

# Integrative Approaches to Infertility for Women

by Jaclyn Chasse, ND

## Increasing Difficulty in Obtaining Pregnancy

The more you learn about what goes into conception, the more amazing it seems that anyone gets pregnant. The process of conception starts with the transformation of germ cells into gametes (egg and sperm) and ends with the complex signaling processes that allow a embryo to properly implant into the endometrium, altering a woman's normal hormonal cycle and creating an environment to nourish and maintain that pregnancy. From a physiological perspective, pregnancy depends on proper functioning of nearly every underlying process that integrative practitioners consider: balanced inflammatory pathways, angiogenesis, oxidative stress, hormonal balance, detoxification, proper nutrient status, and the list goes on. And so, it's not necessarily surprising that we have seen a decline in fertility over the last few decades along with the declining health reported overall in Americans.

According to the CDC report *Fertility, Family Planning, and Reproductive Health of US Women: Data from the 2002 National Survey of Family Growth*, more and more women in every age group have had a more difficult time getting pregnant. Between 1982 and 2002, rates of reported impaired fecundity (inability to carry a pregnancy to term) have risen as high as 15% for women aged 35 to 44, or 1 in 8 couples. Even among women with the highest fertility, aged 15 to 24, impaired

fecundity rates have nearly doubled from 4% to 7% over the 20-year span.<sup>1</sup>

Fertility has been declining in men as well. A review of 61 papers published between 1940 and 1990 reported trends in semen analysis results for 14,947 men. Over the half-century, the participants' average sperm concentration decreased from 113 million/mL to 66 million/mL. In addition, the average seminal volume per ejaculation decreased from 3.4 to 2.74 mL.<sup>2</sup> This means that the average sperm count (per ejaculation) had dropped from 384.2 million to 181.5 million, a 52.8% decrease.

We are aware of several factors that negatively affect fertility, including nutrient deficiency, environmental exposures, and stress. Thankfully, there may be opportunities to positively affect fertility of couples by decreasing exposure to harmful substances and supporting a healthful environment for both mother and father.

A study conducted by the Forsight Group, a UK-based nonprofit dedicated to promoting preconception care, followed 367 couples ranging in age from 22 to 59. Many couples in the study had a previous history of infertility (37% of couples), miscarriage (38%), therapeutic abortion (11%), still birth (3%), low-birth-weight babies (15%), malformations (2%), and SIDS (1%). All couples received basic preconception care including nutritional counseling and a prenatal multivitamin for both partners. After

2 years, 89% of the couples had achieved live births. Of those with previously diagnosed infertility, 81% achieved live births, suggesting that lifestyle modification may positively affect fertility. Also of note is that within this treatment group, there were no reported miscarriages, perinatal deaths, or malformations, and that most children were born full term and of a healthful weight.<sup>3</sup>

## Starting at the Beginning

Several lifestyle factors have been identified that can promote optimal fertility, including dietary behaviors, stress management, and maintenance of a healthful weight. In addition, adequate nutrient status can influence not only the ability to get pregnant, but the health of the egg and sperm, and thus the health of the child born to those parents. The following interventions can greatly influence fertility, and it is recommended that all couples trying to conceive consider these interventions, whether they have trouble with fertility or not.

## Addressing Obesity

Obesity poses a significant threat to fertility as well as for the offspring born to obese parents. In obese men, there is increased aromatase activity, which irreversibly converts testosterone to estradiol, resulting in decreased testosterone and increased estrogen levels.<sup>4</sup> It is likely that this plays a role in the lower sperm counts, lower sperm concentration, and poor sperm morphology seen in men with increased BMI and central

adiposity. Obese men also have fewer motile sperm and lower testosterone levels, as mentioned above.<sup>5,6</sup>

It's not only men who experience decreased fertility as their weight creeps up; women are also affected. Obese women have lower pregnancy rates (20.8% versus 28.3% successful cycles,  $p = 0.04$ ) when they undergo *in vitro* fertilization (IVF) and obese women are more likely to experience preterm births after IVF.<sup>7-9</sup> Although this study represents women undergoing IVF, similar fertility trends exist in women trying to conceive naturally.<sup>10</sup> Together, obese couples experience higher rates of miscarriage in both spontaneous conception and assisted reproduction.<sup>11</sup> In addition to the hormonal changes noted for men, this decreased fertility may be due to increased levels of inflammation which affect ovarian response and the uterine/endometrial environment.

