

# Preconception Considerations for Male Fertility

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## INTRODUCTION

Preconception counseling has traditionally been considered the domain of the female partner. However, it is commonly held among fertility specialists that 50% of couples experiencing infertility have a male contribution. For this reason, there is growing interest in the involvement of men in preconception counseling. In fact, the U.S. Centers for Disease Control (CDC) has published recommendations for pre-conception care of men.<sup>1</sup>

The primary purpose of preconception counseling is to improve the chances of pregnancy. Furthermore, preconception care for men can further improve family planning outcomes, enhance the reproductive health of women, and help men prepare for fatherhood.<sup>2</sup> Moreover, this represents an opportunity for disease prevention and general health promotion for reproductive-aged males, a demographic that has historically underutilized health care (**Box 1**).

### Box 1. Potential Benefits of Preconception Care for Men

- Increased chances of pregnancy
- Improved family planning
- Enhanced female reproductive health
- Preparation for fatherhood
- Primary care disease prevention and health promotion

There is no current consensus on the ideal location and provider of preconception care for men. Primary care providers may screen for those interested in conception as part of their annual visit for reproductive-aged men.<sup>3</sup> Physicians and advanced practice providers at a Men's Health clinic may provide this counseling as a specific offering. Another opportunity for preconception counseling may be with the Reproductive Endocrinology and Infertility specialist or advanced provider during the female partner's visit at a fertility center. The patient may also be referred to a general urologist or a fellowship-trained reproductive urologist, who has received advanced training in these topics.

Preconception counseling for male fertility should occur at least three months before planned conception. This three-month window takes into the account that new sperm is produced approximately every 42–76 days,<sup>4</sup> and assumes that damaged sperm can be replaced within three months

of mitigated exposures. Furthermore, a sufficient time interval may be needed to improve upon habitual behaviors and pursue long-lasting lifestyle changes. It should be noted that while semen parameters are often interpreted as an indication of male fertility, it is by no means a direct proxy for fertility. A more direct outcome for fertility would be confirmed pregnancies and live births, but this data can be difficult to collect and be subjected to numerous confounding elements.

There are a multitude of popular claims circulating around male infertility, ranging from the type of undergarments that men wear to the food they eat and the activities they engage in. Some of this advice does seem logical and may not have much downside. However, many of these claims are supported by very limited data. In an effort to organize the clinical content of preconception care, Frey and colleagues have previously posited a model framework to approach preconception counseling according to three components: risk assessment, health promotion, and clinical interventions.<sup>2,5</sup> In this report, we will review the literature supporting preconception considerations for male fertility according to this framework (**Box 2**).

### Box 2. Components of Preconception Counseling

- Risk Assessment
- Health Promotion
- Clinical Interventions

## RISK ASSESSMENT

The first step in preconception counseling is the assessment of risks that may affect fertility. Men should review pertinent elements of their medical history: sexually transmitted infections (STIs), chronic disease, medications, and family history of congenital disease or infertility. Men should also consider the implications of their age, as well as their partner, prior to attempting to conceive (**Box 3**).

Because STIs can affect both their partner and offspring, men should consider their risk for sexually transmitted infections, and potentially request a screening test. Screening should be conducted for chlamydia, gonorrhea, syphilis, human immunodeficiency virus (HIV), and hepatitis B and C. Urethral discharge and dysuria may be signs of chlamydia

**Box 3. Risk Assessment**

<p>Screen for sexually transmitted infections</p> <p>Manage chronic disease</p> <p>Review medications</p> <p>Review family history of congenital disease or infertility</p> <p>Consider paternal and maternal age</p>
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and gonorrhea, but some men may be asymptomatic, which underscores the importance of screening. Chlamydia and gonorrhea may affect both male and female fertility by causing scarring in the reproductive tracts; for example, pelvic inflammatory disease may result in female tubal infertility. Syphilis may cause epididymitis, and later stages of syphilis may affect nerve and erectile function. Furthermore, it can cause spontaneous abortion or infection of the newborn. HIV and hepatitis should be screened due to the significant potential impact on the partner and offspring. Additionally, these may impact male fertility potential by impairing semen parameters or affecting sexual function.<sup>6,7</sup>

