The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review

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This evidence-based review focuses on the impact of potentially modifiable, non-communicable lifestyle factors on reproductive performance in the general population and the infertile population undergoing assisted reproductive technology (ART) treatment. The impact of several lifestyle factors including; age, weight, smoking, diet, exercise, psychological stress, caffeine consumption, alcohol consumption and exposure to environmental pollutants are included in the review. The databases of Medline, PubMed and Cinahl were searched to identify relevant publications. There is strong evidence that age, weight and smoking impact on general health and adversely on reproductive performance. However there is a need for further research focusing specifically on the relationship between diet and various levels of exercise on reproductive performance. There are several other factors such as psychological stress, caffeine consumption, alcohol consumption and exposure to environmental pollutants that have been implicated but the evidence is equivocal. It is concluded that lifestyle modification can assist couples to conceive spontaneously or optimize their chances of conception with ART treatment.

Key words: age/lifestyle/reproductive performance/smoking/weight

Introduction

Lifestyle factors are behaviours and circumstances that are, or were once, modifiable and can be a contributing factor to subfertility. Fertility is the capacity to produce offspring, whereas fecundity is a woman’s biological ability to reproduce based on the monthly probability of conception (Wood, 1989). Clinical infertility is defined as the inability to become pregnant after 12 months of unprotected intercourse. It has been estimated that approximately 15% of the population in industrially developed countries are affected (Healy et al., 1994). The causes of infertility are wide ranging including diagnoses such as, ovulatory disorders, tubal disease, endometriosis, chromosomal abnormalities, sperm factors and unexplained infertility. The impact of lifestyle on reproductive performance may vary depending on individual aetiology and circumstances.

Lifestyle factors have had a dramatic impact on general health and the capacity to reproduce. Lifestyle issues such as smoking and obesity can affect general health and well-being. For example, smoking increases an individual’s risk of cardiovascular disease (Leone, 2003) and adverse consequences associated with obesity include increased risk of cardiovascular disease, diabetes and some cancers (Haslam and James, 2005). There is an increasing body of evidence that lifestyle factors can impact on reproductive performance. For example, studies have demonstrated that smoking in women significantly decreases the chance of conception (Hughes and Brennan, 1996; Augood et al., 1998).

Post-industrial western society has created the potential for increasing the exposure to specific lifestyle factors and behaviours that can positively or negatively affect reproductive health. For example, obesity is often associated with lack of exercise and inappropriate diet (Cameron et al., 2003), delayed child bearing, smoking and exposure to environmental pollutants and chemicals.

The aim of this paper is to review the impact of a specific range of contemporary lifestyle factors on fertility. The review focuses on the non-communicable aetiology for fertility associated with potentially modifiable lifestyle factors. These factors include female age, smoking, weight, diet, exercise, psychological stress, caffeine consumption, alcohol consumption and exposure to environmental pollutants.

Methodology

This review is divided into two sections. In the first section, individual lifestyle factors are considered where there is conclusive evidence for effect, followed by a review of factors where the evidence is equivocal. For the purpose of this review, a comprehensive search of the literature was performed using the following search strategy.
Conclusive evidence

Female age

By the time women reach 35 years of age, their fertility is declining (Pal and Santoro, 2003; Baird et al., 2005; Kaplan et al., 2005). At an even earlier age, the number and quality of oocytes decrease but manifest clinically at around 35 years of age (Angell, 1994; Benadiva et al., 1996; Baird et al., 2005). In addition, the incidence of genetic abnormalities and spontaneous abortion increase observably with maternal age (Nasseri and Grifo, 1998).

General population

The Hutterite population is an isolated community that live a relatively simple communal lifestyle that excludes the use of contraception. This community provides, therefore, a benchmark of natural fertility when examining fertility in other populations (Wood, 1989). The Hutterite population have a progressive decline in the rate of pregnancies with increasing female age. The magnitude of this decline is clinically and socially important.

Despite the substantial evidence of an age-related decline in female fertility, women are often ignorant of the risks associated with delaying child bearing. A recent study of university students in Sweden found that half of the female students intended to have children after the age of 35 years and were unaware of the age-related decline in fertility associated with increasing female age. The magnitude of this decline is clinically and socially important.

ART population

The effect of the age of women undergoing ART is similar to the general population with pregnancy rates declining with increasing age (Hull et al., 1996; Chuang et al., 2003). In 2002, in Australia and New Zealand, 36 483 ART treatment cycles took place (90.3% in Australia). The average age of these women was 35.2 years and the men 37.6 years. Women in the age range of 25–29 years undergoing fresh non donor treatment cycles, achieved a live birth rate of 25.9%, contrasting starkly with the 6.1% rate of live birth of women 40–44 years (Bryant et al., 2004). These figures concur with the general population trend where peak fecundity occurs at the age of 22 years, begins to decline in the mid- to late- 20s and has plummeted by the age of 40 years (Wood, 1989). The trend in Australia and New Zealand is typical of global experience. A recent study of all IVF clinics in the Netherlands (Lintsen et al., 2005) found that the overall live birth rate per cycle decreased by 2% (P = 0.03) for each additional year of female age. A Belgium study of 249 couples undergoing IVF because of obstructive and non-obstructive azoospermia also found that increasing maternal
age progressively affected live delivery rate per cycle. Females in their 20s had a 46% live delivery rate per cycle, compared with 34% for females aged 30–36, 13% for aged 37–39 and 4% for aged ≥40 (Silber et al., 1997).