Obesity poses such a hindrance to fecundity that many fertility clinics place a BMI limit for candidacy for the procedure. Addressing obesity for patients is essential to support a healthy conception and pregnancy, and maintenance of a healthful weight should be a first goal for couples wishing to get pregnant. If a weight-loss plan is implemented, it is strongly recommended that clinicians encourage a modified Mediterranean diet, as this diet also has fertility-promoting effects.

### **Mediterranean Diet**

The Mediterranean diet is a recommendation based on the traditional dietary patterns of Crete and the rest of Greece, southern Italy, and southern France.<sup>12</sup> It emphasizes an abundance of plant foods, especially fruits and vegetables, and a low intake of red meat. Generally, fat makes up 25% to 35% of total calories, with low intake of saturated fats and high intake of monounsaturated fats such as those in olive oil and omega-3 fats such as in fish. The primary fat consumed in this diet comes from fish, poultry, and olive oil. The diet is high in legumes and whole grains and suggests low

to moderate consumption of dairy products and red wine.

The Mediterranean diet has, of course, been studied for its positive effects on cardiovascular disease and overall mortality.<sup>13</sup> It has been researched for its effects on diabetes, depression, cognitive function, cancer, weight loss, and much more.<sup>14</sup> Of note for this article is the diet's effect on fertility. Observation of 2154 Spanish women aged 20 to 45 years showed that those women with the greatest adherence to a Mediterranean diet pattern (versus Western diet) showed the lowest difficulty of getting pregnant.<sup>15</sup> Additionally, a 2010 study of 161 Dutch couples undergoing IVF or IVF with intracytoplasmic sperm injection (ICSI) found that Mediterranean diet adherence increased the probability of pregnancy (odds ratio 1.4).<sup>16</sup> Mediterranean diet adherence was also associated with higher folate and vitamin B6 levels in red blood cells and in follicular fluid in the same study.

### **Stress Management**

Stress has a documented impact on fertility. Studies have confirmed that stress inhibits the hypothalamic-pituitary-gonadal (HPG) axis.<sup>17</sup> The stress hormones cortisol, epinephrine, and norepinephrine and the hypothalamic-pituitary-adrenal (HPA) axis directly interact with several other hormones, including hormones that regulate the menstrual cycle and gamete maturation (Table 1). Stress can directly modify levels of FSH (follicle stimulating hormone) and LH (luteinizing hormone), which directly affect synthesis of estrogen and progesterone, and dictate follicular maturation and ovulation in women and spermatogenesis and testosterone production in men. Elevated cortisol and ACTH in men can also inhibit the conversion of androstenedione into testosterone in Leydig cells.<sup>18</sup> Higher follicular cortisol/cortisone ratios are associated with higher rates of infertility in women.<sup>19</sup> It has been noted that men with increased stress have a decrease in glutathione and

free sulfhydryl content of semen, both compounds important to combat oxidative stress and toxic exposure.<sup>20,21</sup>

**Table 1: Hormones Directly Affected by the HPA Axis**

Gonadotropin releasing hormone (GnRH)
Prolactin
Luteinizing hormone (LH)
Follicle stimulating hormone (FSH)
Cortisol
Endogenous opioids
Melatonin

Interestingly, the link between stress and female fertility goes beyond an increase in stress hormone levels and their downstream effects. Hans Selye observed ovarian atrophy in response to stress in rats.<sup>22</sup> It is important to acknowledge that stress mediators can be protective, not just damaging, but high levels can lead to allosteric overload, where there is a high likelihood of changes to the physiological systems that affect fertility.<sup>23</sup>

It seems as though various methods of stress management and counseling may be successful for couples trying to conceive. A group mind/body intervention increased IVF pregnancy rates from 43% to 52% in women under age 40 about to start their first IVF cycle at a Massachusetts fertility clinic.<sup>24</sup> Additionally, "letting go" counseling, focused around releasing control of the process of conception, has also shown benefit. This type of counseling nearly doubled pregnancy rates in the treatment group.<sup>25</sup> Many other interventions have showed benefit for both men and women, including standard psychotherapy.

