THEMED REVIEW

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Modifiable Risk Factors and Infertility: What Are the Connections?

Abstract: *Infertility is a relatively common condition, greatly affecting couples medically and psychologically. Although infertility treatment is safe, it can be time-intensive, expensive, and increase the risk of multiple gestations. Thus, to reduce costs and risks, couples may initially consider lifestyle change to increase their fertility and chances of pregnancy. For many of the diet factors studied (eg, caffeine, soy, protein, iron), there are conflicting data. However, there are some items men and women consume that are detrimental to fertility, such as alcohol and tobacco. The data on exercise are varied but may have an effect on ovulation and fertility—positive or negative. Body mass index appears to affect fertility also, with obesity in both men and women negatively affecting pregnancy rates. In addition, there remains concern and a growing body of research on environmental toxin exposures and reproductive health. Finally, supporting patients through infertility diagnosis and treatment is critical, as psychological stress may affect conception. It is imperative that the relationship between lifestyle factors and fertility continue to be explored so as to lessen the morbidity associated with infertility.*

Keywords: infertility; fertility; lifestyle; diet; stress; exercise; weight

Fertility is the ability to conceive and have children, while infertility is a decreased ability to conceive and have children.[1] The clinical diagnosis of infertility is defined as the failure to conceive within 12 months and affects 7% to 8% of reproductive-aged American women.[2] Most infertility treatments involve hormonal oral medications or injections, with or without intrauterine insemination of sperm, or assisted reproductive technologies (ART). ART include infertility treatment when both the eggs and sperm are handled, for example, taking eggs from the woman and fertilizing with sperm in the laboratory.[3]

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Several of the most influential factors on fertility and infertility treatment, such as age and genetic factors, are nonmodifiable. However, there is conclusive evidence that modifiable factors, such as smoking and weight, have a negative effect on ART.[4,5] Do couples have the ability to increase fertility, simply by changing their lifestyles?

Clinicians are routinely asked which foods, drinks, activities, and exercises help or hurt the chances of pregnancy. Books, the Internet, and family members offer advice on what the infertile couple might change to increase fertility. Whether a couple has been diagnosed with infertility or simply wants to expedite conception, many reproductive-aged men and women seek information about their habits and fertility. In this review, we will describe the current evidence regarding the associations between lifestyle and fertility. The effects in both women and men will be mentioned when the data are available,

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Table 1.

Possible Effects of Modifiable Risk Factors on Clinical Outcomes in Reproduction[a].

Step of Reproductive Process	Female	Male
Hormonal regulation	Environmental endocrine disrupting chemicals	Environmental endocrine disrupting chemicals
	Alcohol use	Dietary factors
	BMI	Alcohol use
		BMI
Ovulation	Caffeine use (possible)	
	Dietary factors	
	BMI	
Fallopian tube function	Tobacco use	
Fertilization	BMI	Antioxidants (may be beneficial)
		Alcohol use
Implantation	Tobacco use	
Early fetal growth	Tobacco use	
	Alcohol use	

Abbreviations: BMI, body mass index; ART, Assisted reproductive technology.
[a]The table summarizes the clinical outcomes suggested by the body of infertility and ART-focused literature that are included in this review. We recognize that additional findings related to pathophysiologic and biological associations exist, which may not be included in this table of clinical outcomes.

in addition to a discussion about how lifestyle can influence ART, such as in vitro fertilization (IVF; Table 1).

Several issues surrounding the epidemiologic study of fertility should be mentioned at the outset.

Defining clinical outcomes: We must recognize how fertility is measured in research, as it is assessed differently in various studies. While the clinical diagnosis of infertility is defined as the failure to achieve pregnancy within 12 months, most clinicians also consider evaluation of infertility after 6 months in women 35 year of age or older.[6] Fecundability is the probability of achieving a pregnancy within one menstrual cycle, while fecundity is the probability that a couple will conceive leading to a live birth in any given menstrual cycle.

Bias: We must consider the design of all studies and the potential bias. For example, recall bias must be considered whenever the study participants are aware of the outcome of interest (in infertility/fecundity research, usually pregnancy or live birth) at the time that they provide details of their prior exposure history.[7] In this circumstance, their experience of the outcome may influence differential misclassification of their exposure. This differential misclassification can be of any magnitude and in any direction, but the critical issue with respect to bias is that it differs between those with and those without the outcome of interest.