Men should review their own medical history and chronic illnesses and make sure they are managed to the best of their ability. This may require further guidance of their primary care provider or appropriate specialist. Chronic illnesses such as hypertension and diabetes have been linked to male infertility.<sup>8</sup> For instance, diabetes can affect fertility at multiple levels. Diabetes may result in erectile dysfunction and retrograde ejaculation, and it may directly affect semen quality.<sup>9,10</sup> It may even raise the risk of diabetes in the offspring through epigenetic pathways.<sup>11</sup> Other medical conditions that may predispose men toward infertility include genitourinary conditions (e.g. varicocele, cryptorchidism), surgeries or injuries, infections and malignancies, as well as treatment with prior chemotherapy or radiation therapy. These men may seek reproductive screening with semen analysis earlier, possibly even before attempted conception. Men who have received chemotherapy, or received radiation to the pelvic region, should wait at least 12 months prior to attempted conception due to the risk of genetic alterations to the sperm.<sup>12,13</sup>

Men should review their current medications and make sure these are medically necessary to continue, as these may have an impact on fertility. Medications may influence fertility directly via gonadotoxic effect or indirectly by affecting the central hormonal axis or sexual function. Exogenous testosterone supplementation is well known to suppress the hypogonadal-pituitary-gonadal hormonal axis and decrease or completely shut down sperm production. Other commonly used medications that may affect reproduction include finasteride (for male pattern baldness), anti-hypertensives, and psychiatric medications such as selective serotonin reuptake inhibitors (SSRIs).<sup>14</sup> For example, SSRIs used to treat anxiety and depression have been associated

with delayed ejaculation, which may disrupt the conception process. While certain medications, such as chemotherapeutic agents, are commonly known to exert a direct effect of spermatogenesis, other medications may not have such a clear connection. Providers may consider using a commercial database, such as Reprotox<sup>®</sup>, that enumerates possible toxic side effects of common medications.

Patients who have family history of infertility or congenital diseases may consider earlier evaluation by a reproductive specialist. Congenital diseases such as cystic fibrosis or sickle cell anemia may have an impact on reproduction function, as well as potential impacts for the offspring. For example, men who are carriers for the mutated cystic fibrosis gene may have congenital absence of the vas deferens and are unable to produce sperm in the ejaculated semen. In addition, if the partner is also a carrier, there could be severe consequences for the offspring. Therefore, genetic counseling is commonly recommended prior to conception. Men whose father had difficulty conceiving may also have a chromosomal or Y-chromosome microdeletion abnormality.

The decreasing fertility potential associated with advanced female age is well known. There is a more gradual decline in male fertility. A systematic review examined the association between advancing paternal age and several semen parameters, and demonstrated small age-dependent declines in motility, morphology, volume, but not in sperm concentration.<sup>15</sup> Given the sheer number of sperm production, paternity may be advanced even into the senior years. Aside from the impact on conception, paternal age may influence the characteristics of offspring. Several studies have demonstrated an association between advanced paternal age and psychological illness in the offspring, including schizophrenia and attention-deficit hyperactivity disorder.<sup>16,17</sup>

In addition to considering their own age, men should consider the impact of their partner's age, and to understand the basics of ovulatory timing. Men should be counseled that advanced maternal age is associated with greater difficulty in conceiving, as well as higher impact on medical illnesses on offspring. Female fertility peaks in the mid- to late-20s and then begins to decline,<sup>18</sup> with women above age 35 considered to be of advanced maternal age. Ability to conceive is determined not only by egg quantity, but quality – which is age-related. To optimize chances of conception, we advise couples to attempt conception every other day in the ovulatory window, as sperm may survive in the female vaginal tract for several days.<sup>19</sup> This cadence may reduce male sexual performance anxiety related to “performing on command.” In summary, men should be counseled that there is a “window of fertility” for women and the concept of timing with ovulation. In addition, knowledge regarding the impact of female age may affect family planning – possibly planning to have children earlier, or to consider alternative options for family building (e.g., egg donor, adoption).