It is essential for practitioners to work with patients to develop a stress-management protocol that will work for each couple, and to be sensitive to the fact that a robust treatment plan may create an increased focus on infertility and therefore, an increased stress in and of itself.

### **Basic Preconception Supplementation**

In this author's opinion, every couple trying to conceive should be put on a basic preconception

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regimen. Specific nutrients, such as folic acid, have been shown not only to be beneficial to prevent serious birth defects such as spina bifida, but also to negate deleterious epigenetic effects to the offspring of toxic exposures, poor nutrition, and elevated stress levels in the parents.<sup>26</sup> No couple lives in a perfect world, and these extra precautions may not only promote fertility but also significantly affect the offspring's adult health status. The most simple preconception program would include a good multivitamin and fish oil for both partners.

A prenatal multivitamin provides key nutrients necessary for both mother and baby throughout fetal development. These include iron, calcium, folate, and zinc. Studies have demonstrated significantly improved pregnancy rates in women on multiple micronutrient supplements compared with folic acid alone (66.7% versus 39.3% achieved conception after 3 menstrual cycles, 60% versus 25% ongoing pregnancy rate).<sup>27</sup> Consumption of a prenatal multivitamin has also been associated with significantly improved birth outcomes compared with consumption of folic acid and iron alone, including more healthful birth weight of babies, and decreased rate of stillbirth and miscarriage. A nonsignificant trend of decrease in neonatal deaths has also been observed.<sup>28</sup> The same study also reported, not surprisingly, that mothers who took a prenatal vitamin had better micronutrient status postpartum.

Fish oil is another key supplement to include in a preconception protocol for every couple who is contemplating pregnancy in the next 6 months. It has been observed that fertile men tend to have higher blood and spermatozoan levels of omega-3 fatty acids as well as lower serum ratios of omega-6 to omega-3 compared with infertile men.<sup>29</sup> For men with

oligoasthenoteratospermia (OAT), the worst semen parameters possible, supplementation with omega-3s significantly improved semen parameters including increasing sperm count from 38.7 to 61.7 million and increasing sperm concentration from 15.6 to 28.7 million/mL.<sup>30</sup> It is clinically useful to understand that a sperm concentration greater than 20 million/mL is associated with a much higher rate of clinical pregnancy than below 20 million/mL, where the likelihood of natural conception is considered to be approximately zero.<sup>31</sup> This fact further emphasizes the benefit of fish oil supplementation. Fish oil supplementation has also been correlated with increased superoxide dismutase (SOD)-like and catalase-like activity, which both demonstrate an increased ability to withstand oxidative stress, as well as positive nonsignificant improvements in sperm motility and morphology.<sup>32</sup>

While there are not as many studies to validate the benefit of omega-3 supplementation in women, it is fair to assume that the significant benefits to gamete production in men would have some correlation to the analogous structure in a woman, the egg. Increased dietary intake of omega-3 fatty acids in women, especially alpha-linolenic and docosahexaenoic acids (DHA), have been correlated with an improvement in embryo morphology in couples undergoing IVF with ICSI.<sup>33</sup>

### Improving Female Fertility

Before we discuss the interventions researched to enhance fertility in women, it is interesting to note that far more research exists on interventions for men. This is likely due to the comparative ease of a study in men, where semen can be analyzed before and after an intervention to determine any effect on sperm parameters. For women, analysis is far more challenging, since egg retrieval is a far more invasive process. While the quantity of direct research on female fertility is relatively scant, there are some clinical gems worthy of noting. The remainder of this article will focus

on interventions for women, as that is the topic of interest for this issue.

The process of conception is very complex, and while a man's contribution is significant, the mother's role has more breadth, and therefore there are more areas that could be dysfunctional in a woman trying to conceive. It's essential to identify where a fertility problem lies, and a proper work-up followed by an accurate diagnosis is the first step to effective treatment of infertility. It is necessary to confirm that a woman is ovulating, and that intercourse is timed appropriately around ovulation. As a woman tries to have children later in life, it also has become increasingly important to confirm that her eggs are good enough quality to conceive and to develop into a healthy child. Lastly, a woman's uterine environment must be appropriate to allow for implantation. Inadequate uterine lining thickness, excess inflammation, and many other causes can contribute to an inability of the embryo to implant properly and create the tether to sustain its life.

