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Adult Ovarian Function Can Be Affected by High Levels of Soy[1,2]

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Abstract

Ovarian function in adults is controlled by hormones circulating in the body. The primary hormone responsible for cyclicity in animals and humans is estrogen. Estrogen is mostly produced in the ovary and enters the circulation where it then signals the brain for a response. The parts of the brain that controls reproductive hormones are the hypothalamus and anterior pituitary. Estrogen stimulates the hypothalamus to produce gonadotropin releasing hormone, which in turn signals the anterior pituitary to produce follicle stimulating hormone and luteinizing hormone. These hormones enter the circulation and signal the ovary to ovulate. Substances with estrogenic activity can potentially interfere with this signaling if levels of activity are sufficient to cause a response. Soy foods contain estrogenic substances called phytoestrogens. The predominant phytoestrogens found in soy are genistein and daidzein. The female reproductive system is dependent on hormones for proper function and phytoestrogens at very high levels can interfere with this process. This paper summarizes the literature on adult soy consumption and its effect on ovarian function. J. Nutr. 140: 2322S–2325S, 2010.

Ovarian function

Ovarian function in adult mammals is quite complex and requires not only the ovary but the hypothalamus and pituitary as well [for review, see (1–3)]. The simplified description is as follows. The primary control of ovarian function is the cyclic release of follicle stimulating hormone (FSH)[3] and luteinizing hormone (LH) by the anterior pituitary. Estrogen produced by the ovary stimulates the hypothalamus to release gonadotropin releasing hormone, which in turn stimulates the anterior pituitary to release FSH and LH. The cyclic nature of this hormonal regulation is what results in ovulation. Estrogen provides both a negative feedback loop and a positive feedback loop to the hypothalamus depending on the level of estrogen. Estrogen is produced by the granulosa cells of growing follicles in the ovary. Low levels of estrogen during a time when there are fewer growing follicles signals the hypothalamus/pituitary to release FSH, which stimulates the follicles to grow. These growing follicles produce higher levels of estrogen, which signals the hypothalamus/pituitary to release LH in a surge that stimulates the large follicles with fully mature oocytes to ovulate. Following ovulation, the granulosa cells then luteinize and begin to produce progesterone necessary for supporting pregnancy if pregnancy occurs. If pregnancy does not occur, then the cycle resets and starts all over again.

One can imagine that interference with estrogen signaling would alter ovulation. This is in fact how estrogens in birth control pills work. A steady level of estrogen suppresses the LH surge by providing a constant negative feedback to the hypothalamus/pituitary and not allowing the cyclic release of LH. The lack of an LH surge is what prevents ovulation and therefore prevents pregnancy. The estrogens that we are exposed to exogenously could play a role in diminishing fertility if the levels of estrogenic activity are high enough to interfere with this process.

Phytoestrogen levels found in soy

Soy products are composed of many substances, including phytoestrogens. Phytoestrogens are chemicals that occur naturally in plants and exhibit estrogenic activity. The ones found in

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[3] Abbreviations used: ER, estrogen receptor; FSH, follicle stimulating hormone; HRT, hormone replacement therapy; LH, luteinizing hormone; SHBG, serum hormone binding globulin.

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soy products are predominantly genistein and daidzein (4,5). There are varying levels of phytoestrogens in different food products and this information is readily available in tables presented in this special supplemental issue as well as in the USDA database on the isoflavone content on selected foods (6). The levels of phytoestrogens in foods have also been reported previously in several studies (5,7–9).

Generally, foods containing soy have the highest levels of genistein and daidzein and have a wide range in content. For example, cereals containing soy have ~10–40 mg daidzein and genistein/100 g. Meatless foods also contain higher levels of phytoestrogens, such as meatless bacon bits with 64 mg of daidzein and 46 mg of genistein/100 g. More traditional Asian foods like miso contain 16 mg daidzein and 23 mg genistein/100 g. Soy milk has 28 mg daidzein and 43 mg genistein/100 g. Most processed soy products contain soy protein and the amount of soy protein recommended by the FDA in 1999 as part of a health claim was 25 g/d, which contains ~75 mg of isoflavones (mostly genistein and daidzein). The levels of phytoestrogens found in a traditional Asian diet are much lower than this. Several studies conducted about a decade ago showed that Japanese intakes are ~10–25 mg isoflavones/d (predominantly genistein and daidzein) (10–12).

