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## Fertility Factors

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# SOY AND FERTILITY: A LOOK AT THE EVIDENCE

By Mark Messina, PhD, MS

The fact that concerns have been raised about soy adversely impacting both male and female fertility seems inconsistent with the knowledge that China is the birthplace of the soybean,[1] foods made from soybeans have been consumed there for centuries,[1] and the current population of China is approximately 1.4 billion (https://www.worldometers.info/world-population/china-population/). Yet, in 1994, the first issue of a newsletter produced by the former Perinatal Nutrition Practice Group of the American Dietetic Association (now the Academy of Nutrition and Dietetics) included an article that recommended women wanting to become pregnant avoid consuming excessive amounts of soy.[2] Around the same time, a cartoon appeared in *Vegetarian Times* magazine entitled "Do Soyfoods Stop the Stork?"[3] In addition, there is the persistent myth that soy feminizes men, compromising sperm and semen characteristics, and hence, fertility.[4,5]

In some sense, concerns about fertility are not surprising when recognizing that isoflavones first came to the attention of the scientific community in the 1940s as a result of breeding problems experienced by female sheep in Western Australia[6,7] grazing on a type of clover rich in isoflavones.[8,9] Further, in 1987, it was determined that the addition of soy meal to the diet contributed to the inability of the captive cheetah to reproduce.[10] However, cheetahs metabolize isoflavones differently than humans,[11] and the sheep referenced above consumed quantities of isoflavones that greatly exceeded any human exposure possible via the consumption of reasonable amounts of soyfoods.[12] Nevertheless, the impact of soy on fertility has been widely discussed and debated within the scientific community.[13–15]

The estrogen-like effects of isoflavones underlie concerns about soy and fertility.[16] Although much of the concern is based on animal research,[16] a sufficient amount of fertility-relevant human research, including both epidemiologic and clinical studies, has been conducted; therefore, conclusions about the impact of soy on fertility can be based on the human evidence. This research is discussed below.

## Female Fertility

While the Perinatal Nutrition Practice Group is no longer in existence and the recommendation made at that time is not currently valid, the group's recommendation above came in response to research by Cassidy et al.,[17] who studied the impact of soy on menstrual cycle length (MCL). This work was undertaken because the authors hypothesized that isoflavone-rich soy protein might cause changes in the menstrual cycle reflective of a decreased breast cancer risk. For example, some evidence suggested that longer cycles, which typically implies a longer follicular phase (first 2 weeks of the menstrual cycle) were protective against breast cancer.[18]

In this first of its kind soy study, Cassidy et al.,[17] found that daily consumption for one month of 60g textured vegetable protein containing 45mg isoflavones increased MCL from 27.5 to 29.0 days; an increase attributable to the increase in the length of the follicular phase from 15.0 to 17.5 days. In addition, the midcycle surges of the gonadotrophins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), were markedly suppressed in response to soy. A surge in LH is required for ovulation, although there is a diversity of LH surges in terms of configuration, amplitude, and duration in cycles of normally fertile women.[19]

Cassidy et al.[17] discussed the possible favorable impact of the increased MCL on breast cancer risk, but not whether the results had implications for reproduction. The findings of a follow-up study by Cassidy et al.[20] published one year later were consistent with the initial research and also revealed

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that isoflavones were the soy components responsible for the increase in MCL. Again, no mention of soy and reproduction was made.

The "delay" in ovulation, that is, the increase in follicular phase length, and the suppressed midcycle surges of the gonadotrophins formed the basis for speculation that perhaps in some women, especially those having trouble conceiving, soy may decrease the likelihood of pregnancy. Even though, *short, but not long,* menstrual cycles have been linked to 11–36% longer time to pregnancy.[21–23]