Different from recall bias is selection bias: For selection bias, the study population may not be representative of the population to which the results are being generalized. For example, studies conducted within an ART clinical population will not include those who are experiencing infertility but who could not or did not wish to gain access to ART care. Alternatively, selection bias is present if the study population only includes a subset of the clinical population due to informative enrollment patterns, for example, those couples experiencing less stress or those with short duration of infertility or those with polycystic ovary syndrome but not with male factor infertility. These biases in study population relative to general population may be internally valid but may preclude extrapolation of the observed associations to the larger community.

Establishing causality: Many studies of lifestyle factors suggest an association with fertility. It is also important to consider if causality exists. The criteria for establishing causality includes an assessment of the strength and consistency of the association across studies, dose–response effect, temporal sequence, and biologic plausibility.[8] One of the most effective ways to assess for causality would be to perform randomized controlled trials, intervention trials, or prospective trials. For exposures believed to have an impact on fertility in short duration of exposure and for which the dose and timing for success can be clearly defined, the ART clinic is an ideal setting for randomized controlled trials as the population is well defined and the time to outcome is short and specific. Unfortunately, a majority of lifestyle factors hypothesized to influence fertility cannot be randomized. Nothing believed to impact outcomes that precedes clinical presentation (ie, windows of exposure across the life course) or requires greater than a small number of menstrual cycles of exposure to exert an effect can be randomized in this setting.[9] And, certainly, no factors hypothesized to be detrimental nor those beneficial but without existing evidence for a defined exposure dose and duration can be randomized. Therefore, much of scientific investigation must rely on rigorous and thorough observational studies that focus on maximizing valid quantification of exposure and outcome data as well as potential confounders, mediators, and effect modifiers.

Diet

Women's preconception and pregnancy diet and nutritional status are associated with maternal and neonatal outcomes.[10] But do diet and nutritional status affect the ability to become pregnant? In 2007, Chavarro et al published a "fertility diet" based within the Nurses' Health Study II population that was found to be associated with a lower risk of ovulatory infertility.[11-13] A higher "fertility diet" score was characterized by a lower intake of trans fat with a greater intake of monounsaturated fat; a lower intake of animal protein with greater vegetable protein intake; a higher intake of high-fiber, low-glycemic carbohydrates; greater preference for high-fat dairy products; higher plant-based iron intake; and higher frequency of multivitamin use. Compared with women with the lowest "fertility diet" scores, women with the highest scores had a 66% (relative risk [RR] = 0.34; 95% confidence interval [CI] = 0.23-0.48) lower risk of ovulatory infertility and a 27% (RR = 0.73; 95% CI = 0.57-0.95) lower risk of infertility due to other causes. The authors also considered the role of body mass index (BMI) and physical activity. However, diet composition had a greater apparent impact on fertility than either BMI or vigorous physical activity alone.

Finally, many women consider using antioxidant vitamins to increase fertility. A recent large meta-analysis examined the effectiveness of several types of antioxidants (pentoxifylline, *N*-acetyl-cysteine, melatonin, L-arginine, vitamin E, myo-inositol, vitamin C, vitamin D + calcium, and omega-3-polyunsaturated fatty acids) and outcomes such as live birth and clinical pregnancy.[14] Antioxidants were not associated with an increase live birth rate compared with placebo or no treatment. However, the authors did recognize difficulty with the meta-analysis considering the varied diagnoses and treatment regimens, likely obscuring a clear conclusion and warranting more large studies with harmonized interventions.

Male fertility comparatively has a much smaller body of literature. Diet associations are not different. With regard to men's diets, intake of isoflavones, found in soy, has been studied. Isoflavones may have weak estrogenic activity and their role in male fertility has been questioned. However, in a cross-sectional study, dietary intake of soy foods and isoflavones was inversely related to sperm concentration, but not any other sperm parameter.[15] Men in the highest intake level of soy foods had 35 million sperm/mL less than men who did not consume soy foods, and there was a statistically significant trend toward decreasing sperm concentration with increasing soy foods intake (*P*, trend = .03). The effects of antioxidants have also been studied in men. It is thought that the reactive oxidative species, from factors such as smoking or alcohol, may affect the sperm by damaging the sperm membrane, affecting fertilization, or by affecting sperm DNA. In a large meta-analysis, compared with control, antioxidant use was associated with a higher live birth and pregnancy rate in men with subfertility.[16]