The practice of reporting success by pregnancy rate is contentious. Commonly, success is claimed on the achievement of pregnancy. It must be recognized though that the ‘gold standard’ for couples attempting conception by ART treatment is a live birth. This has been the recommendation by at least one expert panel (Baird et al., 2005). The poor live birth rate in older women is, in great part, due to spontaneous abortion. A study of 201 pregnancies from women undergoing ovulation induction found a 2.1% risk of spontaneous abortion for women aged 35 compared with a 16.1% risk for women aged ≥36 [OR 8.72, 95% confidence interval (CI) 2.3–32.9] (Smith and Buyalos, 1996). Another study of 821 consecutive ICSI cycles undertaken in a New York hospital found a significant decline in clinical pregnancy rate, implantation rate and delivery rate per embryo transfer associated with increasing female age (Spandorfer et al., 1998). Delivery per embryo replaced was 26.9% for women aged 35, 12.9% for women aged 36–39 and 6.6% for those women aged ≥40. However, they were not able to identify an effect of paternal age on the outcomes.

Smoking

Cigarette smoking has been associated with adverse effects on fertility, although this is not widely recognized (Roth and Taylor, 2001). There is strong evidence of the adverse effects of smoking on fertility operating through a range of pathways in both the general and infertile population.

In males, smoking negatively affects sperm production, motility and morphology and is associated with an increased risk of DNA damage (Zenzes et al., 1999; Kunzle et al., 2003). In the female, the constituents of cigarette smoke may affect the follicular micro-environment and alter hormone levels in the luteal phase. Cotinine and cadmium have been detected in the follicular fluid of female smokers and whose partner smokes, thus having access to the developing follicle (Younglai et al., 2005). Menopause has been reported to occur 1–4 years earlier for women who smoke compared to non-smokers (Baron et al., 1990). A recent study demonstrated an increased thickness of the zona pellucida in smokers, which may make it more difficult for sperm penetration (Shiloh et al., 2004).

General population data

A meta-analysis of 12 studies found the overall OR for risk of infertility in the general population was 1.6 (95% CI 1.34–1.91) for smokers compared to non-smokers (Augood et al., 1998) (Table I). A population-based study of 14 893 pregnant women found a significant delay in conception independent of other factors associated with female exposure to both active and passive smoking (Hull et al., 2000). An OR of 1.54 (95% CI 1.19–2.01) was found for delayed conception of >12 months in women who smoked compared with women who did not smoke and an OR of 1.14 (95% CI 0.92–1.42) for passive smoking. A study of couples from 10 European countries also found a strong association between female smoking and subfecundity (Bolumar et al., 1996). A systematic review reported that 12 out of 13 studies demonstrated a negative effect of female smoking on conception (Hughes and Brennan, 1996).

Implications for ART population

A meta-analysis of nine studies found an OR of 0.66 (95% CI 0.49–0.88) for pregnancy per number of IVF cycles in smokers compared with non-smokers (Augood et al., 1998). Another meta-analysis reported that almost twice as many IVF cycles were needed to achieve pregnancy for smokers compared with non-smokers (Feichtinger et al., 1997). In a large study of 8457 women undergoing their first IVF cycle reported that there was a 28% decrease in live birth rate for smokers compared with non-smokers (Lintsen et al., 2005). These effects were observed against a cycle-specific pregnancy rate of 19.1% for non-smokers. Similarly, a study of 159 women undergoing IVF found that smokers did not respond as well to stimulation as non-smokers, fertilization was lower and none of the regular smokers became pregnant (Chra et al., 2001). A prospective study of 221 couples from 7 infertility clinics found that if a woman ever smoked in her lifetime her risk of not becoming pregnant from IVF more than doubled RR = 2.71 (95% CI 1.37–5.35, P < 0.01) (Klonoff-Cohen et al., 2001b). The risk increased with each year of smoking. A study of 301 couples undergoing IVF or ICSI found that male smoking significantly decreased ICSI and IVF success rates (Zitzmann et al., 2003). A recent review of lifestyle habits and IVF concluded that there was compelling evidence of the negative effect of smoking on IVF outcome (Klonoff-Cohen, 2005). In a study of 1196 pregnancies from IVF/ICSI or gamete intra-Fallopian transfer (GIFT), female smoking doubled the risk of early pregnancy loss (P < 0.001) after adjusting for confounding factors (Winter et al., 2002).

There is also emerging evidence of adverse effects on reproduction associated with passive smoking. A recent study of 225 women undergoing IVF found that fertilization rates were similar for smokers, passive smokers and non-smokers, whereas pregnancy rates were significantly decreased for smokers (19.4%) and passive smokers (20%), compared with non-smokers (48.3%) (Neal et al., 2005).

Smoking has been shown to adversely affect the chance of pregnancy from ART, with results of studies suggesting that smokers require nearly twice as many IVF cycles to conceive as non-smokers (Feichtinger et al., 1997).

Weight

Obesity is associated with a range of adverse health consequences. Widely recognized are the increased risks of cardiovascular disease, diabetes and some cancers. Obesity and low body weight can impact on reproductive function by causing hormone imbalances and ovulatory dysfunction. Abnormal weight is usually defined as a high BMI (kg/m²) of ≥25 and a low BMI of <20 and the effects of abnormal weight have been reported in several papers (Rich-Edwards et al., 1994; Bolumar et al., 2000; Rich-Edwards et al., 2002; Pasquali et al., 2003; Fedorcsak et al., 2004; Hassan and Killick, 2004; Norman et al., 2004). High BMI has also been shown to adversely affect the outcomes of ART treatment (Zaadstra et al., 1993; Wang et al., 2000; Nichols et al., 2003; Fedorcsak et al., 2004).

General population data

Data from the nurses’ health study (116 678 American nurses) was examined by Rich-Edwards et al. Of this cohort, there were 2527...
cases of married women who had attempted to become pregnant for >1 year with no success because of ovulatory infertility (Rich-Edwards et al., 1994). The effect of adolescent BMI (at age 18) as a predictor of ovulatory infertility was examined. Compared to women with a BMI of 20–21.9, women with a BMI of 24–25.9 showed a relative risk of infertility of 1.3 (95%CI 1.2–1.6) and rising to 3.7 (95%CI 2.0–3.7) in women with a BMI of 25–39, women with a BMI of ≥25 or <19 had a relative risk of time to conception of >12 months of 2.2 (95%CI 1.6–3.2, P < 0.0001) (Hassan and Killick, 2004). Another large study of women from five European countries (Bolumar et al., 2000) found that a high BMI increased the time taken to conceive, but only for smokers. Smoking women with a BMI of ≥30 was associated with an OR for delayed conception of 11.54 (95%CI 3.68–36.15) and smoking women with a BMI of <20 with an OR of 1.70 (95%CI 1.01–2.83). Male BMI of <20 or ≥25 has also been associated with a reduction in sperm quality (Jensen et al., 2004), which can impact on fertility.

