.

Weiss T and Eckert A (1989) Cotinine levels in follicular fluid and serum of IVF patients: effect on granulosa-luteal cell function in vitro. Hum Reprod 4,482–485.

Yong P, Martin C and Thong J (2000) A comparison of psychological functioning in women at different stages of in vitro fertilization treatment using the mean affect adjective check list. J Assist Reprod Genet 17,553–556.

Zenzes M and Reed T (1997) Effects of cigarette smoking and aging on maturation of human oocytes. Hum Reprod 12,1736–1741.

Zenzes MT, Reed TE, Wang P and Klein J (1996) Cotinine, a major metabolite of nicotine, is detectable in follicular fluids of passive smokers in in vitro fertilization therapy. Fertil Steril 66,614–619.

Zenzes MT, Bielecki R and Reed TE (1999) Detection of benzo(a)pyrenediol epoxide DNA adducts in sperm of men exposed to cigarette smoke. Fertil Steril 72,330–335.

Zitzmann M, Rolf C, Nordhoff V, Schrader G, Rickert-Fohring M, Gassner P, Behre HM, Greb RR, Kiesel L and Nieschlag E (2003) Male smokers have a decreased success rate for in vitro fertilization and intracytoplasmic sperm injection. Fertil Steril 79 (Suppl 3), 1550–1554.

Psychosocial interventions in infertility: What works and what doesn't?

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Learning objectives

- knowing about the differential effects of various psychosocial interventions
- understanding methodological issues in research on psychosocial interventions in infertility

Introduction

The view on psychosocial factors in infertility has changed over the last decades (for an overview: Wischmann 2003). At first, the "psychogenic infertility model" (infertility caused by psychological factors) dominated the research in this field. But there are as yet no convincing systematic studies covering a substantial number of cases that provide evidence of distress as the cause of infertility. Nowadays, the psychological effects of infertility and of assisted reproductive techniques (ART) are in the focus of research ("psychogical consequences model"). General findings show a slightly higher depression, anxiety and physical complaints in infertile women. This can be interpreted as the result of medical diagnosis and/or therapy. About 15 % to 20 % of all couples experience reproductive medicine as so stressful that they require psychological counselling (Boivin & Kentenich 2002). A bunch of various psychosocial interventions in infertility has been recommended for the affected persons. But it remains unclear what their (differential) effects are.

Help-seeking behaviour of subfertile women

The study of Greil & McQuillan (2004) on a non-clinical sample of 123 subfecund women trying to conceive showed the following help-seeking behaviour patterns: Many of the women discussed fertility with friends or family (66 %) or with others who have experienced similar problems (58 %), read articles on fertility in popular magazines (60 %), in technical/scientific journals (50 %) or read a book about fertility (42 %). Less women looked for information about fertility on the Internet (24 %) or contacted a support group or health organization (15 %). Only about 8 % of the women consulted a therapist or other mental health professional about fertility. The same quantity consulted a minister or other spiritual leader, whereas twice as much asked a healer or alternative medicine practitioner about infertility. Two thirds of the subfecund women trying to conceive sought medical help and 48 % had received medical treatment. The authors concluded, that informal actions (e.g. talking to friends or familiy) were more common in educating themselves about infertility than formal strategies (e. g. joining a support group or consulting a medical health professional).

Preparatory information: booklets and multi-media products

Takefman and colleagues compared three groups: 13 infertile couples viewed a videotape on the procedural and the emotional aspects of the infertility investigation. They also read a booklet on potential sexual difficulties developing during the treatment. A second group of 13 couples viewed the videotape only, and a third group of 13 couples was shown a videotape on

solely the technical aspects of infertility investigation. Results: Only the intervention in the third group showed positive effects on reactions to infertility and to certain diagnostic tests. Pook & Krause (2005) showed that in a group of 250 men enrolling for a fertility workup, mailing of a leaflat with preparatory information about this procedure was associated with lower distress scores and a higher attendance rate compared to a group of men who did not receive this leaflat. In a feasibility study by Cousineau and colleagues (2004), a patient education CD-ROM that uses audio, video, interactive tasks and personalized feedback was rated as very satisfying by 12 patients and 12 experts.

Internet

Within two years the proportion of persons using the Internet for health and medical information has increased from 71 % to 86 % in the year 2000. Because no binding guidelines exist about web-based medical information in general, potential users have a high risk to obtain incorrect or incomplete information. Zahalsky and coworkers found that in more than a half of web pages relevant to male infertility that the role of varicocele was not discussed (Zahalsky et al., 2005). The quality of US fertility clinic websites fail to meet most of given health information guidelines for these clinics (Huang et al. 2005).

In the study of Haagen and coworkers (2003) two third of the couples with infertility problems used the Internet with regard to fertility-related issues. About a third of the (few) subfecund women in the above mentioned study of Greil & McQuillan (2004) who sought Internet information reported that they found it very useful, a percentage comparable with the results of the survey of Weissman et al. (2000). About half of the women had talked to a medical professional about the Internet information, a similar percentage like in a German study (Himmel et al. 2005). In this study, requests to the Internet expert forum were also sent in order to obtain emotional support (17 %) or to complain about a doctor (15 %). The efficacy of Internet chat rooms and virtual communities (Eysenbach et al. 2005) on the issue of infertility has not yet been verified. Giving infertile patients access to their medical record via Internet does probably not increase their empowerment (Tuil et al. 2005).

Telephone counselling

Telephone counselling is widely accepted and may be a viable option for people who do not have access to affordable mental health care (Reese et al. 2006). Telephone counselling does not appear to work as well as face-to-face counselling for people with pronounced symptomatology. Most of the infertile patients use this service primarily to clarify or discuss aspects of the medical treatment (Boivin & Kentenich 2002). About 15 % of them – mostly women – also use it to talk about the emotional and psychosocial impact of infertility and its treatment (Bartlam & McLeod 2000).

Support groups

Support groups can be classified into self-help groups and professionally facilitated groups. The advantage of self-help groups is the low threshold for attendance, so patients with reservations about counselling services can be reached. In professionally facilitated groups it is common that fees are charged for participation. The efficacy of support groups has not yet been studied systematically but exploratory studies indicate benefits for women and men for self-help groups (Lentner & Glazer 1991) and professionally facilitated groups (Stewart et al. 1992). The common experience and the exchange or sharing with other infertile people were perceived to be main benefits of support group interventions. This experience seems to facilitate coping with infertility. Most men felt support groups were good because of the practical information and advice they received (Boivin 2003). Especially for people using third party reproduction, group-work approaches seem to be appropiate (Thorn & Daniels 2003).

Counselling and psychotherapy

"Why are infertile patients not using psychosocial counseling?", Boivin and coworkers asked in 1999. In our own study we tried to find some answers from gynecologists and from infertile women. We interviewed 129 gynecologists in the region by telephone. Nearly 50 % of them considered psychosocial counselling as necessary when medical treatment fails. To offer counselling at the beginning of infertility treatment was the opionion of 38 % of them. In contrast to that, only 24 % of the interviewed women (67 patients in a Women's hospital and 109 participants of an Internet survey) wished counselling when treatment was not successful, and 32 % right from the beginning. These lower percentage rates could be ascribed to the fact that 27 % of the affected women feared stigmatization and 18 % feared labilisation, whereas 21 % were in doubt about the efficacy of counselling. Enough coping resources of their own was mentioned by 18 % of the women (Wischmann 2005). When couples actually take up infertility counselling, the women's psychological distress is much more important for attending counselling than those of the men (Wischmann et al. 2006). In a study on 1366 women attending infertility clinics, 57% % of the responders said they would take up infertility counselling if it was offered to them, but it was actually offered to 14 % only (Souter et al. 1998). In a large postal survey, 72 % of the participants were very satisfied or satisfied with the infertility counselling they received during the investigation of their infertility (Monach 2003).

In her comprehensive systematic review, Boivin (2003) indicated that systematic evaluation of intervention effects (with control group and follow-up) only took place in 25 out of 380 studies on psychological infertility counseling (=6.6 %). In total 11 of the 25 studies (=44 %) reviewed were defined as "better quality"-studies. That means they used a control group and either random assignment and/or a pre-to-post design to account for the influence of uncontrolled factors. Only 8 of these 25 studies assessed pregnancy rates. The 25 studies were grouped into counselling interventions, focussed educational interventions, and comprehensive educational programmes. Most of the systematically studied psychological interventions were relaxation therapies, psychodynamic psychotherapies, and behavioural therapies. Although psychoanalytical research added a lot to our understanding of infertility, and the psychogenic model is built on systematic and theoretical grounds, psychoanalytical treatment in infertility has not yet been evaluated systematically. Results: Psychosocial interventions were more effective in reducing negative affect than in changing marital and social functioning. Almost all interventions showed positive effects on at least one of the outcomes assessed and none of the studies reported a negative effect on well-being. Group interventions which had emphasised education and skills training (e.g., relaxation training) were significantly more effective in producing positive change than counselling interventions which emphasised emotional expression and support and/or discussion about thoughts and feelings related to infertility. Men and women were found to benefit equally from psychosocial interventions. Only three of eight good quality studies showed higher pregnancy rates in the intervention group compared to the control group. Boivin concluded that only interventions geared to a behavioural medicine approach and relaxation techniques appear to bring about an increase in the pregnancy rate. There are, however, still insufficient systematic studies indicating a rise in pregnancy rates following psychological interventions.