Caffeine

Many couples attempting pregnancy consume caffeine daily. The role that caffeine plays in fertility is not well defined. In a prospective study of 104 women attempting conception, caffeine intake was associated with reduced fecundity.[17] Women who consumed less than one cup of coffee per day were twice as likely to become pregnant compared with those women who consumed more than that amount. In a large multicentered European retrospective study, consumption of high levels of caffeine (>5 cups of coffee/day or >500 mg) was associated with an increased risk of subfertility (defined as time to pregnancy 9.5 months or more; odds ratio [OR] = 1.45; 95% CI = 1.03-2.04).[18] Conversely, a large, prospective Danish study of 3628 women evaluated the relationship between time to pregnancy and consumption of caffeinated beverages and soda.[19] There was no significant association between caffeine or coffee consumption and fecundability, with fecundability ratio 0.98 to 1.07 for categories of consumption >100 mg/day compared with <100 mg/day. In addition, no significant association was found

between tea or soda and fecundability. Similarly, in a cohort study of women without a history of infertility followed for 8 years to evaluate the effect of caffeine on ovulatory infertility, caffeine intake did not increase the risk of ovulatory infertility, and there was no association between caffeinated coffee, decaffeinated coffee or tea, and infertility.[20] Considering ART, a cohort study of 619 women undergoing IVF, caffeine intake did not reduce overall pregnancy rates; however, a reduction in the numbers of retrieved eggs was observed.[21] These findings are in accord with a larger, prospective study that demonstrated that compared with women who do not drink caffeine, the likelihood of live birth was not significantly different for women who drank low (>0-800 mg/week; OR = 1.00; 95% CI = 0.83-1.21), moderate (>800-1400 mg/week; OR = 0.89; 95% CI = 0.71-1.12), or high levels of caffeine (>1400 mg/week; OR = 1.07; 95% CI = 0.85-1.34).[22] Furthermore, neither the type of drink containing caffeine (tea, soda, coffee) nor men's use had a significant effect on live birth rate. However, increasing caffeine use had a significantly lower peak estradiol level, but no difference in number of oocytes retrieved, fertilization rate, or implantation rate.

The etiology of caffeine's possible effect is not known. Markers of ovarian reserve are not affected by caffeine, demonstrated by a lack of association between recent caffeine use and antral follicle count, inhibin B, estradiol, or follicle stimulating hormone levels.[23] Some studies have suggest that caffeine may affect glucose metabolism or insulin levels, thus correcting the impact of insulin resistance on anovulation, as is found in polycystic ovary syndrome.[24,25] Given the available evidence, the American Society for Reproductive Medicine stated that moderate caffeine consumption (1-2 cups of coffee per day or its equivalent) before or during pregnancy has no apparent adverse effects on fertility or pregnancy outcomes.[26]

Alcohol

The association between alcohol and infertility has yet to be defined. Alcohol is a known teratogen and should be avoided during pregnancy; however, the effect of alcohol on conception is less clear.[27,28] Acute alcohol consumption is associated with increased estrogen levels.[29,30] Potential mechanisms through which alcohol may impair fertility include an alcohol-related rise in estrogen leading to decreased follicle stimulating hormone secretion and impaired ovulation.[31] Studies in animals demonstrate that the egg or very early embryo development may be affected by alcohol, thus reducing fertility.[32-36]

When reviewing studies on alcohol and health outcomes, several epidemiologic factors should be considered.[37] These points are described in relation to cardiovascular disease but may be applicable to decreased fertility as well. One needs to consider the referent group—does it include ex-drinkers who may still have increased risk for a negative outcome? Does it include life-long teetotalers, which is usually a small group, or regular non-drinkers, which may be the least-biased referent category. Also, drinkers, especially moderate and heavy drinkers, decrease alcohol intake over time. This is important to remember when we assess a study that follows a group over time, but asks about alcohol intake at a single point in time. For example, women may report no alcohol use, as they are trying to conceive, but this may not capture use in the years prior. Thus, it is critical to note how often the population is reporting alcohol intake and in what context. In addition, many retrospective studies may demonstrate bias, underestimating the amount reported. Prospective studies or collection tools that include questions about other lifestyle factors, in addition to alcohol, may lead to more accurate reporting.[38,39] Finally, confounding factors, such as smoking and BMI, need to be adjusted for in the analyses.