Supporting these findings is a study that investigated lifestyle factors in 2112 pregnant women. Increased time to conception was found for women with a BMI of ≥25 and <19. After adjusting for other lifestyle variables, the woman’s age and menstrual pattern, compared to normal weight to overweight women with a BMI of 25–39, women with a BMI of ≥25 or <19 had a relative risk of time to conception of >12 months of 2.2 (95%CI 1.6–3.2, P < 0.0001) (Hassan and Killick, 2004). Another large study of women from five European countries (Bolumar et al., 2000) found that a high BMI increased the time taken to conceive, but only for smokers. Smoking women with a BMI of ≥30 was associated with an OR for delayed conception of 11.54 (95%CI 3.68–36.15) and smoking women with a BMI of <20 with an OR of 1.70 (95%CI 1.01–2.83). Male BMI of <20 or ≥25 has also been associated with a reduction in sperm quality (Jensen et al., 2004), which can impact on fertility.

**Implications for ART population**

Obesity has been shown to decrease the probability of pregnancy for women undergoing ART. A large Australian study of 3586 women who underwent ART found that pregnancy rates were halved for very obese women in comparison with women with a normal BMI (Wang et al., 2000) (Table II). Further evidence was found in a study of 372 women undergoing IVF. After adjusting for age and the number and quality of embryos, the chance of pregnancy was halved for overweight women (OR 0.53, CI 95% 0.32–0.86) compared with normal weight women (Nichols et al., 2003).

The distribution of body fat also impacts on reproductive performance but the mechanism for this effect is unclear (Norman et al., 2004). A prospective study of 500 apparently normal women undergoing donor insemination (Zaadstra et al., 1993) found that increasing waist–hip ratio was negatively associated with the probability of conception. A 0.1 increase in waist/hip
ratio was associated with a 30% decrease in pregnancy rate per cycle. These results are particularly significant as the women required ART treatment because of male factor infertility and therefore reflected a relatively normal population with few of them requiring stimulation.

A national study of all IVF clinics in the Netherlands (Lintsen et al., 2005) reported a 33% reduction in live birth rate for women on their first IVF cycle with a BMI >27, compared to women with a normal BMI. This study was based on a survey that elicited a 71% response. Adding to this evidence is a Norwegian study of couples who had undergone IVF or ICSI (Fedorcsak et al., 2004) that found within three cycles the cumulative live birth rate for obese women with a BMI ≥30 was 41.4% (95%CI 32.1–50.7). This contrasts with women with a normal BMI of 18.5–24.9 where it was 50.3% (95%CI 47.0–53.7). The lower rate in the obese group was mainly due to an increased risk of early pregnancy loss. High BMI in women has also been associated with other adverse pregnancy outcomes such as gestational diabetes and hypertension (Michlin et al., 2000).

The evidence for the effects of weight on reproduction from observational studies has given rise to a number of significant intervention studies. Lifestyle modification programmes that include exercise have been shown to assist women to lose weight, improve their fitness, increase psychological well-being and improve reproductive functioning (Clark et al., 1995; 1998). The results of an Australian study of 87 obese (BMI >30) infertile women attending a weekly programme to promote lifestyle changes demonstrate that a relatively small amount of weight loss (average of 6.5 kg) was associated with resumption of ovulation (Clark et al., 1998). The women in this study attended a weekly programme for 6 months that included an exercise component and education relating to diet and psychological issues associated with being overweight. Although the number of women taking part in the study was relatively low, the positive effects of participating in the programme were outstanding. On average, the women lost 10.2 kg/m², and at the beginning of the study, 80% of the women were anovular and at the end of 6 months 90% of these women were ovulating spontaneously. Of the 67 women who completed the study, 77.6% became pregnant and 67% achieved a live birth. The women who did not become pregnant either smoked, attended less than two-thirds of the sessions or had a BMI which remained >40.

Diet

Eating a healthy diet consisting of appropriate composition and caloric intake is fundamental to maintaining a state of optimum physical and psychological health. It is also important in preventing diseases such as obesity, cardiovascular disease, diabetes, osteoporosis and some cancers. Diet mediates body weight and composition and should be considered fundamental to reproduction. However, although a link has been demonstrated between maternal nutritional status and adverse pregnancy outcomes (Fall et al., 2003; Keen et al., 2003), the effect of a women’s nutritional status prior to pregnancy has rarely been studied (Chapin et al., 2004). Early pregnancy is a vulnerable period for embryo and fetal development and the environment at the time of conception can impact on the developing embryo and subsequent long-term health of the child (Chapin et al., 2004).

Studies directly relating dietary components to the chance of conceiving are sparse in humans. However, there is strong evidence that a well-balanced healthy diet is beneficial for general well-being and optimum body functioning (Sanders, 2004) and it has been suggested that diet before pregnancy may influence fetal well-being (Moore and Davies, 2005). Therefore, reproductive performance should be positively influenced by the consumption of a healthy varied diet.