In the meta-analysis of de Liz & Strauss (2005), 11 studies on individual or couple interventions and 11 studies on group interventions were analyzed. Not only studies with comparison groups, but also studies with pre/post design only were included. The authors confirm Boivin's results concerning the reduction of negative affects like depression or anxiety. They also come to the conclusion that psychotherapy possibly enhances conception success, because pregnancy rates over all studies were thrice as high as for the pooled comparison groups rates. But due to the fact that medical infertility treatment might have been

the crucial factor as an interceding variable, the authors conclude that a definite connection between psychotherapy efficacy and successful conception could not be made at this point. Studies carried out after these two reviews showed no significant higher pregnancy rates for the intervention groups compared to control groups too (e. g. de Klerk et al. 2005, Schmidt et al. 2005, Chan et al. 2006), and not for follow-up periods of one year either (Emery et al. 2006). So Boivin's statement has lost none of its validit. She wrote "It seems clear that more research needs to be devoted to the systematic evaluation of pregnancy effects before psychosocial interventions can be recommended as a way of helping couples improve their chances of achieving a pregnancy" (Boivin 2003, p. 2335).

Summary

Providing procedural information concerning the technical aspects of infertility investigation probably facilitates coping with infertility and with ART. This information can be given in the form of booklets or educational films. Written information provided by pharmaceutical companies should be complemented by handbooks of patient organizations to avoid any potential biases and to ensure the provision of psychosocial information (Boivin & Kentenich 2002). Using the Internet is a fast and easy way to obtain information on infertility and its treatment, but with the risk of getting wrong or misleading informations. Interested couples can find references in the Internet (e. g. "Using The Internet For Infertility Information" at www.resolve.org. This website also includes the helpful factsheet "Infertility Myths and Facts"). Telephone counselling can be helpful in providing specific information about the infertility workup but it cannot replace face-to-face counselling on psychosocial issues. Attendance at support groups can be recommended to strengthen coping abilities. Psychosocial counselling and psychotherapy are definitely effective in reducing negative affect, mostly within a short period of time (less than 10 sessions). Pregnancy rates are unlikely to be affected by psychosocial interventions.

References

van Balen, F., Verdurmen, J. & Ketting, E. (2001). Assessment of a telephone helpline on infertility provided by a patient association. Patient Education and Counseling, 42, 289-293.

Bartlam, B. & McLeod, J. (2000). Infertility Counselling: the ISSUE experience of setting up a telephone counselling service. Patient Education and Counseling, 41 (3), 313-321.

Boivin, J., Scanlan, L. C. & Walker, S. M. (1999). Why are infertile patients not using psychosocial counseling? Human Reproduction, 14 (5), 1384-1391.

Boivin, J. & Kentenich, H. (eds.) (2002). Guidelines for counselling in infertility. Oxford, Oxford University Press.

Boivin, J. (2003). A review of psychosocial interventions in infertility. Social Science & Medicine, 57 (12), 2325-2341.

Burns, L. H. & Covington, S. H. (eds.). (2004). Infertility counseling. A comprehensive handbook for clinicans. (2nd ed.). Oxford London New York: Taylor & Francis.

Chan, C. H. Y., Ng, E. H. Y., Chan, C. L. W., Ho, P. C. & Chan, T. H. Y (2006). Effectiveness of psychosocial group intervention for reducing anxiety in women undergoing in vitro fertilization: A randomized controlled study. Fertility and Sterility, 85 (2), 339-346.

Connolly, K. J., Edelmann, R. J., Bartlett, H., Cooke, I. D., Lenton, E. & Pike, S. (1993). An evaluation of counselling for couples undergoing treatment for in-vitro fertilization. Human Reproduction, 8 (8), 1332-1338.

Cousineau, T. M., Lord, S. E., Corsini, E. A., Viders, J. C., Seibring, A. R. & Lakhani, S. R. (2004). A multimedia psychosocial support program for couples receiving infertility treatment: A feasibility study. Fertility and Sterility, 81 (3), 532-538.

Emery, M., Joris, V., Béran, M.-D., Darwiche, J., Capel, R., Guex, P. & Germond, M. (2006). Prospective study of pre-IVF counselling: One-year follow-up. Journal für Reproduktionsmedizin und Endokrinologie, 1, 77-78.

Epstein, Y. M. & Rosenberg, H. S. (2005). Assessing infertility information on the Internet: Challenges and possible solutions. Fertility and Sterility, 83 (3), 553-555.

Eysenbach, G., Powell, J., Englesakis, M., Rizo, C. & Stern, A. (2004). Health related virtual communities and electronic support groups: systematic review of the effects of online peer to peer interactions. British Medical Journal, 328 (7449), 1166-1172.

Greil, A. L. & McQuillan, J. (2004). Help-seeking patterns among subfecund women. Journal of Reproductive and Infant Psychology, 22 (4), 305-319.

Haagen, E. C., Tuil, W., Hendriks, J., Bruijn, R. P. J. d., Braat, D. D. M. & Kremer, J. A. M. (2003). Current Internet use and preferences of IVF and ICSI patients. Human Reproduction, 18 (10), 2073-2078.

Himmel, W., Meyer, J., Kochen, M. M. & Michelmann, H. W. (2005). Information Needs and Visitors' Experiences of an Internet Expert Forum on Infertility. Journal of Medical Internet Research, 7 (2), e20 <URL: http//www.jmir.org/2005/2002/e2020/>.

Huang, J. Y. J., Discepola, F., Al-Fozan, H. & Tulandi, T. (2005). Quality of fertility clinic websites. Fertility and Sterility, 83 (3), 538-544.

de Klerk, C., Hunfeld, J. A. M., Duivenvoorden, H. J., den Outer, M. A., Fauser, B. C. J. M., Passchier, J. & Macklon, N. S. (2005). Effectiveness of a psychosocial counselling intervention for first-time IVF couples: a randomized controlled trial. Hum. Reprod., 20 (5), 1333-1338.

Lentner, E. & Glazer, G. (1991). Infertile couples' perceptions of infertility support-group participation. Health care for women international, 12 (3), 317-330.

de Liz, T. M. & Strauss, B. (2005). Differential efficacy of group and individual/couple psychotherapy with infertile patients. Human Reproduction, 20 (5), 1324-1332.

Marcus, H., Marcus, D. & Marcus, S. (2005). How do infertile couples choose their IVF centers? An Internet-based survey. Fertility and Sterility, 83 (3), 779-781.

Monach, J. (2003). Counselling – its role in the infertility team. Human Fertility, 6 (2), S17-S21.

Pook, M. & Krause, W. (2005). Stress reduction in male infertility patients: A randomized, controlled trial. Fertility and Sterility, 83 (1), 68-73.

Reese, R. J., Conoley, C. W. & Brossart, D. F. (2006). The attractiveness of telephone counseling: An empirical investigation of client perceptions. Journal of Counseling and Development, 84 (1), 54-60.

Schmidt, L., Tjørnhøj-Thomsen, T., Boivin, J. & Nyboe Andersen, A. (2005). Evaluation of a communication and stress management training programme for infertile couples. Patient Education and Counseling, 59 (3), 252-262.

Souter, V., Penney, G., Hopton, J. & Templeton, A. (1998). Patient satisfaction with the management of infertility. Human Reproduction, 13 (7), 1831-1836.

Stewart, D. E., Boydell, K. M., McCarthy, K., Swerdlyk, S., Redmond, C. & Cohrs, W. (1992). A prospective study of the effectiveness of brief professionally-led support groups for infertility patients. International Journal of Psychiatry in Medicine, 22 (2), 173-182.

Strauß, B. (ed.). (2002). Involuntary childlessness. Psychological assessment, counselling and psychotherapy. Seattle: Hogrefe & Huber.

Thorn, P. & Daniels, K. R. (2003). A group-work approach in family building by donor insemination: empowering the marginalized. Human Fertility, 6, 46-50.

Tuil, W. S., Verhaak, C. M., Braat, D. D. M., de Vries Robbé, P. F. & Kremer, J. A. (2005). Empowering IVF-patient by internet access to medical data – a randomized controlled trial. Human Reproduction, 20 (Supplement 1), i60.

Weissman, A., Gotlieb, L., Ward, S., Greenblatt, E. & Casper, R. F. (2000). Use of the Internet by infertile couples. Fertility and Sterility, 73 (6), 1179-1182.
Wischmann, T. (2003). Psychogenic infertility – myths and facts. Journal of Assisted Reproduction and Genetics, 20 (12), 485-494.
Wischmann, T. (2005). Psychosoziale Aspekte bei Fertilitätsstörungen [Psychosocial aspects of fertility disorders]. Der Urologe A, 44, S. 185-195.
Wischmann, T.; Stammer, H.; Scherg, H.; Strowitzki, Th.; Verres, R. (2006). Psychosocial characteristics of women and men attending infertility counselling. Paper presented at the 22nd Annual Meeting of ESHRE, Prague, 20.06.06
Zahalsky, M., Wilson, S. R., di Blasio, C. J., Lam, S. K. & Nagler, H. M. (2005). Male infertility on the internet: An analysis of web-based resources. British Journal of Urology, 95 (4), 481-484.

How do we assess our [own] effectiveness as practitioners?

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Learning objectives

- Understand why outcome research for psychological evaluations in infertility is needed
- Describe the types of research questions that motivate outcome research
- Discuss advantages and disadvantages of designs in outcome research
- Learn about the application of single case experiment in everyday practice

Problem context

There is a long-standing schism between practice and research when it comes to the evaluation of psychological services. Practitioners (e.g., psychologists, clinicians, counsellors) often argue that "data" are not needed to tell them what works; they "know" on the basis of experience (Kendall, 1998). Furthermore, people feel they can ensure good practice through more clinically oriented methods of monitoring (e.g., case supervision, consultation with colleagues) (Asay et al. 2002). However, implementation of evidence based principles in managed healthcare has put significant pressure on practitioners to translate this intuition and clinical judgement into objective data demonstrating the effectiveness and efficiency of their psychological therapies (Asay, et al., 2002; Corrie 2000). One important obstacle in achieving this goal has been knowing how to assess effectiveness, particularly in the context of private (individual) practice. The aim of this talk is to present why such evaluations are important, describe research questions to guide outcome research and describe how individual practitioners can implement satisfactory research designs.