One of the most common causes of anovulation or irregular menses is polycystic ovarian syndrome (PCOS). PCOS affects 10% of women of reproductive age and is characterized by anovulation or infrequent menses, cysts on the ovaries, blood sugar dysregulation, and hormone imbalances such as increased testosterone or an increased LH/FSH ratio. Women with PCOS may experience difficulty maintaining a healthful weight, hirsutism, and frequently, infertility. The current standard of care for women with PCOS is insulin sensitizing agents such as metformin, but metformin is not effective in inducing ovulation in many patients.<sup>34</sup>

Because the phosphoglycan that mediates insulin action contains *D-chiro*-inositol, and because this phosphoglycan is deficient in women with PCOS, it was postulated that restoration of adequate inositol levels may play an important role in restoring proper hormonal function in women with PCOS.<sup>35</sup> Studies

have demonstrated the significantly superior effect of inositol in sensitizing cells to insulin, compared with metformin, in PCOS patients as well as restoring ovulation, which is particularly important for women with PCOS trying to conceive.<sup>36</sup> Administration of both *D-chiro*- and/or *myo*-inositol, typically at a dose of 4 grams daily, has been shown to improve insulin sensitivity, improve ovulatory function, decrease serum androgens, decrease elevated blood pressure, decrease elevated plasma triglycerides, and improve oocyte quality in women with PCOS.<sup>37,38</sup> *Myo*-inositol is the preferred form to dose, as it seems to perform better than the more expensive *D-chiro*-inositol.<sup>39</sup>

In women with PCOS who are undergoing Clomid-supported cycles, coadministration of *N*-acetylcysteine at a dose of 1200 mg daily from cycle day 3 through 8 significantly improved ovulation rates from 17.9% in the control group to 52.1% in the treatment group. In addition to an increased ovulation rate, women in the treatment group also produced more mature follicles, had greater endometrial thickness, higher follicular estradiol levels, and increased luteal phase progesterone levels.<sup>40</sup> These are all signs of improved hormone balance and enhanced fertility.

A thin uterine lining can prevent proper embryo implantation. Unfortunately, a thin uterine lining is a common side effect of "fertility-promoting" medications such as Clomid, or clomiphene citrate. Clomiphene citrate acts as an estrogen blocker to decrease the negative feedback signals that estrogen provides to the hypothalamus and pituitary glands. This communication block can result in enhanced production of GnRH and FSH, which provides additional stimulation to the ovaries to enhance follicular production. One downside of this medication is that with the blocking of estrogen comes the side effects of a decrease in endometrial development and cervical mucus production, both

of which are enhanced by estrogen. For some women, clomiphene use may simply move their fertility problem from one of ovulation difficulty to implantation difficulty. Two small studies demonstrate the promise that black cohosh may have in protecting women who choose to take clomiphene citrate against these negative effects. In a 2009 study by Shahin et al., 134 women were randomized to receive black cohosh extract 120 mg daily or ethinyl estradiol from cycle day 1 through 12. The women receiving black cohosh extract needed fewer days for follicular maturation, had a thicker endometrium, and had higher estrogen levels ( $p < 0.001$ ). Also, their luteal-phase progesterone levels were higher, which can indicate an improved quality of the corpus luteum that develops in the follicular phase of a women's menstrual cycle. Clinical pregnancy rates were also significantly higher in the black cohosh group versus the ethinyl estradiol group (36.7% versus 13.6%).<sup>41,42</sup> Black cohosh appears to provide a safe and viable option for women who experience negative side effects of clomiphene citrate stimulation.

### Improving Ovarian Reserve

For women over 35, ovarian reserve can be one of the most challenging areas of fertility to overcome. Ovarian reserve describes the quantity and quality of eggs produced in response to natural or drug-stimulated follicular development. It is unknown whether poor ovarian reserve is caused by an abnormally rapid loss of a normalized follicular pool, or by a normal rate of degradation of an abnormally small follicular pool. Either way, conventional medical options are limited, and women diagnosed with a low ovarian reserve are typically recommended egg donation as their only option.