## HEALTH PROMOTION

A number of lifestyle exposures, behaviors and habits may potentially affect male fertility, and these should be highlighted during the preconception counseling. Obesity and exposure to tobacco, marijuana or alcohol in excess can disrupt fertility, as can the use of opioids and anabolic steroids. Fertility may be affected by certain toxic substances associated with specific industries and hobbies, such as manufacturing and agriculture (**Box 4**).

### Box 4. Health Promotion

Obesity
"Unhealthy" diet
Alcohol excess
Tobacco
Marijuana
Testosterone/anabolic steroids
Chronic opioid use
Industrial and agricultural toxins

The rate of obesity has increased significantly in the United States. The U.S. obesity prevalence was 30.5% from 1999–2000 and had reached 42.4% as of 2017–2018.<sup>20</sup> Retrospective studies have demonstrated lower sperm concentrations and rates of oligospermia in men with elevated BMI.<sup>21</sup> For instance, one meta-analysis showed that overweight men (BMI 25–29) were 11% and obese men (BMI > 30) were 42% more likely to have low sperm counts than men with normal BMI.<sup>22</sup> Multiple hypotheses have been posited to explain the connection between obesity and lower sperm count. These include disruption of the HPG axis, elevated scrotal temperature due to fat accumulation around the genitals, or even direct effects on spermatogenesis. While it is unclear whether obesity is a cause or a correlation with male infertility, a small, single-center randomized, control trial showed improvements in sperm quality in obese men who were enrolled in a 16-week exercise program.<sup>23</sup>

Several studies have examined specific diets that may affect male infertility. While the quality of evidence is low, observational studies have suggested that dietary patterns that are good for cardiovascular health may be beneficial for male fertility as well. A 2017 systematic review of observational studies associated diets rich in items such as seafood, poultry, whole grains, vegetables and fruits and low-fat dairy with higher quality semen parameters compared to diets rich in processed and sugar-sweetened foods and full-fat dairy.<sup>24</sup> Whether these sorts of diets represent correlation or causation is not clear. However, due to the benefit to the general health of the male in addition to the potential fertility benefit, it is advisable for the provider to recommend adherence to a "healthier" diet favoring seafood, poultry, nuts, whole grains, fruits, and vegetables.<sup>25,26</sup>

Caffeine consumption does not have a strong correlation with semen parameters. A meta-analysis comprising 19,967 subjects did not demonstrate a consistent effect from caffeine from coffee, tea or cocoa drinks.<sup>27</sup> There was a possible association with DNA damage and aneuploidy, but without observable clinical effect.

While moderate alcohol use does not appear to affect male fertility, heavy alcohol use may affect male fertility at multiple levels. A multi-national cross-sectional study of 8,344 healthy men, in which the median weekly intake was eight drinks, in Europe and the US showed no correlation between alcohol use and semen variables.<sup>28</sup> However, additional studies have associated variable semen abnormalities with heavy alcohol use.<sup>29–31</sup> Heavy alcohol use may result in liver dysfunction, disrupt the hypothalamic-pituitary-gonadal hormonal axis, and directly affect testicular function.<sup>32</sup>

A large collection of retrospective data likewise draws a connection between smoking and male infertility. Specifically, smoking tobacco has been associated with a small negative impact on sperm concentration, motility, and morphology, but the quality of evidence is low.<sup>33–37</sup> For example, one cross-sectional study demonstrated a 19% lower sperm concentration in heavy smokers (defined in this study as >20 cigarettes/day) compared to non-smokers.<sup>34</sup> Observational studies also suggest that marijuana use may negatively impact semen parameters such as concentration, motility and morphology, but the data is of limited quality.<sup>38</sup> For instance, a Danish study of 1,215 healthy young men showed that regular marijuana smoking (more than once weekly) was associated with 28% lower sperm concentration.<sup>39</sup>

Chronic opioid use may result affect male fertility by altering the hormonal axis. Chronic opioid use is familiar cause of hypogonadism.<sup>40</sup> Not only can this affect sexual function, but it has been linked to decreased semen parameters.<sup>41</sup> Current use of testosterone-replacement therapy or anabolic steroids, are known to disrupt the hypothalamic-pituitary-gonadal axis and inhibit spermatogenesis.<sup>42</sup> The time to recovery after testosterone replacement was noted to be 67% at six months and 90% at 12 months after cessation in one study.<sup>43</sup> There is not strong evidence suggesting permanent infertility, though the timing of recovery may be variable.