Exercise

Regular exercise affects an individual’s general health and well-being and probably provides some protection from obesity, cardiovascular disease, hypertension, diabetes, osteoporosis and psychological stress. Research in relation to physical fitness and reproduction is primarily focused on athletes rather than women who have a moderate level of fitness. Rich-Edwards et al. (2002) found that exercise was associated with a reduction in risk of ovulatory infertility. After adjustment for BMI, each hour of vigorous exercise per week was associated with a relative risk reduction of 5%, suggesting that physical activity may protect ovarian functioning independent of BMI. However, there was no association with moderate exercise. This is in contrast to the Clark et al. (1995) study of obese, infertile women that found losing weight, improving physical fitness and psychological well-being resulted in significant improvement in ovulation and pregnancy rates. The women in this study underwent a 6-month lifestyle modification programme that included a weekly group fitness component and at least two further exercise sessions per week. In addition to losing weight, each participant’s fitness level improved. Exercise increases insulin sensitivity, which improves ovarian function and the chance of conception (Norman and Clark, 1998). Exercise during pregnancy has also been reported to increase maternal well-being (Morris and Johnson, 2005).

The overall physical, emotional and increased general well-being benefits of being physically fit are well documented (Berlin and Colditz, 1990; Sandvik et al., 1993; Pate et al., 2000).

### Table II. Influence of body mass on probability of pregnancy during ART

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
<th>Age</th>
<th>Number of embryos transferred</th>
<th>Number of cycles</th>
<th>% achieving at least one pregnancy</th>
<th>OR</th>
<th>n = 3586</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;20</td>
<td>31.6 (4.5)</td>
<td>2.4 (0.8)</td>
<td>2.3 (1.5)</td>
<td>45</td>
<td>0.81 (0.65–1.01)</td>
<td>441</td>
</tr>
<tr>
<td>Moderate</td>
<td>20–24</td>
<td>32.9 (4.7)</td>
<td>2.4 (0.7)</td>
<td>2.3 (1.7)</td>
<td>48</td>
<td>1</td>
<td>1910</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29</td>
<td>33.0 (4.8)</td>
<td>2.4 (0.8)</td>
<td>2.2 (1.5)</td>
<td>42</td>
<td>0.81 (0.68–0.97)</td>
<td>814</td>
</tr>
<tr>
<td>Obese</td>
<td>30–34</td>
<td>32.8 (4.7)</td>
<td>2.4 (0.7)</td>
<td>2.1 (1.4)</td>
<td>40</td>
<td>0.73 (0.57–0.95)</td>
<td>304</td>
</tr>
<tr>
<td>Very obese</td>
<td>≥35</td>
<td>32.7 (5.1)</td>
<td>2.4 (0.7)</td>
<td>2.0 (1.3)</td>
<td>30</td>
<td>0.50 (0.32–0.77)</td>
<td>117</td>
</tr>
</tbody>
</table>
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1995; Erikssen, 2001; Kull, 2002). However, there is a need for further research regarding the effects that moderate and low-level exercise may have on reproductive performance.

It is reasonable to assume that the general health benefits associated with moderate levels of exercise and the consumption of a well-balanced diet would also apply to fertility. These lifestyle practices should therefore be recommended to couples attempting pregnancy. Further research is needed to clarify the effect that exercise may play on reproductive performance.

Conclusive evidence associated with age, smoking and weight

The above evidence associated with age, smoking and weight shows that there is strong substantiation of an adverse association between these lifestyle factors and the risk of impaired fertility. Couples wanting to conceive either by natural conception or through ART should be advised to attempt pregnancy before the female partner reaches the age of 35 or earlier, stop smoking and maintain a healthy weight (supplementary Table I).

Inconclusive evidence

Other lifestyle factors such as psychological stress, caffeine and alcohol consumption and environmental pollutants may impact on reproductive health and adversely affect fertility. However, so far, the evidence is limited and not consistent across studies.

Psychological stress

Psychological stress may reduce female reproductive performance in various ways. The autonomic nervous system, the endocrine and immune systems have all been implicated (Hjollund et al., 1999). There is, however, a lack of clear consensus as to the definition and measurement of ‘psychological stress’ (Hjollund et al., 1999; Domar et al., 2000), bringing into question the nature and strength of any putative association. Given that infertility and ART treatment are associated with stress (Hammarberg et al., 2001; Domar, 2004; Olivius et al., 2001), determination of whether stress contributes to or is a consequence of infertility and ART treatment is problematic.

General population data

A randomized controlled trial compared a cognitive behavioural group, a support group and a control in 184 women attempting to conceive for 1–2 years (both naturally and from ART treatment) (Domar et al., 2000). Higher pregnancy rates were found in the two intervention groups (55 and 54%) compared with the control group (20%). Women were randomized into one of three groups: two intervention groups that met weekly for 10 weeks and a routine care control group. The first intervention group was a cognitive behavioural group where participants were taught relaxation and cognitive restructuring techniques. They were also given information about nutrition and exercise. In light of the evidence above, providing this type of information may be a potential confounder of a direct effect on psychological factors. The second intervention group was a support group. Participants were encouraged to discuss issues such as infertility treatment and their emotional feelings, followed by a more structured information session on a topic such as the impact of infertility on self-esteem. The women also met with a psychologist twice during the year of follow-up for testing of stress levels. A limitation of this study is the large numbers of dropouts from the control group (60%) making it relatively small.

An observational study (Hjollund et al., 1999) of 430 couples attempting to conceive reported a dose effect of stress on conception. Couples were followed for six menstrual cycles. On day 21 of each cycle, stress was assessed using a standard psychometric assessment tool the ‘General Health Questionnaire’. Decreased conception was associated with women who reported being most stressed (12.8% per cycle compared with 16.5% in other cycles) and having long menstrual cycles (≥35 days).

Implications for ART population

The effects seen in the general population carry over to women undergoing ART treatment where there is also some evidence of a negative effect of increased levels of stress and IVF success (Thiering et al., 1993; Facchinetti et al., 1997; Demyttenaere et al., 1998; Klonoff-Cohen et al., 2001a; Smeenk et al., 2001; Terzioglu, 2001).