In a prospective study of 430 Danish couples seeking first time pregnancy, the odds of conception decreased with increasing alcohol consumption in a dose-related fashion.[40] Compared with nondrinkers, women who consumed 1 to 5 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). In a Swedish cohort study of 7393 women followed over 18 years, the risk of infertility was significantly increased in women who were high consumers of alcohol (>140 g alcohol, or 10 drinks, per week; RR = 1.59; 95% CI = 1.09-2.31) and decreased in women who were low consumers (less than 50 g, or 4 drinks, per week; RR = 0.64; 95% CI = 0.46-0.90) when compared with women who were moderate consumers (between 50 and 140 g alcohol per week).[41]

In contrast, a Danish study of 29 844 pregnant women who self-reported alcohol intake suggested a shortened time to conception among women who drank wine versus nondrinkers.[42] Another study of 1769 Italian women found no relationship between fertility and alcohol consumption.[43] The relationship between men's alcohol use and male infertility is also contradictory. In a survey of time to pregnancy, men's heavy use (20 drinks per week), but not less use, was associated with a 2-fold longer time to pregnancy and a higher likelihood of subfecundity (RR = 1.9; 95% CI = 1.3-2.7).[44]

Conversely, studies have reported no effect on the probability of conception or fecundability was seen, in any amount or type of alcohol (beer, wine, or liquor) in men.[40,45] When semen parameters have been evaluated, alcohol was not found to be associated with a change in semen quality.[46] However, if men were using alcohol and tobacco concomitantly, there was a significant reduction in seminal volume, sperm concentration, and percentage of motile sperm. Two prospective cohort studies have evaluated alcohol consumption prior to the IVF cycle in relation to cycle outcome. In the first, an increase in one drink per day among women was associated with 13% fewer oocytes retrieved.[47] Also, those who drank

alcohol had a nonsignificant decreased odds of pregnancy. In men, alcohol use was not associated with a change in semen parameters. The strongest association between men's alcohol intake, pregnancy, and spontaneous abortion was seen when the consumption occurred closest to the time of semen sample collection. However, the second study had different findings.[48] This study, which adjusted for age, BMI, cigarette use, and IVF cycle number, found that women's use of at least 4 drinks/week was associated with a decreased live birth rate as compared with those who drank less than 4 drinks a week (OR = 0.84; 95% CI = 0.71-0.99). Couples in which both partners drank at least 4 drinks per week had a decreased likelihood of live birth compared with couples in which both drank less than 4 drinks per week (OR = 0.79; 95% CI = 0.66-0.96).

Tobacco

Cigarette smoking more consistently has been associated with significant detrimental effect on reproductive function and fertility.[49,50] Menopause has been found to occur 1 to 4 years earlier in smokers.[51] An observational study of the Oxford Family Planning Association followed women over time after stopping contraception and found that smoking women had lower rates of fertility, measured as months until delivery.[52] The most notable findings of this study demonstrated the dose-dependent adverse effect of tobacco use. Also, the finding that women who had quit smoking had fertility rates similar to never smokers suggests that the detrimental effect of tobacco is reversible.

A meta-analysis of 12 studies including 10 928 exposed and 19 179 unexposed women found that smokers were much more likely to experience infertility compared with nonsmoking women (OR = 1.60; 95% CI = 1.34-1.91).[53] A population-based study including data from almost 15 000 pregnancies found a significant delay in conception in smokers.[54] After assessing possible confounders including age, ethnicity, education, employment, housing, prepregnancy BMI, and alcohol consumption, the investigators found that conception was delayed >12 months in smokers versus nonsmokers (OR = 1.54; 95% CI = 1.19-2.01). The impact of secondhand smoke exposure was only slightly smaller than for active smoking in either partner (OR = 1.14; 95% CI = 0.92-1.42). Smoking in men has been observed to adversely affect sperm production, motility, and morphology, but the overall effect of smoking on male fertility needs further investigation.[55,56]

The toxic components from cigarette smoking, including cadmium and cotinine, have been found in the ovarian follicular fluid of smokers and even women exposed to secondhand smoke.[57] It is believed that the presence of these compounds may induce intrafollicular oxidative stress.[58] Furthermore, an increased level of DNA damage was found in ovarian cumulus cells in smokers compared with nonsmokers.[59]