In 2009, Hooper et al.[24] published a systematic review and meta-analysis of the effects of soy/isoflavone exposure on MCL and reproductive hormones. Based on 10 intervention studies involving 301 women, MCL was increased by 1.05 days (95% CI 0.13, 1.97). Thus, the literature still supported an increase in MCL in response to soy consumption, but it was considerably smaller than the increase reported by Cassidy et al.[17,20] Neither soy nor isoflavone consumption affected circulating total estradiol, estrone, or sex hormone binding globulin concentrations in premenopausal women. In contrast, soy isoflavones significantly reduced circulating LH (estimated decrease, ~24%; p=0.05) and FSH (estimated decrease, ~22%; p=0.01) levels based on 7 studies involving 73 participants. As was the case for MCL, the decrease in LH and FSH noted by Hooper et al.[24] was much smaller than the decrease found in the 2 studies by Cassidy et al.[17,20] Furthermore, sensitivity analysis in which only studies at low risk of bias were retained, revealed that the LH and FSH results were no longer statistically significant.[24]

Hooper et al.[24] were unable to conclude whether the "observed but tentative premenopausal changes in FSH and LH reflect an estrogenic or anti-estrogenic effect" in part because these hormones were assessed in different studies at different points in the menstrual cycle. During the midcycle gonadotrophin surge, a decrease in LH is best construed as an anti-estrogenic effect, while during the luteal phase a decrease in LH may be an estrogenic effect.

Four observational studies examining the impact of soy intake on MCL have been published: one each in Japan,[25] Singapore,[26] England,[27] and the U.S.[28] In the Japanese study, Nagata et al.[25] found that among 341 women aged 18–29 years, soy intake was unrelated to MCL, whereas polyunsaturated fat and fiber were negatively and positively related to MCL, respectively. In contrast, Jakes et al.[26] found that among Singaporean women in a hospital clinic and nursing college, higher intake of soy protein tended to be associated with a slightly longer MCL based on self-report when assessed cross-sectionally and prospectively by recording 3 consecutive cycles. However, neither finding was statistically significant.

In the British study, Verkasalo et al.[27] found that among 636 premenopausal women, mean MCL was 0.7 days shorter in the highest versus the lowest soymilk intake group (P=0.086 for trend). Due to the low soy intake among the general population of non-Asian countries, non-Asian epidemiologic studies are generally of limited utility for understanding the health effects of soy.[29] However, in this cross-sectional study, 65% of the women were vegetarians or vegans; hence, their isoflavone intake was comparable to Japanese intake.[30] Isoflavone intakes were estimated by Verkasalo et al.[27] to be 12.4 and 36.8mg/day in the intermediate and high soymilk-consuming groups, respectively.

The U.S. study, which involved 326 women aged 18–40 years with self-reported cycles 21–42 days who were followed until pregnancy or for 12 months of attempting pregnancy, showed that urinary levels of individual isoflavones were unrelated to MCL after adjustment for potential confounders.[28] The authors concluded that the results are reassuring for women attempting pregnancy. However, women in this study consumed very little soy.

Two additional observational studies provide insight into the possible impact of soy on female fertility. One is a cross-sectional study of 11,688 North American Seventh-Day Adventist women aged 30–50 years old with data regarding childbearing.[31] High intake of isoflavones was related to increased risk of nulliparity (never having completed a pregnancy) and nulligravidity (the number of pregnancies complete or incomplete). More specifically, women who had an isoflavone intake of ≥40mg/day had a 3% lower risk of being parous than women with a low intake (<10mg/day). The authors of this study called for prospective studies to either refute or confirm their findings.

The other study is a prospective cohort study involving 239 women who underwent 347 in vitro fertilization cycles.[32] It is recognized that this study does not involve questions about ovulation. Soyfood consumption modified the association of urinary bisphenol A (BPA, a possible endocrine disruptor) concentration with live birth rates (P for interaction=0.01). Among women who did not consume soy, the adjusted live birth rates per initiated cycle in increasing quartiles of cycle-specific urinary BPA concentrations were 54%, 35%, 31%, and 17% (P for trend=0.03). In contrast, the corresponding live birth rates among women reporting pretreatment consumption of soyfoods were 38%, 42%, 47%, and 49% (P for trend=0.35). A similar pattern was found for implantation and clinical pregnancy rates per initiated cycle, where urinary BPA was inversely related to these outcomes among women not consuming soyfoods but unrelated to them among soy consumers. Thus, soyfood intake appeared to negate the harmful effects of BPA.