A randomized controlled trial of 60 couples attending a Turkish Hospital for their first IVF treatment (Terzioglu, 2001) found a statistically significant association between providing counselling and support to couples and increased pregnancy rates. A nurse who worked closely with the couples throughout the most stressful periods provided the intervention. The nurse gave couples detailed information about their treatment, made daily contact with the couple from the commencement of stimulation until embryo transfer and was present at oocyte collection and embryo transfer. Standard care was provided to the control group. Three standard psychological tests were used to collect data at the beginning of the treatment cycle and 4–5 days after embryo transfer. Couples who received counselling and support during their IVF cycle had lower anxiety and depression scores and higher pregnancy rates, compared with a control group receiving standard care (Figure 3).

There have been several observational studies to assess stress levels and associations with treatment outcome. A prospective study based on seven Californian clinics followed 151 women undergoing IVF and GIFT. An association between stress levels prior to a treatment cycle and treatment outcomes was found.

Figure 3. Effects of counselling and support on ART pregnancy rates. Republished from Terzioglu (2001) with permission.
Lifestyle and reproductive performance

On balance, reported studies support an association between increased levels of psychological stress and impaired reproductive performance. The level of precision in determining a cause–effect relationship is low because the major measurements of stress are subjective and there is lack of consensus in defining and measuring stress levels.

Caffeine

The stimulant properties of caffeine have led to its widespread use as a beverage (coffee, tea and soft drinks) and some foods such as chocolate. Its consumption has been reported to prolong the time to pregnancy; although the mechanism for this is unclear, caffeine may affect female reproduction by targeting ovulation and corpus luteal function through alterations to hormone levels (Klonoff-Cohen et al., 2002) and has been associated with higher early follicular E2 levels in females (Lucero et al., 2001).

General population data

The consumption of caffeine has been associated with reduced fecundity in the general population. A prospective study of 104 women attempting pregnancy found strong evidence of a reduced chance of pregnancy with increasing caffeine consumption (Wilcox et al., 1988). The women were reviewed at enrolment and again at 3 and 6 months and their consumption of coffee, tea and soft drinks were recorded. The frequency of interviews allowed accurate recall of their caffeine consumption. Daily information was also recorded regarding menstrual bleeding and intercourse until a pregnancy was confirmed. The data were adjusted for variables of age, frequency of intercourse, smoking, weight and age at menarche. Women who consumed less than one cup of coffee were twice as likely to become pregnant compared with the moderate coffee drinkers, with the risk of failing to become pregnant increasing with higher consumption.

Most other studies rely on the collection of retrospective data after the period of caffeine consumption leaving them open to recall bias. A large multicentred study from five European countries found an increased risk of subfecundity for women consuming large amounts (>500 mg) of caffeine per day (Bolumar et al., 1997). The 3187 women were asked about their consumption of coffee, tea and cola from the start of unprotected intercourse and the time it took to become pregnant (Table III). After adjusting for potential confounders of age, smoking, the use of contraceptives and country, the risk of delayed conception with large amounts of caffeine

Table III. Distribution of waiting time to first pregnancy (TTP) in months by coffee drinking habits and caffeine intake of women from Denmark, Germany, Italy, Poland and Spain, August 1991 to February 1993

<table>
<thead>
<tr>
<th>Coffee (cups per day)</th>
<th>Number of women</th>
<th>0–3.4 (%) TTP (months)</th>
<th>3.5–9.4 (%) TTP (months)</th>
<th>≥ 9.5 (%) TTP (months)</th>
<th>Mean</th>
<th>Median</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>707</td>
<td>64</td>
<td>20</td>
<td>16</td>
<td>6.5</td>
<td>2.0</td>
<td>0.003</td>
</tr>
<tr>
<td>1–2</td>
<td>1257</td>
<td>59</td>
<td>21</td>
<td>20</td>
<td>7.4</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>738</td>
<td>62</td>
<td>20</td>
<td>18</td>
<td>7.3</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>475</td>
<td>55</td>
<td>22</td>
<td>23</td>
<td>8.2</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Caffeine (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–100</td>
<td>522</td>
<td>63</td>
<td>21</td>
<td>16</td>
<td>6.5</td>
<td>2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>101–300</td>
<td>1230</td>
<td>62</td>
<td>20</td>
<td>18</td>
<td>6.9</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>301–500</td>
<td>802</td>
<td>61</td>
<td>20</td>
<td>19</td>
<td>7.3</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>≥ 501</td>
<td>601</td>
<td>55</td>
<td>21</td>
<td>24</td>
<td>8.9</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

*P-values obtained from Kruskal–Wallis one-way analysis of variance. Republished from Bolumar et al. (1997) with permission.
consumption remained. A study of 1909 pregnant women relied on interviews about their consumption of tea, coffee, and cola between the time of conception and the date of interview (Hatch and Bracken, 199). After adjusting for the method of birth control, parity, and smoking during the year prior to conception, the consumption of more than three cups of coffee per day was associated with an OR for delayed conception (>1 year) of 2.24 (95% CI 1.06–4.73) compared with women who did not consume caffeine. The assumption was made that pre-pregnancy levels of caffeine consumption were consistent with levels during pregnancy. However, with the achievement of pregnancy, women change many habits and caffeine consumption during pregnancy may not be the same as levels at the time of conception. Coffee aversion in pregnancy is frequently associated with nausea. Other potential confounding variables such as frequency of intercourse were not considered.

A study of 1430 women collected information about caffeine consumption (coffee, tea, and cola) during the first month of pregnancy (Stanton and Gray, 1995). Compared with non-smokers who did not consume caffeine, non-smoking women who drank more than three cups of coffee a day had a 2.7-fold increased risk of delay in conception of more than 1 year. Predictably, smoking reduced the chance of pregnancy, but the effect of caffeine was only found in non-smokers. This study again makes the assumption that levels of consumption remain consistent before and during pregnancy, which may lead to misclassification. In contrast, a Danish study of 10886 pregnant women that also found an association between the consumption of high levels of caffeine (>eight cups of coffee per day) and reduced fecundity, only found this effect for women who smoked (Olsen, 1991). This raises the possibility that caffeine consumption reflects a particular lifestyle that may include a number of confounding factors, of which smoking may be just one. There are also studies that have found no association between caffeine consumption and fecundity (Jøsøe et al., 1990; Hakim et al., 1998).