Exposures to heavy metals (lead, cadmium) and pesticides should be queried. Lead is well recognized as being toxic to gonadal tissue, and may come from lead-based paints, piping, water and industrial sources. Men who work in manufacturing fields may come into contact with heavy metals. Agricultural workers may be exposed to pesticides such as DBCP, DDT, as well as organophosphates, which can impact spermatogenesis. Therefore, screening for type of work and workplace environment, especially in the manufacturing and agriculture, may help men protect themselves from potential exposures.<sup>13</sup>

Studies in the laboratory have demonstrated that increased heat can impair spermatogenesis. Starting from this premise,

researchers have hypothesized that a variety of factors that may increase testicular temperature may also impair spermatogenesis.<sup>44</sup> This includes hot tub use, laptop usage, type of underwear, and types of activities (such as cycling),<sup>45-49</sup> while some studies have pointed toward a correlation, these have been retrospective and have low quality, without the ability to account for confounding variables. In summary, while these studies should not dissuade men from wearing their favorite underwear or sports activities, men who are struggling to conceive may consider these behavior changes with low downside.

## CLINICAL INTERVENTIONS

Pre-natal vitamins, particularly with folic acid, are routinely recommended for women who are planning to conceive. Similarly, vitamins, and particularly antioxidants, have been commonly recommended for male partners who are planning to conceive. The prevailing theory was that antioxidants would reduce the reactive oxygen species and associated free radicals that could be detrimental to DNA in sperm. Indeed, branded “male fertility supplements” containing such antioxidants such as vitamin C, vitamin E, selenium, have been marketed to men who are attempting to conceive. Traditionally, antioxidants have been widely offered to men to improve semen parameters in men for whom targeted medical and surgical therapies are not indicated. This practice was based on limited studies; a 2019 Cochrane review did show a modest improvement of clinical pregnancy rates, but also highlighted the low quality of evidence.<sup>50</sup>

In 2020, the Males, Antioxidants, and Infertility (MOXI) trial, a double-blinded, multi-institutional, randomized controlled trial that was adequately powered with 144 men demonstrated no improvement in sperm parameters or clinical pregnancy for a combination antioxidant pill containing vitamin E, selenium, N-acetylcysteine, and carnitine.<sup>51</sup> While the aforementioned supplements are unlikely to be of benefit, the use of Coenzyme Q10, which was not tested in the MOXI trial, has been associated with improvement in semen parameters in a small prior study.<sup>52</sup> While the benefit is far from clear, the risk of substantial harm has also not been widely proven (Table 1).

**Table 1.** Clinical Intervention: Antioxidants

Unlikely Benefit*	Possible Benefit**
Vitamin C	Coenzyme Q10
Selenium	
N-Acetylcysteine	
L-Carnitine	
Zinc	

\*Based on high quality data<sup>1</sup>

\*\*Based on low quality data<sup>2</sup>

## CONCLUSION

Preconception counseling for men can be a valuable initial step in the journey to fatherhood. This should occur at least three months prior to planned conception, and should include a risk assessment and discussion of health promotion and possible interventions. The risk assessment should involve an STI screen and review of the patient's medical and family history, as well as take into account paternal age. Health promotion should highlight the potential negative impact of lifestyle choices and exposures, including obesity, excessive alcohol, tobacco and marijuana use, and ongoing use of testosterone or anabolic steroids. While laboratory research has demonstrated the negative impact of increased heat on sperm production, the real-world implications for the type of undergarments worn, sauna and hot tub use, and cycling is less clear. Furthermore, antioxidants have traditionally been considered a helpful intervention, but more recent high-quality data does not show reliable improvement with most antioxidants tested. In summary, preconception counseling for the male partner can optimize a couple's chances for pregnancy, as well as improve a man's personal health.

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