Why do we need empirical evaluation of our work?

There are many reasons why practitioners need to evaluate their work. The first and most compelling is the finding that some psychological interventions in infertility are not effective and that others vary significantly in their effectiveness, indicating a need to monitor and modify approaches in infertility counselling (Boivin, 2003; de Liz & Strauss, 2005). Second, such evaluations distinguish clinical applications in psychology from some of the quackery available promoting unfounded cures for well-being and fertility (e.g., flower remedies). A third and more practical reason is that those who fund psychological therapies (e.g., government, insurers, patients) increasingly only want to pay for those therapies that have been validated (e.g., e.g., National Institute of Clinical Excellence, UK, Department of Health, 2001).

Types of questions in outcome research

There are two main types of questions when it comes to the evaluation of psychological interventions. The first type, which is intervention-focused, assumes that an intervention is effective in producing a benefit (e.g., decreased fear response) because of its unique techniques (e.g., desensitisation) derived from a unique theoretical perspective (i.e., self-efficacy theory). The research questions addressed by this approach are whether an intervention is effective, and if so, to what extent it is compared to untreated or differently treated groups. Practitioners interested in specific interventions can evaluate entire intervention packages as they are ordinarily administered or "dismantle" the intervention in an effort to determine which aspect of treatment is the active ingredient. Another form of outcome research involves varying the parameters of an intervention (e.g., number of sessions, number of clients in the group) in order to discover how to maximise the benefits of a specific intervention (Kazdin, 1986).

The second type of research question for treatment evaluation focuses on what makes interventions similar and how that explains positive change. This approach arises from the paradoxical findings of several meta-analyses showing that despite technical and theoretical diversity, psychological interventions all yield more or less the same level of benefit (Shadish et al. 2000; Wampold, 1997). Such findings suggest that it is not the uniqueness of the intervention that is important in generating benefits, but a set of general clinical principles that must underlie all interventions aimed at helping people. The integrationist perspective (or common-factors approach) seeks to determine the core ingredients shared by different therapies in order to develop more efficacious treatments based on these commonalities.

The selection of a research design will be guided by the research question posed. Whilst practitioners can, in principal, design and participate in any kind of evaluation, such involvement is often limited by the constrains of their working environment, in particular their caseload.

Research designs for the evaluation of psychological interventions

Designs for many cases

Many practitioners feel they "know" their clinical interventions are effective because of high client satisfaction or because of visible changes in patient behaviour. However, *treatment efficacy* is most reliably demonstrated in controlled research (Chambless & Hollon, 1998). Controlled research allows the practitioner to know that the changes observed are due to the intervention (or one of its ingredients) and not some other uncontrolled factor (e.g., passage of time, support from social network). In terms of research designs, the gold standard for this unbiased evaluation is the *randomised controlled trial* (RCT), where consecutive patients are randomly assigned to an experimental (i.e., intervention) or control condition. This type of design is the least biased form of evidence because it controls for non-specific factors that may influence the responses of experimental and controls groups on outcome measures and, consequently, ensures that differences between treated, untreated or alternatively treated groups on outcome measures are due to proposed intervention effects rather than to other factors not controlled as part of the experiment (Khan, Riet, Popay, Nixon & Kleijnen, 2001).

A similar design, the *cohort design*, compares people who had the psychological intervention with those who did not on some outcome. The difference with this design quasi-experimental design is that patients/clients are not randomly assigned to their group. This fundamental difference means that outcome scores may potentially be affected by factors that caused people to choose their group (i.e., to seek/not seek treatment). This is a good design that avoids some of the problems noted for the RCT (i.e., ethics, cost, but practitioners need to pay, in their analyses, special attention to pretreatment group differences.

Many practitioners will not have access to large populations, and many others will not have the resources (e.g., time, money), or desire, to invest in protocols that go much beyond their own case load. This means that whatever research contribution clinicians make toward outcome evaluations will need to be based on designs that can be implemented with individual patients. In other words, data would be based on the single-case design, and replications thereof.

Research designs for few cases

The *single-case design* is often viewed as an inferior contribution to the research base because it is a methodology from which scientific inference about causality cannot be made (i.e., due to a lack of control) with as much confidence as in other designs (Kazdin, 1986). In the most basic single case study, the A/B design, assessments are repeatedly taken from one person before and after an intervention, with a follow-up period six or 18 months later (see Hayes (1986) for other single case designs). Single case designs have two important problems, namely that external and internal validity is perceived to be poor. Because a single case is examined, one cannot be sure that a change is based on a "genuine" effect of the intervention (i.e., internal validity threatened). For the same reason, results are not seen as easily generalisable to the rest of the population (i.e., external validity threatened). However, safeguards can be put in place to address both these issues, and practitioners can make important contributions to the outcome research using this design.

Confidence in internal validity in the single-case experiment can be enhanced by (1) repeated and reliable measurement and (2) baseline stability. The measurement of outcomes prior to and after the initiation of treatment is essential. First, response to therapy should be assessed in at least three relevant domains (e.g., behavioural, physiological, cognitive, emotional) (Kazdin, 1986). Second, outcomes need to be measured along criteria that reflect both the client perspective and the therapeutic standard. Therefore, in addition to "helpfulness" ratings, one needs to use well-validated measures. Assessments should be designed so that they can be administered repeatedly over a short space of time. Third, outcomes should also reflect the different needs of those concerned with therapeutic interventions. For example, the efficiency, cost, and cost effectiveness (resources consumed versus outputs produced) of interventions should also be examined, as such information is often required by those who fund healthcare (e.g., government, insurers, etc). Finally, the frequency of assessments should sufficient to establish the stability of the 'problem' both prior to and after the initiation of treatment, and cover a period that allows change to have taken place.

The second problem associated with the single case design, that of poor generalisability, can be addressed through replication. The accumulation of a few cases from the same

practitioner, documenting similar patterns of change over time can substantially increase the external validity of case study findings. This is more so if replicated changes are large, as this will increase the likelihood that the findings can be generalised to other patient groups (Hayes, 1986). External validity further benefits from replication across practitioners and across different types of measurements.

Future directions in infertility research

The field of infertility counselling is young compared to that of psychotherapy, and psychotherapy outcome research offers much insight into the sorts of questions we need to ask. So far, we know that psychological interventions in infertility are generally beneficial so that we may no longer need to ask whether they are warranted – reviews demonstrate that they are (Boivin, 2003, de Liz & Strauss, 2005). However, we do not know what ingredients make useful interventions useful or what ingredients make unhelpful interventions unhelpful. The main finding of these reviews is that educational interventions produce greater benefits than expressive-supportive interventions. However, we do not know why this effect is produced. It may be that the educational programs are critical because most were delivered to women in treatment where distress is caused mainly by procedural events (e.g., waiting for test results, failed treatment). This relative advantage may be diminished (or reversed) were educational programmes administered to people who ended treatment, and were dealing with more existential issues (e.g., what they will do with the rest of their life if they end treatment and decide to remain childless). That is, people out of treatment, may have entirely different needs, which may be better served by supportive interventions, especially when people end treatment (Boivin et al. 2005). Second, educational interventions were mainly delivered to groups whereas expressive-supportive interventions were mainly delivered to individual or couples. Therefore, the "active ingredient" may be group experiences (e.g., validation and normalisation) rather than the educational or knowledge component per se. Third, the successful interventions incorporated many different components, all of which may or may not be important to its success. For example, Domar et al. (2000) and Clark et al. (1995) both include a significant life style component to their interventions so that well-being may have improved because of changes in weight, for example, rather that the opportunity to discuss feelings about infertility. Finally, both reviews whilst providing overall support for interventions noted substantial variation in the amount of change. This variation suggests the presence of moderators impacting on the link between intervention and outcome. For example, Holzle et al. (2002) found that although their expressive-supportive intervention was not successful, it produces some important positive changes for those who experienced high distress at baseline.

Conclusions

It is clear that pressure will continue to be exerted on practitioners to demonstrate the effectiveness of their practice by their code of practice, those who pay for psychosocial interventions (e.g., patients or clients, governments, insurers) and their own desire to deliver the most effective treatment to their patients. The question for counsellors in this field is how best to respond to that pressure, and various approaches to the evaluation of psychological interventions were discussed. Even if practitioners cannot become

involved in large surveys or randomised control trials, research based on their own caseload can contribute meaningfully to the general knowledge base.

References

Asay TP, Lambert MJ, Gregersen AT, Goates MK. Using patient-focused research in evaluating treatment outcome in private practice. Journal of Clinical Psychology 2002;58:1213-25.

Boivin, J. (2003). A review of psychosocial interventions in infertility. Social Science and Medicine, 57 (12), 2325-2341.

Boivin, J. Takefman, J., Braverman, A. (2005) Giving bad news: It's time to stop. In N. Macklon (Ed.). Assisted Reproduction in the Complicated Patient (p.233-240). Taylor & Francis, London.

Chambless, D.L. & Hollon, S.D. (1998). Defining Empirically Supported Therapies. Journal of Consulting and Clinical Psychology, 66, 7-18.

Clark, A.M., Ledger, W., Galletley, C., Tomlinson, L., Blaney, F., Wang, X., & Norman, R.J. (1995). Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Human Reproduction, 10*, 2705-2712.

Corrie S, Callahan MM. A review of the scientist–practitioner model: Reflections on its potential contribution to counselling psychology within the context of current health care trends. Br J Med Psychol 2000;73:413-27.

de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. Human Reproduction 2005;20:1324–1332.