Caffeine consumption has also been associated with other causes of infertility including tubal factors and endometriosis (Grodstein et al., 1993) and increased risk of spontaneous abortion (Fernandes et al., 1998; Cnattingius et al., 2000; Rasch, 2003; Tolstrup et al., 2003). A meta-analysis (Fernandes et al., 1998) found a modest but significant risk of spontaneous abortion and low birth weight associated with moderate to heavy caffeine consumption during pregnancy. However, not all studies have found an association between caffeine consumption and spontaneous abortion (Mills et al., 1993). High levels of caffeine consumption during pregnancy has also been associated with an increased risk of stillbirth (Wisborg et al., 2003). A Danish study of 88 483 pregnant women found that compared with non-consumers, the consumption of four or more cups of coffee was associated with a statistically significant risk of increased fetal death (Bech et al., 2005). However, the concept of reverse causation due to unrecognized fetal problems may explain why women continued to drink large quantities of coffee during pregnancy.

The evidence leans towards an association between the consumption of caffeine (particularly at high levels) and reproductive performance, although most studies have relied on data being collected retrospectively which is subject to recall bias.

**Implications for ART population**

There are fewer studies examining the effect of caffeine on the ART population. A prospective study conducted over 5 years of 221 couples from 7 Californian centres undergoing IVF or GIFT (Klonoff-Cohen et al., 2002) examined the relationship between caffeine intake and various reproductive endpoints. The women and their male partners completed questionnaires at different time points during their treatment regarding their caffeine intake and other factors. They were asked about consumption of a range of caffeine containing products: coffee, tea, cola, chocolate drinks and chocolate. Caffeine consumption during treatment was not related to oocyte retrieval, fertilization, embryo transfer or pregnancy. However, the women’s ‘usual’ caffeine consumption and their intake during the initial clinic visit were strong risk factors for not achieving a live birth (defined as not becoming pregnant or experiencing a miscarriage), even after controlling for potential confounders. Usual caffeine intake of a low dose (>2–50 mg/day) compared with no caffeine (0–2 mg/day) was associated with an OR of 3.1 (95% CI 1.0–9.7) for not achieving a live birth and for usual consumption of a moderate dose (>50 mg/day) was associated with an OR of 3.9 (95% CI 1.3–11.6) for not achieving a live birth. There are potential limitations to this study, including the difficulty in accurately recording exact consumption of caffeine and the relatively small numbers of live births.

**Alcohol**

Alcohol is a known teratogen (Randall, 1987; Chaudhuri, 2000) and its consumption has been reported to decrease fertility, although the level of consumption associated with risk is unclear. Alcohol consumption at the extreme level is known to be dangerous to the unborn child (Astley et al., 2000; Goransson et al., 2003; Krulewitch, 2005) but the effect at lower levels is less certain. The mechanisms by which alcohol could impair conception are unclear but may include an alcohol-induced rise in estrogen, which reduces FSH secretion suppressing folliculogenensis and ovulation. It may also have a direct effect on the maturation of the ovum, ovulation, blastocyst development and implantation (Gill, 2000; Eggert et al., 2004).

Moderate levels of alcohol consumption (seven to eight drinks per week) have been associated with reduced fertility and an increased risk of spontaneous abortion (Windham et al., 1992; Grodstein et al., 1994). Levels as low as one drink per week have also been associated with reduced conception (Hakim et al., 1998). The consumption of alcohol has also been shown to have adverse effects on pregnancy outcome and the most vulnerable time for the unborn child is the first few weeks after conception (Day et al., 1989; Collier et al., 2002). Current evidence is inconclusive regarding what dose of alcohol may be safe to consume during pregnancy, making it difficult to predict the risk (Mukherjee et al., 2005).

**General population data**

A prospective study of 124 healthy women (Hakim et al., 1998) collected monthly information regarding the women’s alcohol and caffeine consumption. A diary was also kept of frequency of intercourse, vaginal bleeding and any pregnancy symptoms. The highest rate of conception (27%) was found to be the women who did not drink alcohol or smoke and consumed less than one cup of coffee per day (Table IV). Similar results were found in a Danish study of 430 couples attempting their first pregnancy...
Lifestyle and reproductive performance

Table IV. Conception rate by smoking, frequency of intercourse, caffeine and alcohol consumption

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of women</th>
<th>Number of conceptions/number of menstrual cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>41</td>
<td>33/192 (17.2)</td>
</tr>
<tr>
<td>30–34</td>
<td>61</td>
<td>57/363 (15.7)</td>
</tr>
<tr>
<td>≥ 35</td>
<td>22</td>
<td>9/123 (7.3)</td>
</tr>
<tr>
<td>Sexual intercourse (per month)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>78</td>
<td>30/270 (11.1)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>46</td>
<td>69/408 (16.9)</td>
</tr>
<tr>
<td>Cigarette smokinga</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>98</td>
<td>90/536 (16.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>9/142 (6.3)</td>
</tr>
<tr>
<td>Alcohol (g/week)a (1 drink = 12.5 g alcohol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28</td>
<td>38/176 (21.6)</td>
</tr>
<tr>
<td>1–2</td>
<td>38</td>
<td>30/210 (14.3)</td>
</tr>
<tr>
<td>13–90</td>
<td>45</td>
<td>24/228 (10.5)</td>
</tr>
<tr>
<td>≥ 91</td>
<td>13</td>
<td>7/64 (10.9)</td>
</tr>
<tr>
<td>Caffeine (mg/day)a (Caffeine estimation: 1 cup of coffee = 100 mg, tea = 50 mg, soda = 40 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–25</td>
<td>30</td>
<td>39/196 (19.9)</td>
</tr>
<tr>
<td>26–100</td>
<td>32</td>
<td>26/184 (14.10)</td>
</tr>
<tr>
<td>101–300</td>
<td>53</td>
<td>28/258 (10.9)</td>
</tr>
<tr>
<td>≥ 300</td>
<td>9</td>
<td>6/40 (15.0)</td>
</tr>
</tbody>
</table>

Republished from Hakim et al. (1998) with permission.

aOn the basis of monthly assessment of cigarette smoking, alcohol and caffeine consumption. Changes were integrated into each menstrual cycle by date of interview and averaged over the cycle.