Smoking also has a detrimental effect on ART; it negatively affects several outcomes and parameters in the IVF cycle and is associated with an increased risk of not conceiving.[8,60] In a study of 159 women undergoing IVF, smokers were found to have less response to ovarian stimulation than nonsmokers and lower fertilization rates, and none of the regular smokers conceived.[61] In a meta-analysis of IVF outcomes in smokers compared with nonsmokers, the OR for pregnancy after IVF in smokers was 0.66 (95% CI = 0.49-0.88).[53] Similarly, a meta-analysis found that smokers required almost twice as many IVF cycles to conceive versus nonsmokers.[62] The negative effect of smoking on reproduction also may influence pregnancy outcome. In a large study of more than 8000 women undergoing IVF, a 28% decrease in live birth rate was observed in smokers versus nonsmokers.[63] Smoking is also associated with an increase in spontaneous abortion in both assisted and natural conception cycles.[64-66]

Finally, the effect of secondhand smoke exposure has been evaluated. Initial studies found that women's secondhand smoke exposure did not increase the risk of failed fertilization, failed implantation, or spontaneous abortion among couples undergoing IVF.[67] However, the same authors conducted a larger study of 3270 IVF cycles and found different results. After adjusting for age, BMI, year and type of IVF treatment, there was an increase in the risk of implantation failure among women exposed to secondhand smoke compared with those unexposed (OR = 1.52; 95% CI = 1.20-1.92; risk ratio = 1.17; 95% CI = 1.10-1.25) and a decrease in the odds of live birth (OR = 0.75; 95% CI = 0.57-0.99; risk ratio = 0.81; 95% CI = 0.66-0.99).[68]

Body Mass Index

Both undernutrition and overnutrition can negatively affect fertility and pregnancy outcomes.[69-71] Rich-Edwards et al demonstrated a U-shaped association between BMI and ovulatory infertility, with an increase in the relative risk of ovulatory infertility for BMI below 20.0 or above 24.0 kg/m^2.[72] By studying the Nurses' Health Study II, they suggested that 12% (95% CI = 7% to 20%) of ovulatory infertility in the United States may be attributable to underweight (BMI < 20.0) and 25% (95% CI = 20% to 31%) to overweight (BMI ≥ 25).

Body mass index and weight are closely related to reproductive function, with amenorrhea, anovulation, subfertility, and infertility occurring at higher body weights, with and without controlling for height.[18,44,73] In a study investigating lifestyle factors, time to conception increased in both overweight (BMI > 35) and underweight (BMI < 19) individuals. After adjusting for age, menstrual status, and other lifestyle variables, compared with women with a normal weight, women with a BMI of 25 to 39 or <19 had a relative risk of time to conception >12 months of 2.2 (95% CI = 1.6-3.2).[44] Obesity's negative effect on fertility may be mediated by ovulatory dysfunction or by other mechanisms.[70] Prior evidence from the assisted reproduction donor–recipient model supports both ovarian and endometrial

mechanisms.[74-79] However, large-scale studies suggest that the primary impact of female obesity may be at the level of the oocyte or embryo.[80]

Recent studies have also found a relationship between men's body weight and risk for infertility. In a study of 520 men presenting for a semen analysis, there was an inverse relationship between BMI and total motile sperm count.[81] Similarly, a retrospective study of men presenting to an infertility clinic demonstrated that obese patients were more likely to have oligozoospermia (low total progressively motile sperm per ejaculate) compared with patients with normal BMI (OR = 3.3; 95% CI = 1.19-9.14).[82] Also, obese patients were more likely to have high percentage of abnormal morphology when compared with normal weight and overweight men (OR = 1.6; 95% CI = 1.05-2.59). The relationship between obesity and changes in sperm parameters and infertility is multifactorial, but it is likely related to the hormonal changes in the obese man, including elevated estrogen and lower testosterone.[83]