Domar, A.D., Clapp, D., Slawsby, E., Kessel, B., Orav, J., & Freizinger, M. (2000). The impact of group psychological interventions on distress in infertile women. *Health Psychology*, *19*, 568-575.

Hayes SC. The role of the individual case in the production and consumption of clinical knowledge. In: Hersen M, Kazdin AE, Bellack AS, eds. The Clinical Psychology Handbook. New York: Pergamon, 1986;181-96

Holzle, C., Brandt, U., Lutkenhaus, R. & Wirtz, M. (2002). Solution-focused counselling for involuntarily childless couples. In B. Strauss (Ed.), *Involuntary Childlessness: Psychological assessment, counselling and psychotherapy* (pp. 105-126). Seattle: Hogrefe & Huber Publishers.

Kazdin AE. Treatment research: The investigation and evaluation of psychotherapy. In: Hersen M, Kazdin AE, Bellack AS, eds. The Clinical Psychology Handbook. New York: Pergamon, 1986;265-88.

Kendall, P.C. (1998). Empirically supported psychological therapies. Journal of Consulting and Clinical Psychology, 66, 3-6.

Khan, K.S., Riet, G., Popay, J., Nixon, J. & Keijnen, J. (2001). Study quality assessment. In Khan, Riet, Glanville, Sowden & Kleijnen (Eds.). *Undertaking systematic reviews of research on effectiveness: CRD's Guidance for those carrying out or commissioning reviews. CRD Report number 4* (2nd ed. pp. 1-20). York: NHS Centre for Reviews and Dissemination.

NICE, National Institute of Clinical Excellence. Treatment Choice in Psychological Therapies and Counselling: Evidence Based clinical Practice Guidelines. London:Department of Public Health, 2001.

Shadish WR, Matt GE, Navarro AM, Phillips G. The effects of psychological therapies under clinically representative conditions: A meta-analysis. Psychological Bulletin 2000;126:512-29.
Wampold, B.E., Mondin, G.W., Moody, M., Stich, F., Benson, K., & Ahn, H. (1997). A meta-analysis of outcome studies comparing bona fide psychotherapies: Empirically, “All must have prizes”. Psychological Bulletin, 122 (3), 203-215.

Follow up of children conceived with fertility treatment

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Learning objectives

1. Briefly describe follow-up studies of children born following fertility treatment (behavioural, cognitive and neurological sequelae)

2. Evaluate the evidence from these follow-up studies

Summary
A considerable number of children have been born following some sort of assisted reproductive technology (ART) and there are now a large number of studies, which have evaluated various indices of the development of children born following ART. Theoretically, concern about the long-term development of children born following ART might be warranted for a number of reasons including: Psychological issues (e.g. difficulties in the transition to parenthood for ART parents, concerns for the well-being of parents and children where donated gametes are used in ART); obstetric risks linked with ART (e.g. increased multiple birth rate (and therefore increased rates of prematurity and low birth weight); effects that the process of assisted reproductive techniques *per se* may have on the developing embryo (e.g. culture media, cryopreservation, micromanipulation associated with ICSI). Theoretically, these and other factors could influence outcomes for ART children. Considerable effort has been put into evaluating the long-term development of children born following assisted reproductive technologies (ART). Follow-up studies can be grouped according to the outcome they examine:
1) Parent-child relationship in ART families; 2) socio-emotional development of ART children; 3) cognitive development of ART children; 4) prevalence of physical and neurological problems/anomalies in ART children; 5) neonatal outcomes in ART children. The primary focus of this summary will be studies that examine outcomes 2 - 4 as these outcomes are measures of child adjustment, development and health. On the other hand, outcomes 1 and 5 are not *direct* measures of child development but rather, are factors that are associated with child adjustment.

1. Parent-child relationship
The primary focus of a large number of studies that follow-up ART children has been the adjustment of parents, parenting qualities (e.g. expressed warmth, perceived parenting stress) and the parent-child relationship. Research has examined parenting behaviour and the parent-child relationship because these factors show significant associations with children's behaviour and adjustment in naturally conceived (NC) children. Studies of parenting behaviours in ART versus NC control groups have generally reported few significant mean level differences. Parenting differences reported once the offspring reach childhood (rather than studies of infants) tend to be of slightly more positive parenting characteristics in the ART group. For example, lower parenting stress, less inconsistent discipline, higher maternal warmth and higher levels of commitment to parenting have been reported in IVF groups compared to NC control groups (e.g. Golombok et al 2001; Golombok et al 2002; Hahn & DiPetro, 2001; Tully et al., 2003; Barnes et al., 2004). The only replicated negative differences reported have been of over-protectiveness in the ART parents and a perception that the child is vulnerable. Cultural differences and the social context in which the child is

brought up appear to influence results. For example, Cook and colleagues (1997) found differences between IVF families in Eastern and Western Europe with greater levels of parenting stress reported in the Eastern European sample.

Although statistically significant, these differences in parenting style appear to be relatively small in magnitude (i.e. they are within the normal range). For example, several studies have reported differences in parenting characteristics in ART groups (IVF, DI and IVF with oocytes donation) yet no significant differences on child adjustment measures have been reported. The implication therefore is that these differences in parenting behaviours are not of a sufficient magnitude to have an impact on the assessments of child adjustment. To date, the longest follow-up studies include children in early adolescence (age 12). Therefore, studies with longer follow-up periods are needed to examine the impact of potential parenting differences in ART families on the adjustment of children once they reach the transition to adolescence and young adulthood. For example, some authors have suggested that parental over-protectiveness may have deleterious effects on children's adjustment as children approach adolescence since autonomy and personal independence become more important for an individual's development during this transition period. Birth order and plurality may also be important influences (Colpin, 2002).

2. Socio-emotional development and child behaviour

Studies examining the socio-emotional development of children have examined a variety of outcome measures including temperament and personality traits, self concept (e.g. self esteem), emotional and behavioural problems (e.g. anxiety, concentration difficulties, disruptive behaviour). The approach used by most studies has been to compare scores on questionnaire measures of child behaviour (as rated by the parents, sometimes by teachers and less often by the children themselves) in ART groups versus various NC control groups. Some studies differ in that face-to-face interviews have been used. A multi-informant approach where information is obtained from multiple informants is considered the 'gold standard'. Generally, studies report that psychologically, children born following a variety of assisted reproductive technologies (homologous IVF, DI, IVF with oocyte donation) are relatively well adjusted and do not show substantial differences compared to children conceived naturally. The majority of studies have not found significant mean level differences between ART and NC groups. Those that have reported significant differences have tended to be rather subtle differences and there is no clear pattern of results. For instance, some studies have reported slightly more positive outcomes in children born following ART, while others have reported the opposite result. For example, a UK study reported that children aged 4-8 born following DI rated themselves as more cognitively competent than NC children (Golombok et al, 1999). Similarly, an international study reported that 5 year old children born following ICSI showed lower levels of externalising (disruptive) behaviour than NC controls (Ponjaert-Kristoffersen et al., 2004). On the other hand, an Israeli study, reported that children born following IVF had more emotional and behavioural problems (as assessed by teachers and the children themselves) compared to NC children (Levy-Shiff et al., 1998).

An alternative approach to research on child behaviour has been to link fertility treatment records to child health records. For example, Stromberg et al (2002) examined behavioural or developmental problems that required assessment/treatment by a health care professional e.g suspected developmental delay. In a large cohort of IVF twins and singletons suspected developmental delay was more common than in NC controls (odds ratio=4.0, 95% CI = 1.9, 8.3) but there was no difference in the prevalence of behavioural disorders that received health care treatment. These sorts of record linkage studies are much larger than those that use questionnaires or interviews to assess children's development but the measures of adjustment used are not as comprehensive. Nonetheless, in the main, studies to date report

that children born following ART are functioning well in terms of socio-emotional development.

3. Cognitive development

The majority of studies that have obtained detailed assessments of children's cognitive development (e.g. Bayley scales of infant development, Wechsler IQ tests) have been carried out in young children (aged 1 to 5 years) and have focussed on children born following ICSI. Results have been mixed. The study of Bowen and colleagues (1998) reported lower levels of infant development in ICSI children compared to IVF and naturally conceived control groups. They also reported that infants born after ICSI were more likely to score 1 standard deviation below the mean (i.e. show mild developmental delay). Since then, there have been a number of studies. One UK study of young children aged 17 months on average reported no significant differences in cognitive development in ICSI versus NC children. A small Greek study again found no significant difference. A follow-up of the original Bowen cohort at age 5 found that the differences reported had reduced to a trend (the percentage of children scoring 1 standard deviation below the mean was 5.2%, 2.5% and 0.9% in the ICSI, IVF and NC groups respectively). Another small study found differences between ICSI, IVF and NC children at age 3 with both of the ART groups scoring lower than the NC group. However, once parental education was controlled for, this pattern of results was reduced to a trend. In a large international study comparing ICSI and NC children at 5 years of age, Ponjaert-Kristoffersen et al (2004) found evidence of poorer performance in children born following ICSI on 3 performance-scale tasks of the Wechsler Preschool test (object assembly, block design and mazes - visuo-spatial tasks that require fine motor coordination). This difference appeared to be clinically relevant in that ICSI children were more likely to score 1 standard deviation below the mean on the 3 performance scale tests. In addition, ICSI children performed slightly more poorly on a test of fine motor coordination. However, in another large, international sample Ponjaert-Kristoffersen et al (2005) found no significant differences in cognitive functioning and motor ability between ICSI, IVF and NC children at age 5. Differences between NC control groups might account for some of the differences in results across studies. Although results are mixed, on balance, it seems that there may be *slight* differences in cognitive performance in young children born following ICSI in comparison to NC children. . It is unclear whether these differences are sufficiently large to be of clinical relevance, and whether ICSI children perform more poorly on cognitive assessments in comparison to children born following IVF treatment who would be similar on obvious confounders (e.g. prematurity, plurality). It is also not known if reported differences in children born following ICSI will persist into middle childhood.