Estrogen action of phytoestrogens and target tissues

Estrogens exert their activity through nuclear receptors found in target tissues [for review, see (13)]. There are 2 subtypes of the estrogen receptor (ER) found in mammals: ERα and ERβs (14). Phytoestrogens bind to both ERα and ERβ but have a higher affinity for ERβ (15). Phytoestrogens also exhibit estrogenic activity in both in vitro and in vivo assays (16,17). Tissues of the mammalian reproductive system have both ERα and ERβ and are targets of chemicals with estrogenic activity. These tissues include but are not limited to the hypothalamus, pituitary, mammary gland, ovary, female reproductive tract, testis, and male reproductive tract (14). Phytoestrogens elicit gene expression changes in reproductive tissues, confirming that they are biologically active in a living system. The doses at which these effects occur are quite variable, are tissue dependent, and are most likely due to the interaction of either ERα or ERβ within a given tissue. For example, the ovary expresses the highest level of ERβ in the body and genistein and daidzein preferentially bind to ERβ, so one might anticipate that phytoestrogens in general may have greater effects on the ovary itself. More research will have to be done to demonstrate this possibility.

There have been a few studies examining the estrogenic activity of soy isoflavones in humans. One small study (23 women) published 20 y ago showed estrogenization of the vaginal epithelium in postmenopausal women supplemented with soy flour (45 g/d) or red clover sprouts (10 g/d dry seed) for 2 wk each. The increased maturation index increased during the intervention and then regressed to normal levels 2 wk postintervention (18). Another larger study was a randomized double-blind trial of 187 postmenopausal women who consumed either a soy-rich diet, e.g. soymilk, miso soup, tofu, tempeh, or soybeans containing 20–30 mg isoflavones/d for 6 mo (19). Urinary phytoestrogen levels were measured throughout the intervention to attain knowledge of compliance. This group also included a hormone replacement therapy (HRT) positive control group where estrogenic activity should have been readily achieved. They measured vaginal cell maturation by a karyopycnotic index and a maturation value at the start of the intervention and 6 mo later. They found a significant increase in vaginal epithelial cell maturation by both indices in the HRT group and the soy group compared with controls, with the HRT group exhibiting the greatest increase, suggesting a dose response. These data clearly demonstrate that a soy-rich diet can exert enough estrogenic activity to have a biological effect in women.

Potential interference of phytoestrogens on ovarian function

Phytoestrogens have estrogenic activity, but at what dose would they potentially cause a disruptive effect on the reproductive system? Because all of the reproductive tissues have ERα and ERβ, they could potentially be acted upon by phytoestrogens. The hypothalamus and pituitary respond to estrogen by producing gonadotropins, FSH, and LH, which control ovulation. Increased estrogen signaling in these tissues would most likely result in the negative feedback action of estrogen and reduce ovulation. Estrogen signaling in the ovary is important for controlling gene expression necessary for follicle growth and the expression of FSH receptors and LH receptors that respond to gonadotropin signaling from the hypothalamus and pituitary. Very high levels of estrogen are produced in the ovary and it is not clear if excess estrogen would disrupt processes in this tissue. The uterus is very responsive to estrogen signaling and the rise and fall of estrogen is very critical to embryo implantation and pregnancy. Excess estrogen stimulation of the uterus in a continuous manner can inhibit implantation. It is therefore conceivable that interference or excess in any of this signaling can lead to subfertility or infertility.

Effects of soy and/or phytoestrogens on ovarian function

Animal studies. There are 2 clear examples in nature that confirm the possibility that naturally occurring phytoestrogens found in a natural diet cause reduced fertility. The first is an observation made in the 1940s where ewes grazing on clover-rich fields in Australia suffered from high rates of infertility, spontaneous abortion, and reproductive abnormalities (20). It was later determined that there were high levels of phytoestrogens in the clover (21–23). A second example is in cheetahs in a zoological population. These animals were being fed a soy-based diet and suffered from infertility. It was determined that there were high levels of phytoestrogens in this diet and replacement with a non-soy–based diet returned their fertility (24). These studies demonstrate that in high enough levels, phytoestrogens can override the natural cyclicity of animals, most likely due to anovulation. This mode of action is similar to birth control pills and their ability to apply constant negative feedback to the hypothalamus, subsequently suppressing ovulation.

Another example in laboratory rodents is a study that was published about a decade ago. This study showed that a particular lot of laboratory rodent unpuriefied diet containing soy had higher levels of genistein and daidzein than typical batches and this resulted in estrogenic stimulation of the uterus of ovariectomized rats (25). This again demonstrates that a diet can have levels of phytoestrogens high enough to produce an estrogenic response.