(Jensen et al., 1998). Alcohol consumption was monitored over six menstrual cycles and records were kept of vaginal bleeding and frequency of intercourse. The chance of conception decreased with increasing alcohol intake in a dose-related fashion; women consuming one to five drinks per week had a fecundability OR of 0.61 (95%CI 0.04–0.93) and women consuming >10 drinks per week an OR of 0.34 (95%CI 0.22–0.52), compared with those women who did not consume any alcohol. Alcohol intake for men was not associated with a reduction in fecundability.

A Swedish study followed a cohort of 7393 women over 18 years (1969–1987) (Eggert et al., 2004). Information was collected on rates of attendance to hospital for various reasons including infertility examinations. During this period, almost all infertility examinations in Sweden were treated in hospitals. A questionnaire at the beginning of the study was used to assess alcohol intake and medical records were reviewed for admissions for infertility. The effect of high or low alcohol use was compared with moderate use. Levels of alcohol consumption, greater than 140 g/week, had a higher risk of undergoing an examination for infertility (OR 1.59, 95%CI 1.09–2.31) and the risk for low consumers, <50 g/week, was lower (OR 0.64, 95%CI 0.46–0.90). Therefore, this study demonstrated a dose–response relationship between level of alcohol consumption and fertility examinations. Limitations of the study include the single point collection of data on alcohol consumption (prior to the start of the study) and no analysis of smoking and lifestyle.

Only weak support was provided by a study of 6630 randomly selected women and 4035 pregnant or recently delivered women from a range of different European countries (Olsen et al., 1997). Data were collected on alcohol consumption and other lifestyle factors such as smoking, age and frequency of intercourse prior to conception. Only at the highest levels of alcohol consumption was an association found between alcohol consumption and decreased fecundity. Other studies have found no effect of alcohol consumption on fertility or the risk of spontaneous abortion (Parazzini et al., 1990; Florack et al., 1994; Curtis et al., 1997).

Implications for ART population

A prospective study of 221 couples undergoing IVF or GIFT at six Californian fertility clinics (Klonoff-Cohen et al., 2003) reviewed male and female alcohol consumption in the year prior to treatment as well as during treatment. Both male and female alcohol consumption affected some measures of reproductive performance. Female alcohol drinking during the year prior to treatment was associated with a 13% (P = 0.02) decrease in the number of oocytes retrieved for each additional drink per day. A higher risk of miscarriage was associated with female alcohol consumption 1 week prior to the procedure after adjusting for variables including smoking and age–RR 2.21 (95%CI 1.09–4.49, P = 0.03). Male alcohol consumption was also significant. In contrast, a study (Zaadstra et al., 1994) of women undergoing donor insemination found no association between alcohol consumption and female fecundity.

Although adverse effects of any level of alcohol consumption on reproductive performance is highly plausible, studies generally have relied on women or couples recalling their levels and timing of alcohol consumption. Clearly, the randomized controlled trial to quantify the effect of alcohol consumption on fertility cannot be done.

Inconclusive evidence associated with psychological stress, caffeine and alcohol consumption

The summation of evidence of associations between psychological stress, caffeine, alcohol consumption and reproductive performance is inconclusive. Although better evidence is required, it is...
biologically plausible that these factors may affect reproductive performance. It is therefore prudent to adopt recommendations that address these factors. Increased psychological stress has been implicated in impaired fertility and the efficacy of ART treatment. Therefore, couples should be assisted to minimize and cope with psychological stress when attempting pregnancy. Some reports regarding the effect of alcohol and caffeine consumption on fertility are conflicting and there is potential for error in the recall of consumption of exact dosage and residual confounding. However, there is sufficient evidence of adverse effects of alcohol consumption on fertility to recommend that couples attempting to become pregnant should limit or abstain from consuming alcohol and comply with established dietary recommendations for the consumption of caffeine (supplementary Table II).

**Environmental pollutants**

The potential for environmental and occupational exposures to chemicals and pollutants to adversely affect fertility is not surprising, as environmental and lifestyle factors are said to be key factors in human disease (Czene et al., 2002). Certain environmental exposures have been implicated in adverse effects on reproduction.

Adverse effects of radiation on male and female reproduction have been demonstrated in various animal species as well as human beings (Kumar, 2004). The reproductive system in males and females is sensitive to radiation causing temporary or permanent sterility dependent on dose, duration and dose rate (Schieve et al., 1997; Parker et al., 1999; Kumar, 2004). However, there is a lack of evidence to support an association between exposure to electrical and magnetic fields and fetal loss or adverse pregnancy outcomes (Shaw, 2001).

Exposure to pesticides and solvents has been associated with sperm threshold values below normal (Oliva et al., 2001; Kumar, 2004). Sperm counts were reported to be 40% lower in fertile men in an agricultural area of Missouri than for men in three urban areas and they also had higher urine concentrations of commonly used pesticides (Oliva et al., 2001; Swan et al., 2003). Supporting these findings is a study of 726 couples undergoing IVF in the Netherlands (Tielemans et al., 2000). A reduced implantation rate was found in women whose partners worked in occupations with high levels of organic solvent exposure. Men exposed to pesticides and welding have been shown to be at risk for oligozoospermia (Wong et al., 2003) and other chemicals such as phthalates have also been linked to infertility. Certain phthalate metabolites are related to reduction in semen quality (Duty et al., 2003) and endometriosis in women (Cobelli et al., 2003). In females, cosmetics have been associated with an increased risk of spontaneous abortion (John et al., 1994) and exposures to various factors in the home, such as glues, have been associated with infertility (Ford et al., 1994).