4. Low birth weight and prematurity

It has been widely demonstrated that children conceived following IVF or ICSI have an increased risk of experiencing obstetric complications. Much of this effect is likely to stem from the increased rate of multiple births associated with ART and perhaps also sub-fertility of the couple - parents with children conceived via ART tend to show a number of characteristics, which might also influence obstetric risk e.g. older age at birth of first child, high rates of primiparity. Many studies have shown that once one accounts for plurality either by using statistical controls or by including only singletons in analyses, the obstetric risks for an IVF baby are reduced compared to naturally conceived (NC) controls. However, a number of peri-natal risks have been reported in IVF singletons compared to NC controls and these have the potential to impact upon these children's later development. For instance, even singletons born following IVF treatment are more likely to be low birth weight (<2500 grams) than NC controls (Schieve et al., 2004), more likely to be born prematurely and more likely to be born small for gestational age (Helmerhorst et al., 2004; Jackson et al., 2004). The deleterious effect of low birth weight and prematurity on children's later emotional/behavioural and cognitive development and physical health has been well documented (e.g. Bhutta et al., 2001; Marlow et al., 2005). Therefore, even when one

accounts for multiple births, children born after IVF and ICSI experience neonatal disadvantage, which could impact on their later development. However, some interesting preliminary evidence suggests that a positive rearing environment may buffer some of the risk of being low birth weight. For example, Tully and colleagues (2004) found that maternal warmth moderated the relationship between low birth weight and ADHD (attention deficit hyperactivity disorder). Given the findings of positive parenting in ART groups this is reassuring.

5. Congenital abnormalities

A number of reports have suggested that children conceived following IVF and ICSI show an elevated rate of congenital abnormalities compared to NC children (e.g. heart defects, chromosomal abnormalities, neurological problems including cerebral palsy) (Lancaster, 1987; Bergh et al., 1999; Anthony et al., 2001; Stromberg et al., 2002; Hansen et al., 2002; Hansen et al., 2005 – meta analysis). Hansen and colleagues undertook a meta-analysis of existing data and found that 15 of 25 studies showed a 25% or greater increased risk of congenital abnormalities in infants born following ART. This meta-analysis also showed a significant increased risk even when only singletons were included in the analysis (odds ratio= 1.3, equivalent to a 30% increase in the ART group). One study, by Bonduelle and colleagues (2005) found that the rate of congenital abnormalities was significantly higher only in the ICSI group not the IVF group compared to NC children.

The low incidence of congenital abnormalities in the general population means that large samples are needed to examine the prevalence in ART versus NC children. Consequently, most work has been carried out in countries or states which have computerised registers where IVF registers can be linked to registers that document congenital abnormalities or child health centres (e.g. Sweden, Australia) or establishment of international cohorts (e.g. Bonduelle et al., 2005). However, sample sizes may still be too small to examine the risk of narrowly defined congenital abnormalities (rather than abnormalities lumped together) because of the low prevalence of these problems in the general population. Low statistical power to detect effects may mean that smaller studies fail to report true associations (type 2 error) (Buck Louis et al., 2004). Thus, it is unclear whether there is a true increase in the rate of congenital abnormalities in ART families.

Evaluation and Future research

Larger samples

Research examining outcomes of children born following ART is well underway.
One difficulty of carrying out studies of child adjustment (emotional, behavioural and cognitive) is that the process is labour intensive. Thus, although sample sizes are increasing, they are still relatively small and probably under-powered to detect subtle effects on children's emotional and behavioural development and this highlights the need for collaborative studies which are underway.

Follow-up studies of rarer treatment groups

Follow up studies are obviously only possible once a techniques has become common clinical practice. This means that the number of follow-up studies differs according to how long different treatments have been common practice – with fewer studies of children born following egg donation compared to DI or IVF and even fewer of children born following embryo donation or surrogacy. Thus, more follow-up studies of rarer treatment groups are needed to evaluate outcomes for children and families in these groups.

Longer follow-up periods

Even studies with the longest follow-up periods have only begun to assess children in early adolescence. Longer term follow up studies are essential to examine the transition to adulthood and also to examine physical and emotional health outcomes in adulthood – many

chronic health problems have their onset in adulthood. Furthermore, reproductive outcomes for children born following ART can obviously only begin once the children have reached adulthood.

Follow-up studies of multiple births

Many studies have excluded twins and higher order multiples from follow-up studies. There are methodological reasons for doing this – to avoid detecting effects in the ART group due to plurality and because of the effects of twinning on early cognitive development. However, an elevated rate of multiple births is an important consequence of ART and has been the subject of much debate. Multiple births are associated with poor neonatal outcomes in comparison to singleton births. Moreover, parenting twins is often associated with particular stresses both in ART and NC groups. Thus, excluding twins from follow-up studies underestimates difficulties that ART parents may experience in raising their children. Excluding twins from follow-up studies also means that effects, which are due to plurality rather than ART or characteristics of ART families, are not identified. It is important to be able to disentangle effects of ART and effects of plurality on outcomes for children as this has implications for advice prospective parents receive from fertility clinics. Further work that examines outcomes in groups of ART twins versus NC twins is warranted.

Variation within the ART groups

Most studies have compared mean scores between ART and NC groups. Few studies have looked at individual differences within the ART group. Thus, although most ART children do not show problems, it is important to identify the reasons why a small number of children do experience problems and also to evaluate whether the fertility treatment experience could have contributed.

Suggested reading

1. Golombok, S. and MacCallum, F. (2003). Practitioner review: Outcomes for parents and children following non-traditional conception: what do clinicians need to know? J Child Psychol Psychiatr., 44, 303-315.
2. Colpin, H. (2002). Parenting and psychosocial development of IVF children: review of the research literature. Dev Review 22, 644-673.
3. Devroey, P. and Van Steirteghem, A. (2004). A review of 10 years of experience of ICSI. Hum Reprod Update. 10,19-28.

References

1. Anthony, S., Buitendijk, S. E., Dorrepaal, C. A., Lindner, K., Braat, D. D., & den Ouden, A. L. (2002). Congenital malformations in 4224 children conceived after IVF. Hum Reprod, 17(8), 2089-2095.
2. Barnes, J., Sutcliffe, A. G., Kristoffersen, I., Loft, A., Wennerholm, U., Tarlatzis, B. C., et al. (2004). The influence of assisted reproduction on family functioning and children's socio-emotional development: results from a European study. Hum Reprod, 19(6), 1480-1487.
3. Bergh, T., Ericson, A., Hillensjo, T., Nygren, K. G., & Wennerholm, U. B. (1999). Deliveries and children born after in-vitro fertilisation in Sweden 1982-95: a retrospective cohort study. Lancet, 354(9190), 1579-1585.
4. Bhutta, A. T., Cleves, M. A., Casey, P. H., Cradock, M. M. and Anand, K. J. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA, 288(6), 728-737.
5. Bonduelle, M., Wennerholm, U. B., Loft, A., Tarlatzis, B. C., Peters, C., Henriet, S., et al. (2005). A multi-centre cohort study of the physical health of 5-year-old children conceived after intracytoplasmic sperm injection, in vitro fertilization and natural conception. Hum Reprod, 20(2), 413-419.
6. Buck Louis, G. M., Schisterman, E. F., Dukic, V. M., and Schieve, L. A. (2005). Research hurdles complicating the analysis of infertility treatment and child health. Hum Reprod, 20(1), 12-18.