Human studies. There have been several recent symposiums and studies that examined the effect of consuming soy-rich foods on circulating levels of hormones in adult women. A symposium on soy and prevention of disease reviewed 7 studies with intakes of 32–200 mg of isoflavones/d (9). The summary from this symposium showed a decrease in midcycle gonadotropins, trends for increased cycle length, and lower estradiol, progesterone, and serum hormone binding globulin (SHBG) following soy intake.

There are apparently some differences between effects observed in premenopausal women compared with postmenopausal women. A large review of 47 studies (11 pre-, 35 post-, and 1 perimenopausal women) showed no differences in postmenopausal women, whereas studies involving premenopausal women showed no effect on estradiol, estrone, or SHBG but did show decreased FSH and LH along with increased cycle length (26). One study showed no effect on LH, FSH, estradiol or SHBG in 191 postmenopausal women exposed to a dietary intervention of soy foods that totaled 165 mg total isoflavones/d for 4 wk (27). A 2-y randomized study in 220 premenopausal women showed that 2 servings/d of soy (50 mg isoflavones) caused no difference in serum hormone levels (28). Another study conducted in premenopausal women showed decreases in LH and FSH following 64 or 128 mg/d isoflavones over 3 menstrual cycles (29).

Another very interesting study found suppressed luteal estrogen levels following increased soy intake of 32 mg isoflavones/d for 7 mo, but only in women of Asian descent (30), indicating that ethnicity could be an underappreciated factor when considering the potential human health effects of soy isoflavones. The finding in this study could also be explained by higher soy intake in the Asian women and that the intervention was in addition to a diet that already contained some soy. Overall, these data suggest that lower levels of soy isoflavones, such as those found in a typical Asian diet, would most likely have little or no effect on hormone levels in adult women that would affect fertility. However, exposure to much higher levels of soy may lead to reductions in hormone levels, particularly the gonadotropins, LH, and FSH, and also particularly in premenopausal women or women in their reproductive years.

In addition to these larger studies, physicians at SUNY Downstate Medical Center submitted a 2008 clinical case report when 3 women (aged 35–56 y) were treated for a similar suite of symptoms, including abnormal uterine bleeding, endometrial pathology, and dysmenorrhea. In all 3 cases, symptoms improved after soy was withdrawn from their diet, suggesting that high intake of soy isoflavones can compromise female reproductive health (31). The youngest of the women had consumed a soy-rich diet since age 14 y and was experiencing secondary infertility, a condition that resolved and resulted in a pregnancy once she reduced her soy consumption. Isoflavone intake was not quantified but was estimated to exceed 40 g/d (>100 mg isoflavones) in the oldest of the 3 patients.

Summary

Ovarian function and female reproduction rely heavily on the action of estrogen on its target tissues in the body. Adult women during their reproductive years have tightly regulated cyclic levels of estrogen with negative and positive feedback on the hypothalamus and anterior pituitary. Alterations in either the cyclic nature of these hormones or the levels produced can affect ovarian function and therefore fertility. Because soy products contain estrogenic substances, studies have been conducted to assess the levels of phytoestrogens in these foods and whether these levels are adequate to interfere with reproduction. Foods containing soy vary widely in their content and the levels of phytoestrogens are wide ranging (6). The levels of phytoestrogens that we consume may be more important than the amount of soy itself when thinking about reproduction, because estrogens play such a great role. There is some caution indicated from several of the studies reviewed in this manuscript. These data suggest that consuming soy protein in excess (>100 mg soy isoflavones/d) can lead to reduced ovarian function as determined by lower circulating levels of hormones, with the most prevalent finding being lowered gonadotropin levels. This is particularly true in premenopausal women during their reproductive years when these decreases could have the greatest effect.

For the most part, the studies conducted to date suggest that a diet containing lower levels of soy, e.g. 1–2 servings of soy/d, as part of a well-balanced diet should not pose harmful effects on the function of the ovary as it relates to ovulation. These levels are similar to that found in a traditional Asian diet (10–25 mg/d isoflavones) and even up to 50 mg/d isoflavones has little impact on serum circulating levels of hormones involved in reproduction. Although the levels of phytoestrogens typically found in soy foods pose minimal risk in the adult female, the female reproductive system is dependent on hormones for proper function and phytoestrogens at very high levels can interfere with this process.

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