While the deleterious effects of obesity on female reproduction are well recognized, the literature on obesity and ART outcome remains inconsistent. Fecundity was found to be lower in underweight and obese women undergoing IVF compared with those with normal body weight and may require a higher dose of gonadotropins.[84-89] Shah et al demonstrated that compared with women of normal BMI, a BMI of 35 to 39.9 and a BMI ≥ 40 was associated with fewer normally fertilized oocytes ($P < .03$) and lower estradiol levels ($P < .001$).[90] Odds of clinical pregnancy (OR = 0.50; 95% CI = 0.31-0.82) and live birth (OR = 0.51; 95% CI = 0.29-0.87) were 50% lower in women with a BMI ≥ 40 as compared with women of normal BMI. In contrast, a 2007 systematic review concluded that overweight and obese women with a BMI ≥ 25 have poorer outcomes following IVF; however, the authors concluded that there was insufficient evidence regarding the effect of BMI on cycle cancellation, oocyte recovery, and live birth.[85] Although Dokras et al found no differences among the BMI groups undergoing IVF in respect to clinical pregnancy or delivery rates, obese women were more likely to have cycle cancellation, and were more likely to develop preeclampsia or gestational diabetes.[91] There may also be an association between early pregnancy loss and BMI ≥ 30 kg/m^2.[92]

Furthermore, the implications of male obesity on ART are a more recent area of study. While a prospective study of 172 ART cycles demonstrated no statistically significant associations between men's BMI and pregnancy rate and live birth rate among couples undergoing conventional IVF.[93] However, in couples undergoing ICSI cycles, male obesity was related to lower odds of having a live birth. Among the couples undergoing ICSI, the odds of a live birth in couples with an obese male partner were 84% (95% CI = 10% to 97%) lower than the odds in couples with male partners of normal BMI (P, trend = .04). Conversely, an additional study found that after adjustment for female age, female BMI, number of embryos transferred, and sperm concentration, male overweight status was negatively associated with ART outcome in IVF but not in ICSI cycles.[94] For men with a BMI over 25 kg/m^2, there was an approximately 79% reduction in the likelihood of clinical pregnancy in conventional insemination cycles (OR = 0.21; 95% = 0.07-0.69).

Overweight or obesity affects more than about one third of American adults.[95] If overweight and obesity (defined by the World Health Organization as a BMI of 25.0-29.9 kg/m^2 and ≥30.0 kg/m^2, respectively) detrimentally affect fertility, then the national and international trend of weight gain can be expected to result in a significant increase in the proportion of couples experiencing infertility, thus having further implications on maternal and fetal health.

It is worth mentioning how one of the common treatments of morbid obesity, bariatric surgery, affects fertility. Seventy-one percent of anovulatory women with obesity regained ovulatory cycles after surgery, and those with a greater absolute loss or BMI decrease were more likely to regain ovulatory cycles.[96] Twenty-nine women were followed for 24 months postoperatively and were found to have a decrease in their follicular phase length (a normalization of the longer follicular phase associated with obesity) and an increase in sexual arousal and desire.[97] Furthermore, Musella et al conducted a retrospective study of 110 women and found that 63% of the women who had infertility preoperatively were able to conceive and have a live birth after bariatric surgery.[98] When simultaneously assessing for age, type of surgery, BMI before and after surgery, amount of weight lost, and comorbidities, only BMI after surgery and amount of weight lost were found to be predictors of pregnancy after bariatric surgery. Although it does seem that bariatric surgery may help fertility in women with morbid obesity, more studies need to be done, specifically on obese women with ovulatory cycles and anovulation. In men, interestingly, there have been 2 case reports demonstrating the negative impact of bariatric surgery on semen analysis parameters.[99,100] Sermondade et al described 3 men, 2 of whom had worsening sperm concentration postoperatively. This was thought to be due to undernutrition and subsequent disrupted gonadotropin release, poor absorption of vitamins, and the release of lipid-soluble toxins after surgery. It is notable that 2 of 3 were able to conceive with IVF.

Stress and Psychological State

Women with high levels of stress were found to have decreased fecundability, 12.8% versus 16.5% in women with lower stress levels (adjusted OR = 0.6; 95% CI = 0.4-1.0).[101] Furthermore, women with infertility have a higher rate of depression. In fact, infertile women had significantly higher depression scores and twice the prevalence of depression compared with fertile women, and women with an identified causative factor for their infertility had significantly

higher depression scores than women with unexplained infertility.[102] We must also consider if stress or psychological factor can be associated with higher rates of infertility compared with women who do not have increased stress levels.

