In order to take optimal care of patients who seek preconceptional counseling and of patients who present with infertility, the treating physician needs to have an extensive knowledge of the multiple factors that influence human reproduction.

Fecundability and time to pregnancy (TTP) are used in the literature as markers of fertility. Fecundability is defined as the probability of conceiving in a single menstrual cycle while TTP is the length of time in months that it takes a couple to conceive. Infertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse in a woman under the age of 35 years and 6 months without success in a woman 35 or older.

Although the current literature describes a number of factors that are likely to play a role in the ability that a patient or couple has to conceive, it is important to highlight that evidence from randomized controlled trials is lacking for the majority of these regarding quantification and certainly causality of each factor.

In this chapter we summarize the most relevant factors that affect fertility, making evidence-based recommendations where appropriate to better counsel our patients to improve their ability to conceive. Our recommendations will include the practice committee opinions of the American Society for Reproductive Medicine (ASRM) and the American College of Obstetricians and Gynecologists (ACOG) as leading institutions in reproductive medicine and women’s health in the United States.

**Weight**

Body mass index (BMI) is used in the literature as an objective marker to classify underweight, overweight and obesity in adults. BMI is a calculated measurement that compares a person’s weight and height and it is defined as the weight in kilograms divided by the square of the height in meters (kg/m²). Even though there is a growing debate on the possible need to develop different BMI cut-off points for each ethnic group, BMI is applicable to all ethnic groups, is the same for both sexes and is age-independent.

The World Health Organization (WHO) and the National Institutes of Health (NIH) describe underweight as a BMI < 18.5, normal weight as BMI 18.5–24.9, overweight as BMI 25–29.9 and obesity as BMI > 30.

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**TIPS & TRICKS**

Always calculate and document your patient’s BMI in the first office visit (weight in kilograms divided by the square of the height in meters) and determine if she falls under the category of underweight (BMI < 18.5), normal weight (BMI 25–29.9), overweight (BMI 25–29.9) or obese (BMI > 30). Appropriate counseling should follow.

BMI should then be calculated in the follow-up visits to determine any changes as well as to track response to treatment or interventions.
Fecundability has been found in multiple studies to be lower at the extremes of BMI in patients trying to conceive spontaneously. This finding was confirmed in a recent prospective cohort study by Wise et al., in which a longer TTP was seen in women who were overweight, obese and very obese (BMI ≥ 35), compared with normal weight women. Additionally being underweight (BMI < 20) was associated with reduced fecundability among nulliparous women.

Although some authors have linked male obesity with subfecundity, the evidence is not compelling and there are no randomized controlled studies to address this association. Male obesity was not linked to subfecundity in the recent prospective cohort study by Wise et al.

The direct effect of being overweight and obese on assisted reproduction technologies (ART) is less clear than for spontaneous pregnancies. In a meta-analysis by Maheshwair et al., women with a BMI ≥ 25 had a lower chance of pregnancy following in vitro fertilization (IVF) [odds ratio (OR) 0.71], required a higher dose of gonadotropins and had an increased miscarriage rate (OR 1.33) in comparison to women of normal weight. In a recent study by Bellver et al., implantation, pregnancy and live birth rates were lower in obese women; in fact, pregnancy and live birth rates were reduced progressively with each unit of BMI, independent of embryo quality, suggesting an alteration in the uterine environment as a likely factor in these patients.

Evidence is accumulating that suggests that effective treatment of women with elevated BMI may improve reproductive outcome. Nonsurgical treatment for patients with overweight and polycystic ovary syndrome (PCOS) was shown to improve fertility in patients that lost at least 5% of their weight in a small prospective study by Crosignani. Surgical treatment may show benefit as well, as evidenced by a recent meta-analysis by Merhi which concluded that although “the majority of the present data tend toward reporting an improvement in fertility status after surgical weight loss, it remains unclear whether this is a direct result of the significant weight reduction per se”.

**Recommendations**

All patients should be advised to follow a healthy diet according to the United States Department of Agriculture (USDA) guidelines. Patients should consume a variety of nutrient-dense foods and beverages within and among the basic food groups while choosing foods that limit the intake of saturated and trans fats, cholesterol, added sugars, salt and alcohol.