7. Cook, R., Vatev, I., Michova, Z. and Golombok, S. (1997). The European study of assisted reproduction families: a comparison of family functioning and child development between Eastern and Western Europe. J Psychosom Obstet Gynaecol, 18(3), 203-212.
8. Golombok, S., MacCallum, F. and Goodman, E. (2001). The "test-tube" generation: parent-child relationships and the psychological well-being of in vitro fertilization children at adolescence. Child Dev, 72(2), 599-608.
9. Golombok, S., MacCallum, F., Goodman, E. and Rutter, M. (2002). Families with children conceived by donor insemination: a follow-up at age twelve. Child Dev, 73(3), 952-968.
10. Golombok, S., Murray, C., Brinsden, P. and Abdalla, H. (1999). Social versus biological parenting: family functioning and the socioemotional development of children conceived by egg or sperm donation. J Child Psychol Psychiatry, 40(4), 519-527.
11. Hahn, C. S. and DiPietro, J. A. (2001). In vitro fertilization and the family: quality of parenting, family functioning, and child psychosocial adjustment. Dev Psychol, 37(1), 37-48.
12. Hansen, M., Bower, C., Milne, E., de Klerk, N. and Kurinczuk, J. J. (2005). Assisted reproductive technologies and the risk of birth defects--a systematic review. Hum Reprod, 20, 328-338.
13. Hansen, M., Kurinczuk, J. J., Bower, C., & Webb, S. (2002). The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. N Engl J Med, 346(10), 725-730.
14. Helmerhorst, F. M., Perquin, D. A., Donker, D. and Keirse, M. J. (2004). Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ, 328(7434), 261.
15. Jackson, R. A., Gibson, K. A., Wu, Y. W. and Croughan, M. S. (2004). Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol, 103(3), 551-563.
16. Lancaster, P.A. (1987). Congenital malformations after in-vitro fertilisation. Lancet, 2(8572), 1392-3.
17. Levy-Shiff, R., Vakil, E., Dimitrovsky, L., Abramovitz, M., Shahar, N., Har-Even, D., et al. (1998). Medical, cognitive, emotional, and behavioral outcomes in school-age children conceived by in-vitro fertilization. J Clin Child Psychol, 27(3), 320-329.
18. Marlow, N., Wolke, D., Bracewell, M. A. and Samara, M. (2005). Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med, 352(1), 9-19.
19. Murray, C., MacCallum, F. and Golombok, S. (2006). Egg donation parents and their children: follow-up at age 12 years. Fertil Steril, 85(3), 610-618.
20. Ponjaert-Kristoffersen, I., Bonduelle, M., Barnes, J., Nekkebroeck, J., Loft, A., Wennerholm, U. B., et al. (2005). International collaborative study of intracytoplasmic sperm injection-conceived, in vitro fertilization-conceived, and naturally conceived 5-year-old child outcomes: cognitive and motor assessments. Pediatrics, 115(3), e283-289.
21. Ponjaert-Kristoffersen, I., Tjus, T., Nekkebroeck, J., Squires, J., Verte, D., Heimann, M., et al. (2004). Psychological follow-up study of 5-year-old ICSI children. Hum Reprod, 19(12), 2791-2797.
22. Schieve, L.A., Meikle, S.F., Ferre, C., Peterson, H.B., Jeng, G., Wilcox, L.S. (2002). Low and very low birth weight in infants conceived with use of assisted reproductive technology. New Engl J Med, 346, 731-7.
23. Stromberg, B., Dahlquist, G., Ericson, A., Finnstrom, O., Koster, M., & Stjernqvist, K. (2002). Neurological sequelae in children born after in-vitro fertilisation: a population-based study. Lancet, 359(9305), 461-465.
24. Tully, L. A., Arseneault, L., Caspi, A., Moffitt, T. E., and Morgan, J. (2004). Does maternal warmth moderate the effects of birth weight on twins' attention-deficit/hyperactivity disorder (ADHD) symptoms and low IQ? J Consult Clin Psychol, 72(2), 218-226.
25. Tully, L. A., Moffitt, T. B., and Caspi, A. (2003). Maternal adjustment, parenting and child behaviour in families of school-aged twins conceived after IVF and ovulation induction. J Child Psychol Psychiatry, 44(3), 316-325.

TRANSITION TO BIOLOGICAL CHILDLESSNESS

Judith C. Daniluk, Ph.D.

Transition Literature

- **Considerable literature addressing:**
  - adjustment to infertility during medical treatment
  - the transition to parenthood following infertility
  - coping with failed treatment cycles
- **Very little literature addressing:**
  - what happens to couples after infertility treatments fail and they are faced with adapting to permanent, biological childlessness (Sandelowski, 1993; Wirtberg, 1992)

Daniluk, J.C. (in press; 2001)

- **3 year, longitudinal study on transition to biological childlessness after failed fertility treatment (based on Schlossberg's '94 non-event transition conceptualization)**
  - **Situation** - cause, nature and situation characteristics *(diagnostic and parental status)*
  - **Self** – demographic characteristics & psychological resources of the individual *(gender, age, perceived physical and emotional health)*
  - **Support** - social supports and available options
  - **Strategies** – coping methods *(problem vs. emotion-focused coping)*

Daniluk, J.C. (in press; 2001)

Research Questions:

1. How do women and men adapt over time to the transition to biological childlessness, as evidenced by their *marital, sexual and life satisfaction, self esteem*, and *symptomatic psychological distress*?
2. Does *parental status* by the conclusion of the study predict adaptation to biological childlessness?
3. Are there significant differences across time in adaptation to biological childlessness, based on: *gender, age, diagnostic status, physical and emotional health, coping style, perceived support,* and *the availability of other acceptable parenting and role options*?

Daniluk, J.C. (in press; 2001)

- **Mixed-Methods Study**
  - **4 questionnaire packages**: completed independently by partners, within 3 months of termination and at 13, 23 & 33 months post-treatment termination
  - **4 in-depth, semi-structured, tape-recorded, qualitative, couple interviews**: 10 month intervals beginning within 3 months after Rx termination

Daniluk, J.C. (in press; 2001)

Sample Description

- **38 infertile couples (25 – 58 yrs.; M = 37.36)**
- **94% Euro-Canadian, 5% Asian-Canadian**
- **Highly educated, economically advantaged**
- **Mean years trying to conceive = 6.92**
- **Mean years seeking treatment = 5.91**
- **Percentage who did IVF = 49.4**
- **Percentage with "unexplained" = 53%**

Daniluk, J.C. (in press; 2001)

- Treatment termination self-initiated by 95% of couples because of:
  - Emotional exhaustion 50%
  - Health concerns 20%
  - Successful adoption 15%
  - Financial issues 15%
  - Relationship strain 10%

Daniluk, J.C. (in press; 2001)

- Acceptable parenting or role options at Rx termination:
  - Adoption 50%
  - Life without children 12%
  - No acceptable role options 30%

NOTE: 50% had made the transition to adoptive parenthood by the conclusion of the study

Quantitative Findings

- *Four Factors* related to poorer adaptation over time:
  - Perceived lack of available and acceptable parenting or role options
  - Perceived lack of social support (from sign. Others & medical staff)
  - Poor subjective emotional and physical health
  - Use of emotion-focused coping

Quantitative Findings

- Poorer adaptation evidenced by:
  - More, and more severe symptoms of psychological distress
  - Lower marital, sexual, and life satisfaction
  - Lower self esteem

Quantitative Findings

Other Important Findings

- Significantly better adjustment for those who became parents versus those who had not, by the conclusion of the study (especially those awaiting adoption)
- Continued and persistent decrease in sexual satisfaction for all couples throughout the study

Qualitative Findings

FOUR Thematic Categories

- *Hitting the Wall* (3 months)
- *Reworking the Past* (13 months)
- *Turning Toward the Future* (23 months)
- *Renewal and Regeneration* (33 months)

Theme 1: Hitting the Wall

- Futility and hopelessness
- Physical, emotional & spiritual depletion
- Profound loss and grief
- Feelings of emptiness & missed experience
- Marginalization and isolation

Theme 1: Hitting the Wall

- Sense of failure and despair
- Cocooning or turning inward
- Identity confusion
- Ambiguity and dread related to the future
- Relief at being released from the pursuit of medical treatment

Theme 2: Reworking the Past

- Feelings of anger, outrage and sometimes guilt
- Sense of lethargy and ennui
- Lack of purpose and future direction
- Sense of paralysis regarding future decisions
- Critical assessment of significant relationships and values
- Growing acceptance of infertile identity

Theme 2: Reworking the Past

- Reworking notions of femininity and masculinity
- Attempts to initiate and achieve closure
- Attempt to make sense of infertility and treatment efforts
- Public acknowledgement of fertility status
- Growing acknowledgment & acceptance of the uncontrollability of life

Theme 3: Turning Toward the Future

- Tentative steps towards re-envisioning the future
- Rejection of traditional notions of parenthood and family
- Clearer sense of personal boundaries
- Diminished faith in medical system
- Increased sense of personal responsibility for own health and healing
- Growing sense of possibility and hope

Theme 3: Turning Toward the Future

- Increased sense of balance and control
- Reinvestment of energy in other creative labours
- Greater self-acceptance and self redefinition
- Renewed commitment to their marriage
- Reestablishment of social networks
- Surprise at residual aftermath of infertility

Theme 4: Renewal and Regeneration

- Sense of being a survivor vs. a victim of circumstance
- Recognition of gains associated with surviving infertility
- Integration of infertility into self structure
- Renewed sense of efficacy and agency
- Strong sense of the rights of the infertile

Theme 4: Renewal and Regeneration

- Sense of normalcy and restored equilibrium (personally and in their relationships)
- Sense of infertility as "part of their history"
- Sense of closure and having come "full circle" for those who became parents
- Sense of continued uncertainty about the future, for those awaiting adoption

Clinical Implications

Important Clinical Considerations

- Coping with infertility during treatment may be qualitatively different than adapting to permanent biological childlessness:
  - don't assume women struggle more than men
  - don't assume that younger clients adapt easier than older clients
- Adapting to failed treatment and permanent biological childlessness is a *process* that occurs over time:
  - be aware of where clients are in this process
  - appreciate the fact that "time heals"

Early Intervention: Hitting the Wall

- **Facilitate griefwork** (pregnancy, childbirth, parenting, genetic continuity, time, opportunities, etc.)
  - *art therapy, rituals, letter to unborn child*
- **Assess physical and psychological health** (emotional exhaustion; somatic complaints; depression)
  - *Consult and refer if necessary*
- **Emphasize self-care** (physical and emotional health critical)
  - *sleep, nutrition, exercise, "quiet time"*
- **Encourage moratorium on major life decisions**
  - *career decisions, moving, parenting*

Year 1: Reworking the Past

- **Acknowledge and work through anger** (injustice of infertility, pain and humiliation of medical investigations and treatment, false hope, interpersonal insensitivity of others, invasive adoption process, structural barriers to adoptive parenting, etc.)
  - *journaling, body work, letters to offenders, direct communication (with ownership)*
- **Help work through guilt and shame** (humiliation, perceived punishment, inadequacy)
  - *reworking targeted event, forgiveness rituals, separate biological reality from punishment, spiritual guidance*

Year 1: Reworking the Past

- **Deal with "identity shock"** (Matthews & Matthews, 1986; no longer "not yet pregnant," Griel, 1991)
  - *"who am I" exercise*
- **Begin to rework notions of masculinity and femininity**
  - *gender assessment pre-infertility; other childless wo(men)*
- **Separate personal worth and value from fertility status**
  - *nonparental contributions, values*