The influence of an individual patient's psychological characteristics on their fertility treatment outcome remains unclear. Domar et al studied the effect of 10 weeks of cognitive behavioral therapy versus support versus no intervention on women presenting for infertility treatment.[103] The cognitive–behavioral participants had significantly different viable pregnancy rates than the control women (P = .001), and support participants had significantly different viable pregnancy rates than the control women (P = .0146). There were no significant differences between the cognitive–behavioral and support study participants (P = .2016). Viable pregnancies in the participants who remained in the study for the full year were as follows: 55% of the cognitive–behavioral and 54% of the support group participants experienced a viable pregnancy, in contrast to 20% of the controls. It is notable to mention that the subjects' depression of mood was not measured. The authors speculate that their findings may be explained by several factors. Psychological factors, such as depression, could hamper fertility, and psychological assistance relieves these symptoms, women who receive supplemental psychological assistance may feel more prepared to pursue medical treatment that carries a greater likelihood of conception, women who receive supplemental group psychological assistance may hear from others of newer technologies and pursue these treatments, and pregnancy rates are actually not higher but are what would be expected of women who aggressively pursue treatment.

Some studies have demonstrated a prospective relationship between potentially modifiable factors, such as stress, anxiety, and optimism, with IVF outcomes.[104-109] However, other studies have shown no association.[110-112] For example, a prospective study of stress and ART found that higher scores on the positive affect scales were associated with a 7% lower risk of not having a live birth.[113] Conversely, general anxiety and anxiety scores were not associated with IVF outcomes, such as live birth.[114] While the stressor of an infertility diagnosis may not be modifiable, the regulation of one's own emotions may be possible and perhaps have treatment ramifications. In a prospective study of women undergoing treatment with IVF, the cognitive strategy of "letting go" (or behavioral disengagement) was positively and significantly associated with pregnancy.[115] A randomized controlled study examining the effectiveness psychosocial group intervention to achieve anxiety reduction demonstrated a significant drop in anxiety level (measured by the State Anxiety mean score) in the intervention versus control group.[116] A nonsignificant trend of a higher pregnancy rate was observed in the intervention group. Further studies in larger groups of patients are needed to confirm these findings.

The mechanism for how stress affects fertility is under investigation. Two different biomarkers have been studied: salivary cortisol and α-amylase. Cortisol is a marker of the hypothalamic–pituitary–adrenal axis resulting in the secretion of glucocorticoids including cortisol into the circulatory system, and α-amylase represents the sympathetic medullar system, resulting in the release of catecholamines (eg, dopamine, epinephrine, norepinephrine). A recent study noted that women with higher concentrations of α-amylase, but not cortisol, were less likely to conceive than women with lower concentrations.[117]

In summary, the data on stress and fertility are inconclusive. Not only is the most appropriate stress marker (either biochemical or psychological testing scale) yet to be determined, we must be cautious when discussing the possible association with patients. If a person has infertility or fails treatment after being told about the influence of stress may make the patient, and care givers, feel additional stress. This may add to the challenges our infertility patients face, as they may feel that their emotions are yet another facet of their infertility they cannot control.[118]

Exercise

Many women do regular exercise, and some use exercise to reduce stress related to infertility, or to treat obesity.[119] A large population study in Norway sought to evaluate physical activity (leisure activity and occupational activity) and fertility.[120] Compared with women who had no physical activity, women who had physical activity everyday were over 3 times (OR = 3.2; 95% CI = 1.3-7.6) more likely to have fertility problems. Regarding duration, there was decreased risk of infertility in those whose exercise was moderate (16-30 and 30-60 minutes) compared with less than 15 minutes (OR = 0.5; 95% CI = 0.3-0.9). However, women who reported the highest intensity of activity at baseline had the lowest frequency of continuing nulliparity and highest frequency of having 3 or more children during follow-up. The authors speculate that either these women changed lessened their activity, decreasing the odds of infertility, or that the effects of activity were reversible. Green et al studied the relationship between exercise and ovulatory infertility.[121] Both women with primary and secondary infertility were evaluated, but only those with primary infertility demonstrated a significant association between vigorous exercise (running, bicycling, swimming) and infertility. Specifically, for women who had over 60 minutes of activity/day, the relative risk of ovulatory infertility was 6.2 (90% CI = 1.0-39.8) compared with women who did not exercise. In contrast, a large cohort study of Nurses' Health Study II observed that adding a lifestyle factor of 30 minutes of vigorous physical activity per day may be beneficial was linearly associated with decreased risk of ovulatory infertility.[11]

Wise et al assessed the association between physical activity and semen parameters in men presenting for infertility treatment.[122] In this study, 2261

men, contributing 4565 fresh semen samples, were evaluated. The number of subjects with male factor infertility was similar among various amount of exercise. None of the semen parameters were associated with amount or intensity of exercise. However, compared with men who rode a bicycle, men who rode ≥5 hours per week had a greater odds of a total motile count (<23 × 10^6 motile sperm; OR = 2.05; 95% CI = 1.19-3.56).