ACOG recommends folic acid supplementation of 400 μg/day on all women capable of becoming pregnant, since it has shown to reduce the occurrence and recurrence of neural tube defects.

Weight loss and exercise should be advised for all women who are overweight or obese for all the associated health benefits.

There is not enough evidence to recommend surgical treatment for obesity on the ground of fertility improvement. Patients who wish to pursue bariatric surgery should have appropriate medical management with an expert in the field to monitor possible nutritional deficiencies and other complications.

**Age**

The incidence of infertility increases with advancing maternal age. In a prospective study by Dunson et al., the percentage of infertility was 8% for women aged 19–26 years, 13–14% for women aged 27–34 years and 18% for women aged 35–39 years.

There is also evidence that the age of the male partner may affect fertility after the age of 35 years. In the study by Dunson et al., the proportion of couples failing to spontaneously conceive within 12 cycles increased from 18% when the male partner was 35 years old to 28% when the male partner was 40.
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There is a similar decline in the success of IVF as the age of patient increases. In 2007, the percentage of transfers of fresh embryos from non-donor oocytes resulting in live births in the United States was 46.1 for patients <35 years of age and showed a progressive decline to 16.4 in patients 41–42 years of age.

**Recommendations**

Although according to the ASRM guidelines a patient is diagnosed with infertility after 12 months or more of being unable to achieve a successful pregnancy, earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years.

The ASRM additionally states that “times to conception increases with age. For women over age 35 years, consultation with a reproductive specialist should be considered after 6 months of unsuccessful efforts to conceive.”

Important reproductive potential and ovarian reserve tests that are commonly performed by specialists include a sonogram to assess general pelvic anatomy and basal antral follicular count (BAFC) as well as the day 3 serum biomarkers follicle stimulating hormone (FSH) and estradiol.

As part of the counseling process for treatment of infertility, the reproductive specialist should be familiar with the new and innovative options that are available for each individual patient, including options that halt the reproductive aging process such as oocyte cryopreservation.

**Smoking**

Approximately 30% of reproductive age women and 35% of reproductive age men in the United States smoke, and up to 13% of infertility may be attributable to cigarette smoking. Most studies that address the effect of active smoking of the female partner on fertility to date report a decreased fecundibility independent of other confounding influences. In the largest available population study by Hull et al., the increasing delay to conception correlated with increasing daily numbers of cigarettes smoked.

In a meta-analysis by Waylen et al., which included 22 studies, patients who smoked had significantly lower odds of live birth per cycle (OR 0.54), significantly lower odds of clinical pregnancy per cycle (OR 0.56), significantly higher odds of spontaneous abortion (OR 2.65) and significantly higher odds of ectopic pregnancy (OR 15.69).

The ASRM in the Practice Committee Opinion on Smoking and infertility concluded that smoking (1) appears to accelerate the loss of reproductive function, (2) may advance the time of menopause by 1–4 years and (3) is associated with an increased risks of spontaneous abortion, ectopic pregnancy and gamete mutagenesis. Additionally, smokers require nearly twice the number of IVF attempts to conceive as nonsmokers.

A definite causality between male partner smoking and infertility has not been proven but there are data that suggest that there may be adverse effects in male smokers, as well. Smokers have an average 23% decrease in sperm concentration and 13% decrease in sperm motility in comparison to nonsmokers.

The largest meta-analysis to date on the effect of female and male smoking on IVF included 22 studies and despite the variations in results between studies, there was compelling evidence that smoking had a negative influence on IVF outcome.

**Recommendations**

The United States Public Health Service (USPHS) guidelines recommend that advice to quit and brief counseling be done at all or nearly all office visits by a smoker, regardless of the reason for the visit.