Year 1: Reworking the Past

- **Begin healing and strengthening relationship** (communication, sexual rel's, recommitment, assessing strengths)
  - *"In this together" – shared journey*
- **Help identify and access reliable sources of support**
  - *friends, family members*
  - *other infertile individuals or couples (support groups can be helpful at this time if ready)*

Year 2: Turning Toward the Future

- **Consideration of other life options, including childless/free living**
  - *"If not children, then what?"*
  - *examination of meaning and importance of "parenthood" and "genetic ties"*
  - *separating desire to reproduce from desire to parent*
  - *values clarification (individual and couple) with attention to critical differences in parenting goals*

Year 2: Turning Toward the Future

- **Challenging of traditional notions of family**
  - *"Must we have children to be a family? Can a couple be a family?"*
  - *"What can we cope with?" (race, colour, etc.)*
- **Encourage refocusing and reinvestment of energy into other meaningful and creative labours** (school, hobbies, travel, other passions, adoption, etc.)
  - *values clarification*
  - *(re)visioning the future (guided fantasy: 10 years; 20 years; later life)*

Year 2: Turning Toward the Future

- **Encourage re-establishment of old, and/or creation of new social networks** (consistent with current and future lifestyle choices and values)
  - *healing of significant relationships*
  - *reconnecting with family and friends*
  - *public acknowledgment of infertility*

Year 3: Renewal and Regeneration

- **Emphasis on meaning-making and "taking stock" of gains rather than losses** (individual, couple, social)
  - *lessons learned, growth, etc.*
- **Continue work on intimacy and sexuality**
  - *problem assessment*
  - *body work, sensate focus, communication, non goal-directed intimacy*

Year 3: Renewal and Regeneration

- **Reinforce and support active pursuit of other role options**
  - *love and work*
- **Continued support for those awaiting adoption**
  - *taking and relinquishing control*
  - *taking life "off hold"*
- **Assist with transition to parenthood issues for new parents**

Indicators of Continued Distress

- Inability to make, and act on, other important life decisions
- Inability to bond with non-genetic child (through adoption or collaborative reproduction)
- Ongoing, non-specific lethargy, sadness or depression (ongoing/incapacitating grief)
- Inability to "make sense of" and "let go of" infertility experiences
- Inability to identify and accept other parenting or role options
- Inability to "forgive" self or partner for infertility or treatment decisions
- Lack of agreement with partner re: future parenting or life options

Indicators of Healing

Adaptation (Schlossberg, 1994)

- Event no longer takes up a great deal of personal or psychological space
- Event no longer taxes the individual's psychological or emotional resources
- Event no longer has a negative influence on the individual's self evaluations

Indicators of Healing

- Freedom to pursue other life options – life is no longer "on hold" (including parenting options or childfree living)
- Ability to "make sense" of fertility experience
- Grief is no longer incapacitating
- Ability to interact more freely and openly with significant (and insignificant) others
- Diminished reactivity/hypersensitivity to fertility-related stimuli
- Infertility like an "old friend" – incorporated into sense of self

Adaptation & Resolution

"Out of all of this, I found me."

"If we never have a child living with us that's going to be OK ... and I'll still be a good person and I'll still be fulfilled and our marriage will still be very happy. We don't have children. I am a wedded unmother ... and that's who I am. Among other things, I'm many other things as well that come higher up on the list."

"To me the past is the past ... it's gone. It's not like I've forgotten it all but it's just that we've lived through it and dealt with it and now it's finished with and we're living for right now rather than carrying around this luggage behind us that we don't need. We've been through so much together, and we're stronger for it. We've survived infertility ... that's what we are – survivors."

Transition Study References

Daniluk, J.C. & Tench, E. (in press). Long-term adjustment of infertile couples following unsuccessful medical intervention. *Journal of Counseling and Development.*

Daniluk, J.C., & Hurtig-Mitchell (2003). Themes of hope and healing: Infertile couples' experiences of adoption. *Journal of Counseling & Development, 81*, 389-399.

Daniluk, J.C. (2001). Reconstructing their lives: A longitudinal, qualitative analysis of the transition to biological childlessness for infertile couples. *Journal of Counseling & Development, 79*, 439-449.

Transition Study References

Daniluk, J.C. (2001). "If we had it to do over again...": Couples' reflections on their experiences of infertility treatments. *The Family Journal: Counseling and Therapy for Couples and Families, 9*, 122-133.

Daniluk, J. C. (1999). When biology isn't destiny: Implications for the sexuality of childless women. *Canadian Journal of Counselling, 33*, 79-94.

Sandelowski, M. (1993). *With child in mind: Studies of the personal encounter with infertility.* Philadelphia: University of Pennsylvania Press.

Wirtberg, I. (1992). His and her childlessness. *Doctoral dissertation*, Karolinska Institutet, Stockholm, Sweden.

Outcome for families using donated gametes in the current context of greater openness

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1. Learning objectives

This presentation aims to update participants' knowledge regarding the outcome of families built with the use of gamete donation. It provides an overview of current research, and discusses clinical aspects and challenges in the light of greater acceptability of and openness about gamete donation.

2. Outcome of families using donated gametes

The possibility of using donated gametes has resulted in a range of different family compositions. These include families with heterosexual and homosexual parents as well as single-parent families who have used donor insemination (DI) or oocyte donation (OD). It also included embryo donation (ED), an option which is receiving increasing attention.

2.1. Families after donor insemination

While previous research was concerned with psychological adjustment of couples undergoing treatment, more recently, a number of studies have investigated into the psychological and social development of children conceived by DI and the dynamics of families built as a result of DI. One of the most comprehensive studies compared children conceived by DI with those conceived by other assisted human reproduction methods as well as with adopted children and those conceived spontaneously (Golombok et al. 2002). Children conceived by DI were found to develop as healthily as other children and the authors concluded that the absence of a genetic link between the father and the child did not interfere with the development of a positive father-child relationship. Similar results were obtained in other studies (Brewaeys 2001, Golombok et al. 2004). In all of these studies, only a proportion of the parents had informed their children of their biological origins. Apparently this had not resulted in negative consequences arising from the secrecy for children aged 12 years and younger.

The nature of information sharing – whether parents talk to their children about their use of DI – has received increasing attention. Whereas previously, there was considerable debate amongst professionals about whether parents should be advised to talk to their children about the nature of their conception, more recently, legislation and professional guidelines in several countries have become supportive of information sharing. Furthermore, there is some indication that disclosure rates are rising (Rumball and Adair 1999, Gottlieb et al. 2000, Leeb-Lundberg et la. 2006, Thorn and Daniels in progress). A number of surveys and studies have sought to shed light on the impact of sharing information. In three projects, the experiences of teenagers and adults who had learnt about their conception later in life were examined (Cordray 1999/2000, Hewitt 2002, Turner and Coyle 2000). In all three, respondents reported feelings of mistrust, distinctiveness from the rest of the family and feelings of loss and frustration regarding the unobtainable donor information. They also described the lack of information about their full genetic history as a threat to their identity. Many of the offspring

voiced curiosity about the semen provider; they wanted to have access to medical information as well as information about physical features of the donor and considered it their right to obtain such information. Research on the small number of children who have been aware of their conception from an early age suggests that these children do not show any negative reactions regarding their conception. Though some referred to the semen provider as their "biological father", they did not seem to be looking for a father-figure but used terminology suggesting that this was a significant person for them (Lindblad et al. 2000, Rumball and Adair 1999, Scheib et al. 2004). In 2004, Lycett et al. compared families who endorsed information sharing to those who did not. They reported fewer difficulties amongst the disclosers; mothers in this group reported less frequent and less severe arguments with their children and both parents perceived themselves to be more competent. There was no difference between the groups regarding the father-child relationship. Though the higher numbers of arguments in the non-disclosing group did not represent dysfunctional relationships, the authors concluded that disclosure could benefit family relationships.

In a number of countries including Australia, New Zealand, USA, the UK and The Netherlands, lesbian couples can access DI. Initially, considerable concerns were expressed. Children were feared to develop homosexual tendencies and the absence of a father was considered detrimental to child development. Furthermore, it was feared that children may be ostracized by peers as a result of the unusual family composition. Several studies comparing children conceived by DI growing up in lesbian and heterosexual families indicated that that there is little difference regarding their emotional and behavioural or gender development (Brewaeys 2001, Golombok et al. 2003). Disclosure rates in lesbian families tend to be higher than those in heterosexual families (Brewaeys 2001, Scheib et al. 2003). In a study examining the needs of these children, Vanfraussen et al. (2001) found that, similar to children born to heterosexual couples, these children indicated curiosity and interest in the personality of the semen provider.

Only few studies have investigated the outcome of families built by DI headed by single women. Murray and Golombok (2005a, 2005b) examined 21 solo mothers and compared them to 46 heterosexual families who had used DI. The authors found that "the first cohort of solo DI mothers and their children … continue to function well as the child reaches 2 years of age " (Murray and Golombok 2005b:4). Most mothers intended to disclose their use of DI to their children, but given the young age of these children, it is unknown how these children will react to this information.

As a result of the absence of a father figure in both lesbian and single-mother families, Brewaeys et al. (2005) suggest that only identifiable donors should be used. Given the higher rate of disclosure in these family compositions, more children may voice a need to access their male genetic origins.

2.2 Families after oocyte donation

Oocyte donation has only become possible since the advent of In-vitro-Fertilitsation (IVF), the first cases of OD were reported in 1983. OD is similar to DI in that the child is genetically related to one parent. Unlike DI, however, oocyte donors tend to be more often relatives or friends of the parents and therefore are not anonymous and may have ongoing contact to the family.