## Male Fertility

As noted, the idea that soy feminizes men is a persistent myth.[4,5] A few animal studies published around the year 2000 raised the possibility that isoflavones could lower testosterone.[33,34] However, the primary basis for the myth is comprised of a case-report describing feminizing effects (including the presence of gynecomastia and an increase in estradiol levels) in an older man due to the consumption of soymilk,[35] and a small cross-sectional study[36] that found soy intake was inversely related to sperm concentration. This myth may not have been started if not for an article in *Men's Health* about soy published in 2009 entitled "Is This the Most Dangerous Food For Men?" A decade later, *Men's Health* acknowledged its hyperbolic reporting on this issue; but the damage had been done.[37]

In regard to the case-report,[35] often not reported is that the man in question consumed 3 quarts of soymilk daily, an amount that was estimated to provide 360mg isoflavones, approximately 9 times typical Japanese intake.[30] A second case-report was published in 2011 also describing feminizing effects, but in a younger man.[38] However, he also consumed an estimated 360mg/day isoflavones, via an estimated 12–20 servings of soy daily. Although speculative, it is almost certain that the excessive isoflavone intake in the younger[38] man and older[35] man occurred in the context of a nutrient-deficient diet given the percentage of calories derived from a single food.

The false equating of isoflavones with estrogen also has much to do with why the myth about feminization refuses to die despite the overwhelming evidence to the contrary.[5] The general concern that environmental estrogens play a role in the declining sperm count occurring among men worldwide[39-41] also creates an environment that allows the myth about male feminization to more easily survive.

In contrast to these 2 case-reports, a meta-analysis of clinical studies found no statistically significant effects of isoflavone exposure via supplements or foods on circulating levels of total testosterone, free testosterone, sex hormone binding globulin, or the free androgen index.[42] This analysis included 15 placebo-controlled treatment groups with baseline and ending measures and 32 reports involving 36 treatment groups. The average age of study participants ranged from 21–74 years; study length ranged from one week to 4 years (although one-year data were used in the analysis for a 4-year study[43]) and daily isoflavone and soy protein intake from 20–900mg and from 0–71g, respectively. In addition to this meta-analysis, a comprehensive narrative review published in the same year concluded that neither soy nor isoflavones raised estrogen levels in men or exerted any feminizing effects.[44] (The above-referenced meta-analysis, which will include estrogen as an outcome measure, is currently being updated.)

Regarding the cross-sectional study, about half of the decreased sperm concentration resulted from the higher ejaculate volume in the fourth (4.1ml) soyfood intake quartile compared to the first (3.5ml) quartile.[36] The higher ejaculate volume associated with soy intake seems biologically implausible. In contrast to sperm concentration, total sperm count was only reduced by ~10% when comparing extremes of soy intake, a decrease which was not statistically significant; nor was there an effect of soyfood intake on sperm motility or morphology.[36] Furthermore, a follow-up study involving 184 men from couples undergoing infertility treatment with in vitro fertilization, found that male partner's intake of soyfoods and soy isoflavones was unrelated to fertilization rates, proportions of poor quality embryos, accelerated or slow embryo cleavage rate, implantation, clinical pregnancy, and live birth.[45]

Three clinical studies, 2 published in full manuscript form and one described in the proceedings from a scientific meeting, have evaluated the impact of soy on sperm and semen parameters.[46-48] None of the studies reported any adverse effects. In one study, healthy volunteers took a placebo or a daily supplement containing 40mg isoflavones for 2 months.[46] In the other study, which utilized a cross-over design, 32 healthy young men consumed diets in random order for 57 days which were supplemented with milk protein isolate or isolated soy protein that provided either 0.02 or 0.75mg/kg body weight per day.[47] In the third study, 20 volunteers were randomized to 3 different groups in which they were provided 60, 320, or 480mg/day isoflavones for 3 months.[48]

Finally, a case report described a benefit from isoflavone supplementation in a male with low sperm concentration who was unable to father a child.[49] Daily isoflavone supplementation for 6 months led to normalization of sperm quality and quantity and to the birth of a healthy infant. As a result, the authors of this report suggested that isoflavones may be a treatment for low sperm concentration.

