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Exposure to isoflavones in diet is not good for reproductive health of premenopausal women ---- A short review.

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Abstract

Isoflavones, plant secondary metabolite, abundant in Soy (*Glycine max*) are genistein, daidzein and glycitein. They bind to and activate intracellular estrogen receptors: ERα and ERβ mimicking the effects of estrogen. Estrogen-like effects have raised concern regarding soy/isoflavones consumption particularly in the case of postmenopausal women at high risk of breast cancer. It causes an increase in estrogen which stimulates the uterus in a continuous manner and inhibits implantation which can lead to sub fertility or infertility. Increased estrogen signaling in ovary would most likely result in the negative feedback action of estrogen which reduces ovulation. It has been found that soy intake in human causes a decrease in midcycle gonadotropins, increased cycle length, abnormal uterine bleeding, endometrial pathology, dysmenorrheal, lower estradiol and progesterone and serum hormone binding globulin (SHBG). The review dealt with the effect of isoflavones on female reproductive system particularly.

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1. Introduction

The isoflavones phytoestrogens- glycitein, genistein and daidzein are abundant in soy [1]. Over the past few years, there has been increasing interest in determining the hormonal effects of soy. Consumption of soy has been suggested to exert potentially cancer-preventive effects in premenopausal women [2].

Clinical and experimental studies showed that the impact of soy or soy phytoestrogens consumption on human health have produced mixed and often conflicting results. However, the greater concern is that emerging evidence suggests that exposure to these compounds may pose a risk to some groups. So are they helpful or harmful? The answer is undoubtedly complex and it ultimately showed that its effect depends on age, health status, level of consumption, and even the composition of an individual's intestinal micro flora [3].

In foods, phytoestrogens are present as mixtures, of which the isoflavones may only constitute a small part. Isoflavones are naturally found as biologically inactive glycoside conjugates containing glucose or carbohydrate moieties and gets unconjugate to form the bioactive molecule. The proportion of conjugated to unconjugate forms varies substantially among foods, but fermented soy foods, such as miso or tempeh, often contain higher levels of the unconjugate than other soy-based foods. Once consumed, they are rapidly metabolized and absorbed, entering systemic circulation predominantly as conjugates with limited bioavailability. Conjugated isoflavones transported through the enterohepatic circulation returned to the intestine for further deconjugation by intestinal microbes. Genistein and daidzein can be derived from their glucosides or from biochanin A and formononetin respectively, by the action of intestinal glucosidases [4].

Cereals containing soy have approximately 10–40 mg of daidzein and genistein per 100 gm. Meatless foods also contain higher levels of phytoestrogens, such as meatless bacon bits contain 64 mg of daidzein and 46 mg of genistein per 100 g. More traditional Asian foods like miso contain 16 mg daidzein and 23 mg genistein per 100 g. Soy milk has 28 mg daidzein and 43 mg genistein per 100 gm. However as

recommended by the FDA in 1999 one should consume 25 gm per day the processed soy products which contains approximately 75 mg of isoflavones (mostly genistein and daidzein) [5].
Genistein, inhibit pathways important for cell growth and proliferation and affects multiple organ systems. Genistein inhibits the activity of protein tyrosine kinases (PTKs) in numerous tissues including breast cancer cells. PTKs catalyze phosphorylation of their own tyrosine residues and those of other proteins, including growth factors involved in tumor cell proliferation. By inhibiting PTKs, it can potentially reduce the rate of tumor genesis. Phytoestrogens can also manipulate steroid biosynthesis and transport by stimulating hormone-binding globulin (SHBG) synthesis in liver cells and competitively displace either 17β-estradiol or testosterone from plasma SHBG [6].
However the amount of soy consumption affects reproduction because isoflavones in soy regulates amount of estrogens which play a great role in reproduction. There are several studies reviewed in this manuscript to correlate isoflavones and its effect on reproductive status of pre menopausal women.

2. Research Method (12pt)

The literature search was performed using the Pubmed databases on articles published till December 2014. All the well-designed original studies published in English that covered the effect of isoflavones in soy on different physiology. The literature was also enhanced by articles obtained as cross references from the bibliography of the selected articles. There have been lots of articles published on the effects of isoflavones on reproductive system or a cellular pathway. The aim of this article is to review and highlight the effects of isoflavones on reproductive status of pre menopausal women in a concise form.

3. Results and Analysis (12pt)

3.1. Effects on ovary and uterus

Increased estrogen due to intake of genistein causes a rise in signaling in ovarian tissues which most likely result in the negative feedback action reduces 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 [7]. The underlying mechanism may be perhaps due to isoflavones eliciting changes in gene expression 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. The ovary expresses the highest level of ERβ by up regulation of VEGF [8] and isoflavones preferentially bind to ERβ, so one might anticipate that isoflavones in general may have greater effects on the ovary itself [9]. However there have been reports showing an increase in number of atretic follicular count, a decreased number of corpus luteum and down-regulation of estrogen receptors-α in the uterine tissues of the Genistein-treated animals compared to the control animals [10].
Excess estrogen on other hand stimulates the uterus in a continuous manner which can inhibit implantation. It is therefore suggested that excess of signaling on uterus can lead to sub fertility or infertility. Physicians at SUNY Downstate Medical Center submitted a 2008 clinical case report when 3 pre menopausal women were treated with 40 mg per day of isoflavones showed abnormal uterine bleeding, endometrial pathology, and dysmenorrheal conditions [11]. Prolonged use of soy tablets containing isoflavones may increase the risk of endometrial hyperplasia, the thickening of the uterus lining. Endometrial hyperplasia is linked with endometrial and uterine cancer [12].
The epidemiological study reported that soy products intake is inversely associated with diseases leading to hysterectomy. Genistein is a soy-derived phytoestrogens and its inhibitory effect on leiomyoma cell proliferation is reported. The significant inhibitory effect of genistein on estradiol induced leiomyoma cells proliferation. These experimental findings in vitro show that the repressive effect of genistein on estrogen induced ELT-3 cell proliferation is through the activation of PPAR gamma. Therefore genistein may be used as an alternative therapy for leiomyoma [13].

3.2. Effect on levels of circulating LH, FSH, Estrogen and SHBG in blood

50 gm of textured soy protein containing 60 mg of total isoflavones consumed daily for 10-14 days caused fall in LH and FSH concentration and rise in sex hormone levels in premenopausal women which caused an increase in menstrual cycle length [14]. It has been reported that isoflavones have been shown to increase the synthesis and secretion of SHBG by human HepG2 hepatoblastoma cells [15] which may be a cause behind longer duration of menstrual cycle. It has been also reported that menstrual cycle length increased by 3.52 days in pre menopausal women treated with isoflavones for 4 weeks due to prolonged activity of corpus luteum [16].

3.3. Effect on gestation and post natal health

It has been reported that isoflavones genistein does not have significant impact on maternal reproductive health while high dose brings about masculinisation in pups of rats affecting post natal development by

inhibition of aromatase [17]. High concentration of daizedin cause significant increase in amniotic fluid concentration in pregnant woman [18].

4. Conclusion (12pt)

Collectively, the isoflavones possess a lot of adverse effects on ovary and uterus and also shows some potential side-effects on female reproductive physiology like menstrual cycle, implantation and gestational development of foetus. Beside adverse effects it has been found that it has some therapeutic action in treating breast cancer and leiomyoma. In the future, more investigations are needed to reduce consumption of soy by pre menopausal women.

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