Just as oxidative stress plays a significant decrease in quality of sperm in men, it is also believed to play a major role in the reduction of egg quality in women. For

women with decreased egg quality, additional antioxidant support should be considered over and above that provided through a standard prenatal vitamin.

An Italian study published in 2010 has suggested that melatonin may be a useful antioxidant to support egg quality. 65 women undergoing IVF were randomized to receive *myo*-inositol and folate or an identical preparation of the same combination plus melatonin. The melatonin group experienced a significant increase in the number of mature oocytes and decrease in the number of immature oocytes produced after GnRH stimulation. There was no difference in total oocytes produced, but the melatonin group had a significant increase in quality and maturity.<sup>43</sup> A similar study showed positive trends in clinical pregnancy rates and implantation rates in the melatonin group, although the results were not statistically significant.<sup>44</sup> In another study by Tamura et al., 115 women with a history of failed IVF and low fertilization rate of their oocytes (<50%) in previous cycles were randomized to receive melatonin 3 mg daily at bedtime or placebo. Fertilization rate improved significantly in the melatonin group only after 8 weeks of supplementation.<sup>45,46</sup>

DHEA is commonly prescribed to women with poor ovarian reserve. In fact, it is used by over one-third of all IVF centers worldwide.<sup>47</sup> DHEA is thought to improve ovarian function and ovarian reserve by promoting preantral follicle growth and reducing follicular atresia. Several studies have looked at the effect of DHEA supplementation in women undergoing IVF with decreased ovarian reserve, and generally, supplemented women have higher pregnancy rates and lower miscarriage rates (by reducing aneuploidy), especially among women over age 35.<sup>48</sup> One such study supplemented



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women with 25 mg of DHEA three times daily. Supplementation significantly increased women's levels of anti-Müllerian hormone (AMH;  $p = 0.002$ ), a hormone produced by developing follicles that is currently considered the best indication of good egg quality and quantity. Improvement of AMH was approximately 60% ( $p < 0.0002$ ), and longer use (up to 120 days) showed the greatest improvement. In addition to improvement in tests for egg quality, treated women also experienced a significant increase in the number of fertilized oocytes ( $p < 0.001$ ), normal looking day 3 embryos ( $p = 0.001$ ), transferred embryos ( $p = 0.005$ ), and improved total embryo scores ( $p < 0.001$ ).<sup>49,50</sup> It is interesting to note that in the studies of DHEA supplementation, there are few reported side effects; however, supplementation of DHEA at 25 mg three times daily is a high dose in this author's opinion, and should be done only under the supervision of an experienced clinician.

## Conclusion

Infertility has become a widespread problem in the US. Amazingly, the rate of infertility is the same as the rate of breast cancer in the US. Although the suffering incurred with infertility is not comparable to that of breast cancer, couples experiencing infertility do incur amazingly high

stress levels, and increased rates of divorce, depression, and anxiety. Furthermore, those suffering with infertility often do so in isolation, as they feel a social stigma around not being able to easily conceive. While rates of fertility are on the rise, so are the rates of the use of technological medical approaches to overcome infertility. While procedures such as IUI and IVF are not without merit, there is little focus on correcting any underlying dysfunction, deficiency, and imbalance leading to trouble conceiving. Integrative practitioners serve an essential bridge to bring these health-promoting practices into the field of reproductive endocrinology, and should take a leadership role in bringing preconception practices to every couple wanting to have a child.

## Notes

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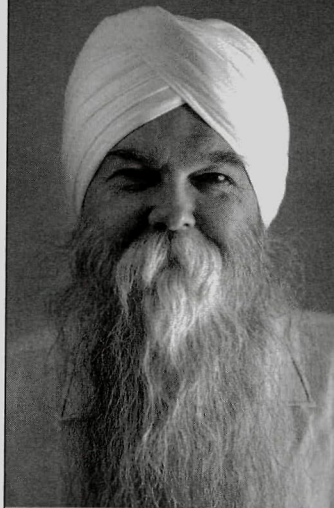


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