With regard to exercise and IVF, the associations are complex. When compared with women who do not regularly exercise, women who exercised 4 or more hours per week for 1 to 9 years were 40% less likely to have a successful live birth after the first cycle of IVF (OR = 0.6; 95% CI = 0.4-0.8).[123] The most detrimental effect was observed in cardiovascular exercisers, who had a 30% lower chance of successful pregnancy after their first cycle of IVF than women who did not exercise (OR = 0.7; 95% CI = 0.6-0.9). When compared with women who did not exercise, women who participated in cardiovascular exercise (≥4 hours per week for 1-9 years) had a 50% reduction in live births (OR = 0.5; 95% CI = 0.3-0.8), a more than 5-fold increase in cycle cancellation (OR = 5.1; 95% CI = 2.3-11.5) and an approximately 2.5-fold increase in failed implantation (OR = 2.6; 95% CI = 1.5-4.6) and pregnancy loss (OR = 2.4; 95% CI = 1.1-4.9). The authors stress that they do not advocate women refrain from exercise but rather more studies be completed to investigate the relationship between exercise and ART. An additional study evaluated the association between exercise and IVF through the use of self-reported physical activity for the year prior to IVF and the weeks following the embryo transfer. Subjects also used an accelerometer to measure physical activity intensity after the transfer.[124] Those with higher active living and exercise/sports indices in the past year were more likely to have a clinical pregnancy. Most women did not exhibit moderate or vigorous activity after the transfer and there was no association between accelerometer measured behavior and any IVF outcome.

Environment

Care providers and citizens alike are becoming more aware of exposure to toxic environmental agents and reproductive health. In 2013, the American Congress of Obstetricians and Gynecologists and the American Society for Reproductive Medicine published a joint statement relaying the risks of some environmental toxins and suggestions for prevention.[125] Endocrine-disrupting chemicals (EDCs) can interfere with hormone biosynthesis, metabolism, and reproduction.[126,127] As EDCs are in our environment, food, and consumer products, numerous reproductive disorders appear to be correlated with EDC exposure.[127] Lower fecundity has been reported in women with higher serum levels of perfluorinated chemicals, found in animal products, plastics, and carpets.[128] Phthalates, found commonly in consumer products such as deodorants, adhesives, and food storage items, may increase the risk for endometriosis.[129,130] Bisphenol A, a common ingredient in plastics including food storage containers, has been linked to an increased risk for polycystic ovary syndrome as well as recurrent pregnancy loss.[131,132] Polychlorinated biphenyls (PCBs) have been banned since the 1970s, but their half-life may be greater than 10 years, and can be found in the serum of most Americans. Exposure is primarily through ingestion of contaminated foods (eg, fish, meat, and dairy products), although occupational, ambient, and indoor sources of exposure may exist as well. Meeker et al found a dose-related decrease in the odds of live birth, from 12% to 41%, with increasing levels of PCBs found in the serum of women undergoing IVF.[133]

There are many epidemiologic issues that arise when considering a causal relationship between the environment and reproductive outcomes. Again, study design challenges include accurately measuring the exposure, including an appropriate comparison or control group, and trying to isolate the specific factor.

Conclusions

Infertility treatment is costly, in terms of time, money, and emotional energy. As there are several factors that dictate the success of treatment that are not under the patients' control, we must focus our efforts to optimize modifiable lifestyle factors that increase fertility or the effectiveness of infertility treatment. Although most of the lifestyle factors discussed in this review have been found to have variable effects, some, like obesity and tobacco use, are confirmed to be detrimental to fertility. It is critical that we consider potential limitations in epidemiologic studies of lifestyle and modifiable risk factors and foster research that allows us to draw appropriate conclusions and make recommendation to our patients and the public at large. AJLM

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