## Conclusions

Although the large populations of soyfood-consuming countries might argue against any adverse effects of soy intake on fertility, this relationship should be evaluated based on findings from high-quality studies. In premenopausal women, research indicates that soy intake may slightly increase the length of the menstrual cycle (~one day) and slightly decrease LH and FSH levels (~20%),[24] but there is no evidence from clinical studies that soy prevents ovulation. In men, clinical research indicates that neither soy nor isoflavones, even in amounts greatly exceeding typical Japanese intake, lower testosterone levels,[42] raise estrogen levels,[44] or adversely affect sperm or semen parameters.[46-48]

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# WHAT TO EAT WHEN TRYING TO CONCEIVE

By Elizabeth Ward, MS, RD

A growing body of evidence suggests what women eat influences conception and pregnancy outcomes. While women become pregnant on a variety of diets, nutrient-rich, plant-based eating patterns are associated with a greater likelihood for conception. In the Nurses' Health Study II, women who ate more of certain foods and supplements experienced a lower rate of ovulatory disorder infertility, one of the leading causes of infertility in women. Regardless of weight, age, and parity, consuming more of these items seemed beneficial: vegetable protein sources, monounsaturated fats rather than trans fats, low glycemic carbohydrates, full-fat dairy foods, multivitamins, iron from plant foods, and from dietary supplements that contain iron.[1]

It is possible that in addition to providing nutrients necessary for well-being, plant-based diets with adequate calories help promote a healthier weight. Obesity (body mass index of 30.0 and above) has been associated with reduced female fertility, and time to conception appears to increase with increasing body weight.[2] Maternal obesity also increases the risk for gestational hypertension and diabetes, cesarean delivery, and heart and neural tube defects (NTDs).[3]

## Must-Have Preconception Nutrients

### *Folate/folic acid*

Adequate folate helps reduce the risk for NTDs during the first month of pregnancy, often when a woman does not realize she is pregnant. Women of childbearing age are advised to consume 400mcg daily of folic acid from dietary supplements and/or enriched grains, and to include folate-rich foods, such as edamame and spinach.[4]

### *Iron*

About 10% of non-pregnant women ages 15–49 years living in the U.S. have iron deficiency.[5] Lower iron stores at conception are associated with increased risk for iron-deficiency anemia in pregnancy, which increases chances for preterm delivery and low-birthweight infants. Women should regularly consume sources of iron, such as meat, tofu, and fortified grains, and take an iron supplement if necessary, to get the suggested 18mg/day prior to pregnancy.[6]

A daily multivitamin/multimineral supplement with 100% of the Daily Value for folic acid, iron, and other nutrients help to bridge nutrient gaps. A statistical analysis of 41 studies suggests a link between multivitamin use and reduced risk of NTD, heart and limb defects, and cleft palate.[7] Research also suggests multivitamin use may decrease risk for preterm delivery.[8]

## What to Limit and Avoid Prior to Pregnancy

### *Caffeine*

Observational studies have linked caffeine, found in beverages and certain food and medications, with miscarriage. Currently there is insufficient evidence from randomized controlled trials to recommend completely avoiding caffeine before, and during, pregnancy. Women trying to conceive should limit caffeine consumption to 200mg per day, about the amount in 12oz of coffee and four 12-oz servings of sugary or diet soda, such as cola and soft drinks with added caffeine.[9]

### *Alcohol*

Experts suggest abstaining from alcohol when trying to conceive as women may become pregnant and not know they are expecting for up to 6 weeks. Alcohol can cause irreversible damage to the central nervous system and may result in miscarriage.[10]

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