Other studies have not found an association between occupational exposures and infertility (Gracia et al., 2005).

There is evidence of an adverse effect of some pollutants and chemicals on human reproduction and of an association with exposure to other environmental factors. Although further research is needed to clarify and improve the existing knowledge in this area, couples attempting pregnancy should be individually counselled regarding any potentially harmful occupational exposures.

**Combined effects of lifestyle factors**

The combined effect of several negative lifestyle factors has been associated with a progressive reduction in fertility. A cohort of 2112 pregnant women were surveyed about their lifestyle and the time taken to conceive (Hassan and Killick, 2004). A progressive increase was found in the time taken to become pregnant with increasing numbers of negative lifestyle factors (Figure 4).

**Opportunities for intervention**

There is a large body of evidence relating to the impact of lifestyle on reproductive performance. However, motivating patients to modify their lifestyle can be difficult and challenging. Changing lifestyle behaviours requires time, considerable effort and motivation (Rollnick and Heather, 1992). A patient-centred approach to counselling and advice has been shown to produce the best outcomes (Britt et al., 2004).

The provision of evidence-based information relating to the impact of lifestyle and reproductive performance can assist in motivating couples to modify their lifestyle. Motivational interviewing has also been used effectively to assist patients in lifestyle changes (Britt et al., 2004).

The concept of an individualized health-care plan in the form of a ‘reproductive health pathway’ may be an effective means of motivating patients to make positive changes to their lifestyle.

![Figure 4. The effect of increasing numbers of negative lifestyle variables on the cumulative conception rates within 1 year for a pregnant population. These variables include women’s smoking >15 cigarettes/day, men’s smoking >15 cigarettes/day, men’s alcohol >20 U/week, women’s coffee or tea intake >7 cups/day, women’s weight >70 kg, social deprivation score >60, women’s age >35 years and/or partner’s age >45 years at the time of discontinuing contraception. The lines represent the cumulative conception rates for subgroups with different numbers of negative lifestyle variables as follows: ○, no negative variables; ■, one negative variables; ×, two negative variables; Δ, three negative variables; ●, four or more negative variables. Republished from Hassan et al. (2004) with permission.](image-url)
A pathway designed around individual aetiology and lifestyle would be planned for each couple. The aim being to provide the most effective and appropriate methods towards reaching the goal of improved reproductive performance, pregnancy and ultimately a healthy child. The pathway would aim to facilitate both immediate and long-term lifestyle changes. To maximize compliance and success, pathway should be planned in conjunction with the couple and be both appropriate to their individual needs and achievable (Figure 5). Figure 5 illustrates the potential differences in pathways. Each couple has a common starting point of

![Individualized pathways to conception and a healthy child](image)

Figure 5. Individualized pathways to conception and a healthy child (two examples of health pathways).
infertility and a clinical consult incorporating a medical assessment and identification of modifiable lifestyle factors. Pathways would then diverge, being tailored to individualized needs. The endpoint is a common goal of pregnancy and the delivery of a healthy baby. Examples of two pathways are shown. Pathway 1: the female partner is diagnosed with anovulation. Identified lifestyle factors include obesity, poor diet and inadequate exercise and a high level of psychological stress. She is advised and assisted to increase her exercise and improve her diet, and strategies to decrease her stress levels are discussed. The pathway is aimed at assisting her to establish spontaneous ovulation, optimize the chance of pregnancy and delivering a healthy baby and to improve her general health and well-being. The male partner has no physiological problems on medical assessment, but his diet is inadequate and he does not exercise. He is advised to improve his diet and exercise to optimize the chance of conception and to improve his general health (the pathway of the female is shown). Pathway 2: the female partner has tubal damage, does not exercise and drinks four to five cups of coffee per day. The male partner has a sperm defect, smokes cigarettes and eats an unhealthy diet. She is advised to decrease her caffeine intake and to exercise, and he is advised to stop smoking and improve his diet. The goal is to improve the quality of his sperm and to improve both partners’ general health to optimize the chance of pregnancy and a healthy child through IVF (the pathway of the male is shown).

The allocation of resources for planning and implementing a reproductive health pathway as an initial strategy in health care would lead to positive long-term outcomes. The need for costly high-technology infertility treatment would be minimized and the efficacy of treatment improved. The general health and well-being of the couples involved would also be improved.

**Conclusion**

The literature has clearly identified a series of modifiable lifestyle factors that potentially impact on fertility in the general population and the population undergoing ART. Moreover, the risk factors for fertility identified here often have other related serious health implications, such as the importance of smoking as a risk factor for cardiovascular disease and cancer. Efforts to improve reproductive health may, therefore, have other associated health benefits and vice versa. That lifestyle modification has the potential to improve reproductive performance raises a number of health-care issues. For the general population, there are opportunities for primary prevention to protect reproductive health, and for those undergoing ART, there are opportunities for secondary prevention to improve reproductive outcomes from treatment. Most lifestyle factors are theoretically modifiable, and couples attempting to conceive should be counselled and advised regarding their individual lifestyle factors. A structured programme of education, support and access to specialist health professionals should back counsellling to encourage and facilitate appropriate lifestyle changes. This will facilitate the provision of optimum health care to couples attempting to become pregnant, improving their chances of success and minimizing the need for costly and invasive infertility treatment.

**Supplementary material**

Supplementary data are available at http://humupd.oxfordjournals.org/.

**References**


Chuang CC, Chen CD, Chao KH, Chen SU, Ho HN and Yang YS (2003) Age is a better predictor of pregnancy potential than basal follicle-stimulating hormone levels in women undergoing in vitro fertilization. Fertil Steril 79,63–68.


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Neal MS, Hughes EG, Holloway AC and Foster WG (2005) Sidestream smoking is equally as damaging as mainstream smoking on IVF outcomes. Hum Reprod 20,2531–2535.


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