**TIPS & TRICKS**

The USPHS and ACOG recommend using the “5 A’s” algorithm for brief counseling in the office:

- Ask about smoking status
- Advise smokers to quit
- Assess their readiness to quit
- Assist them with their smoking cessation effort
- Arrange follow-up visits or contact
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A meta-analysis by Klonoff-Cohen on the effect of female and male caffeine consumption on IVF found only one study that directly examined the effect of female and male caffeine consumption on IVF. In this study, female caffeine consumption had an effect on spontaneous abortions (OR range from 6.2 to 19.8, depending on the dose and timing of consumption), failure on achieving a live birth (OR 2.9–3.9) and infant gestational age (OR decreases of 3.5–3.8 weeks). Male consumption of caffeine did not have an effect on sperm, IVF or neonatal endpoints.

Given the limitations of available data, more studies are needed to further evaluate this possible association.

Recommendations

Patients attempting to conceive naturally or through ART who consume more than 500 mg of caffeine/day (>5 cups of coffee/day) should be advised to limit consumption to 100–200 mg of caffeine/day (1–2 cups of coffee or equivalent).

The ASRM states in their Committee Opinion that “moderate caffeine consumption (1–2 cups of coffee/day or equivalent) before or during pregnancy has no apparent adverse effects on fertility or pregnancy outcomes.”

Alcohol

The data reflecting the effect of alcohol on fertility have shown conflicting results. The most recent prospective study on 18555 women addressing this possible effect, by Chavarro et al., did not find an association between alcohol consumption and infertility after adjusting for other possible confounding factors (e.g. smoking, parity), confirming the findings of a prior prospective trial by Florack et al., where the level of alcohol consumption in the female partner was not related to fecundability. In the study by Chavarro et al., an even split on the results of the available prospective trials is reported (three positive and three null studies).

In the meta-analysis on the effect of female and male alcohol consumption on ART by Klonoff-Cohen, the author found one study that examined female and male alcohol consumption as a primary risk factor for ART. In this study, female alcohol consumption was associated with a 13% decrease in the number of oocytes.
Alcohol consumption should cease completely once pregnancy is established, since the level of alcohol consumption that is safe during pregnancy is not known. In fact, the U.S. Surgeon General’s advisory on alcohol use in pregnancy advises women who are pregnant or considering becoming pregnant to abstain from using alcohol.

Summary
Factors that play an important role in fertility include the age and weight of the patient, as well as maternal consumption of tobacco, caffeine or alcohol.

Weight
Fecundability has been found in multiple studies to be lower at the extremes of BMI in patients trying to conceive spontaneously. The direct effect of being overweight and obese on ART is less clear than for spontaneous pregnancies. In a recent prospective cohort study, male obesity was not linked to subfecundity.

Age
The incidence of infertility increases with advancing maternal age, as does the likelihood of success with ART. There is some evidence that the age of the male partner may affect fertility after the age of 35 years.

Smoking
Smoking is associated with an increased risk of spontaneous abortion, ectopic pregnancy and gamete mutagenesis. Additionally, smokers require nearly twice the number of ART attempts to conceive as nonsmokers.

A definite causality between male partner smoking and infertility has not been proven.

Caffeine
Subfertility has been linked to heavy caffeine consumption (>500 mg/day). Female caffeine consumption has been linked to an increased risk of spontaneous abortion, failure to achieve a live birth and a decrease in gestational age of the infant. Male consumption of caffeine has not been proven to have a deleterious effect on fertility.
Alcohol
The data reflecting the effect of alcohol on fertility have shown conflicting results. A recent prospective study did not find an association between alcohol consumption and infertility.

Recommendations
The following advice should be given to patients attempting to conceive spontaneously or through ART:

• follow a healthy diet according to USDA guidelines (including folic acid supplementation of 400 μg/day)
• quit smoking
• limit caffeine consumption to 1–2 cups of coffee/day or equivalent
• avoid alcohol consumption greater than 2 drinks/day (quit completely once pregnancy confirmed).

Additionally, weight loss and exercise should be advised for all women who are overweight or obese, for all the associated health benefits. Evidence is accumulating to suggest that effective treatment of women with elevated BMI may improve reproductive outcome.

Although the diagnosis of infertility is established until 12 months of not being able to conceive, earlier evaluation and treatment may be justified in some patients based on medical history and physical findings and is warranted after 6 months for women over the age of 35 years.

Selected bibliography
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