A few studies have assessed the outcome of families who have used OD and their psychosocial functioning. Both children's development and family outcome has been reported to be healthy; currently, there is no evidence that children conceived by OD fare less well than

those conceived by IVF, DI or those adopted. (Golombok et al. 2004, Golombok et al. 2005, Murray et al. 2006, Söderstrom-Antilla et al. 1998).

There is anecdotal reporting of gay couples using surrogacy and OD to have a child genetically related to one male partner; to date, little is known how these families fare.

More recently, lesbian couples have asked, in addition to DI, for OD amongst the partners, hoping thus to share more fairly the genetic, gestational and social bonds between the mothers and the child. Little is known about the development of these families.

2.3 Families after embryo donation

In the last months, embryo donation has been discussed in several countries. The reasons this option has received increased attention is the possibility of using the so-called "surplus" embryos. This refers to embryos of those couples who have successfully completed treatment and achieved the desired number of children but still have cryopreserved embryos they do not wish to use anymore; these can be donated. Donated embryos can also stem from two individuals who respectively donated sperm and oocytes but do not have a relationship. Typical indication for embryo donation include couples in which the woman suffers from premature ovarian failure and the man from infertility or where both are carriers of a hereditary disease. There is emerging knowledge regarding the motivations and needs of embryo donors. Newton et al. (2003) found that potential donors include not only those who have completed their family building but also couples who have not yet attained their family goals but empathise with couples experiencing infertility; they also include couples who are more comfortable with sharing personal, non-identifying information. De Lacey (2005) described the decision-process to be ambivalent: on the one hand, couples had altruistic motivations and a desire to help other, on the other hand, this conflicted with their moral values of family and kinship; it seems as if embryo donation in this respect is much closer to the concept of adoption than DI or OD. In New Zealand, this has led to the development of guidelines for ED, which provide for comprehensive counselling, including mutual counselling with both recipient and donor couple. A study comprising 27 recipient women who gave birth to 14 infants suggests a higher risk of obstetric complications but a healthy and normal development of the infants (Söderstrom-Antilla et al. 2001).

2.4 Summary

It appears that children conceived by OD and DI and their families fare well. However, in many studies, young children who have not (yet) been informed about their conception were examined. Little is known about the outcome of those families who have used gametes from a known donor, a family composition that may have much more far-reaching effects on the family relationships. Furthermore, differences within lesbian families (for example single versus two-parent lesbian families) have not received sufficient attention (Bos et al. 2005), and studies on the outcome of families after ED to date are limited. Systematic and long-term research is required to fully understand the consequences of gamete donation for all individuals involved.

3. Implications for clinical practice

Despite ongoing controversy regarding the tolerability of gamete donation, it has become more acceptable and less stigmatised. There are, however, numerous issues and challenges when counselling both donors and recipients. In some countries, there are legal requirements and/or professional guidelines determining the scope of counselling in this area; this has resulted in mandatory counselling in some countries, but there are many countries without any provision for counselling. The following provides an overview of the clinical issues

counsellors are confronted in the light of greater openness; these will be discussed in more detail during the presentation.

- Mandatory versus voluntary counselling for recipients
- Mandatory versus voluntary counselling for donors
- Exploring the option of egg sharing with women undergoing IVF/ICSI
- Supporting individuals and couples undergoing gamete donation abroad because it is illegal in their home country; understanding legal implications regarding paternity and maternity; helping to manage the feeling of illegality
- Assessing the potential for joint counselling for donors and recipients, both in those cases where the donor is a friend/family member or an unknown person
- Counselling for embryo donation/adoption, exploring the meanings when children have genetically full-blood siblings in other families.
- Helping parents to develop and explore meanings and terminology for their family composition, esp. the role and level of involvement of the donor; for heterosexual and homosexual parents as well as for single women
- Supporting parents in their decision for or against information sharing
- Exploring openness under a legal system whereby gamete providers remain anonymous
- Exploring openness in a context where there is little or no educational material for families
- Exploring information sharing in families with teenage and adult offspring

4. References

Bos H, van Balen F, van den Boom D (2005) Lesbian families and family functioning: an overview. Patient Education and Counselling 59:263-275.

Brewaeys A (2001) Review: parent-child relationships and child development in donor insemination families. Human Reproduction Update 7, 38-46.

Brewaeys A, Dufour S, Kentenich H (2005) Sind Bedenken hinsichtlich der Kinderwunschbehandlung lesbischer und alleinstehender Frauen berechtigt? Journal für Reproduktionsmedizin und Endokrinologie 1, 35-40.

Cordray, B. (1999/2000, Winter). An open letter to the HFEA. Donor Conception Network Journal, 3-5.

Golombok, S., Brewaeys, A., Giavazzi, M. T., Guerra, D., MacCallum, F., & Rust, J. (2002). The European study of assisted reproduction families: The transition into adolescence. Human Reproduction, 17(3), 830-840.

Golombok S, Perry B, Burston A, Murray C, Mooney-Somers J, Stevens M, Golding J (2003) Children with lesbian parents: a community study. Developmental Psychology 39, 20-33.

Golombok S, Lycett E, MacCallum E, Murray C, Rust J, Abdella H, Margara R (2004) Parenting infants conceived by gamete donation. Journal of Family Psychology 18, 443-452.

Golombok S, Jadva V, Lycett E, Murray C, MacCallum F (2005) Families created by gamete donation: follow-up at age 2. Human Reproduction 20, 286-293.

Gottlieb, D., Lalos, O., & Lindblad, F. (2000). Disclosure of donor insemination to the child: The impact of Swedish legislation on couples' attitudes. Human Reproduction, 15(9), 2052-2056.

Hewitt, G. (2002) Missing links: Identity issues of donor conceived people. British Journal of Infertility Counselling 9, 14-20.

de Lacey S (2005) Parent identity and "virtual" children: why patients discard rather than donate unused embryos. Human Reproduction 20, 1661-1669.

Leeb-Lundberg S, Kjellberg S, Sydsjö G (2006) Helping parents to tell their children about the use of donor insemination (DI) and determining their opinions about open-identity sperm donors. Acta Obstetricia et Gynecologica Scandinavica 85, 78-81.

Lindblad F, Gottlieb C, Lalos O (2000) To tell or not to tell – what parents think about their children that they were born following donor insemination. Journal for Psychosomatic Obstetrics and Gynaecology 21, 193-203.

Lycett E, Daniels K, Curson R, Chir B, Golombok S (2004) Offspring created as a result of donor insemination: A study of family relationships, child adjustment, and disclosure. Fertility and Sterility 82, 172-179.

Murray C, Golombok S (2005a) Going it alone: solo mothers and their infants conceived by donor insemination. American Journal of Orthopsychiatry 75, 242-253.

Murray C, Golombok S (2005b) Solo mothers and their donor insemination infants: follow-up at age 2 years. Human Reproduction Advanced Access published February 25, 2005, 1-6.

Murray C, MacCallum F, Golombok S (2006) Egg donation parents and their children: follow-up at age 12 years. Fertility and Sterility 85, 610-618.

Newton C, McDermid A, Tekpetey F, Tummon I (2003) Embryo donation: attitudes toward donation procedures and factors predicting willingness to donate. Human Reproduction 18, 878-884.

Rumball, A., & Adair, A. (1999) Telling the story: Parents' scripts for donor offspring. Human
Reproduction, 14, 1392-1399.

Scheib J E, Riordan M, Rubin S (2003) Choosing identity-release sperm donors: the parents' perspective 13-18 years later. Human Reproduction 18, 1115-1127.

Scheib, J. E., Riordan, M., & Rubin, S. (2004) Adolescents with open-identity sperm donors: Reports from 12 – 17 year olds. Human Reproduction 20, 239-252.

Söderström-Antilla V, Sajaniemi N, Tiitinen A, Hovatta O (1998) Health and development of children born after oocyte donation compared with that of those born after in-vitro-fertilization, and parents' attitude regarding secrecy. Human Reproduction 13, 2009-2015.

Söderstrom-Anttila V, Foudila R, Ripatti U, Siegberg R (2001) Embryo donation: outcome and attitudes among embryo donors and recipients. Human Reproduction 16, 1120-1128.

Thorn P, Daniels K. Work in progress.

Turner, A., & Coyle, A. (2000) What does it mean to be a donor offspring? The identity experiences of adults conceived by donor insemination and the implications for counselling and therapy. Human Reproduction, 15, 2041-2051.

Vanfraussen, K., Ponjaert-Kristoffersen, I., & Brewaeys, A. (2001) An attempt to reconstruct children's donor concept: A comparison between children's and lesbian parents' attitudes towards donor anonymity. Human Reproduction, 16, 2019-2025.

Resources for clinical practice

American Society for Reproductive Medicine (2003) Family members as gamete donors and surrogates. Ethics Committee Report. Fertility and Sterility 80, 1124-1130.

American Society for Reproductive Medicine (2004). Informing offspring of their conception by gamete donation. Fertility and Sterility, 81, 527-531.

Blood J (2004) Mandatory counselling. Journal of Fertility Counselling. 11, 31-35.

Boivin J, Kentenich H. (2002) ESHRE Monographs: Guidelines for Counselling in Infertility. Oxford University Press.

Hammer Burns L, Covington S. (1999) (Eds.) Infertility Counselling. A comprehensive handbook for clinicians. New York: Parthenon.

National Ethics Committee on Assisted Human Reproduction (2005) Guidelines on embryo donation for reproductive purposes (http://www.newhealth.govt.nz/ecart/documents/embryo-donation.pdf).

National Ethics Committee on Assisted Human Reproduction (2005) Guidelines on within-family gamete donation (http://www.newhealth.govt.nz/ecart/documents/within-family-gd.pdf).