Soy food intake and treatment outcomes of women undergoing assisted reproductive technology

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Objective: To study the relation of dietary phytoestrogens intake and clinical outcomes of women undergoing infertility treatment with the use of assisted reproductive technology (ART).
Design: Prospective cohort study.
Setting: Fertility center.
Patient(s): A total of 315 women who collectively underwent 520 ART cycles from 2007 to 2013.
Intervention(s): None.
Main Outcome Measure(s): Implantation, clinical pregnancy, and live birth rates per initiated cycle.
Result(s): Soy isoflavones intake was positively related to live birth rates in ART. Compared with women who did not consume soy isoflavones, the multivariable-adjusted odds ratios of live birth (95% confidence interval) for women in increasing categories of soy isoflavones intake were 1.32 (0.76–2.27) for women consuming 0.54–2.63 mg/d, 1.87 (1.12–3.14) for women consuming 2.64–7.55 mg/d, and 1.77 (1.03–3.03) for women consuming 7.56–27.89 mg/d.
Conclusion(s): Dietary soy intake was positively related to the probability of having a live birth during infertility treatment with ART. (Fertil Steril® 2015;103:749–55. ©2015 by American Society for Reproductive Medicine.)
Key Words: Cohort studies, isoflavones, phytoestrogens, soy foods, assisted reproductive techniques

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Phytoestrogens are a group of pharmacologically active nonsteroidal polyphenols found in a variety of plants and dietary products, including soy and soy-based foods and supplements (1). Phytoestrogens are peripheral partial agonists of estradiol receptors with varying affinity for each receptor subtype but generally exerting weak estrogenic activity (2–5). These compounds first gained prominence in the reproductive literature in the late 1940s, when remarkable breeding problems in sheep, subsequently known as Clover disease, were linked to feeding on newly introduced clover pastures rich in phytoestrogens (6–8). Ever since, potentially deleterious effects of phytoestrogens on reproduction have been described in other mammalian species (9–11).

Whether phytoestrogen intake results in clinically relevant reproductive impairment in humans is less clear. Most of the human literature concentrates on isoflavones, a class of phytoestrogens primarily found in soy. In men, soy supplementation leads to small changes in the hormonal milieu (12, 13). In addition, inverse

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associations of dietary (14) and urinary levels (15) of isoflavones with sperm concentration have previously been reported. However, this apparently deleterious effect on semen quality has not been observed in other studies (16). On the other hand, isoflavones appear to have beneficial reproductive effects among women. Two clinical trials among women undergoing infertility treatment found that supplementation with isoflavones during treatment cycles resulted in significantly higher pregnancy and live birth rates (17, 18). However, the isoflavone content of the supplements used in those trials was >100 times higher than typical intakes in Western populations (19) and >10 times higher than those among Asians (20). A study by Mumford et al. found significant shortening of time to pregnancy with higher urinary lignan concentrations among female partners of couples attempting to conceive, but no significant association for isoflavones (21). Therefore, it remains unclear whether similar benefits to those observed in high-dose supplementation trials could also be expected among women exposed to isoflavones through diet alone. To address this question, we evaluated the association between pretreatment dietary intake of soy-based foods and infertility treatment outcomes among women presenting to the Massachusetts General Hospital Fertility Center.

MATERIALS AND METHODS

Study Population

Participants were women enrolled in the EARTH study, an ongoing prospective cohort study started in 2006 aimed at identifying determinants of fertility among couples presenting to the Massachusetts General Hospital Fertility Center (Boston). All women who meet age eligibility requirements (18–46 years) were approached by study personnel to participate in the EARTH study. Approximately 60% of those contacted by the research nurses participated in the study. Out of the 461 women enrolled during the study period, 398 had data on soy food intake, of whom 315 had fully completed at least one assisted reproductive technology (ART) cycle through June 2013 (520 cycles in total), including cancelled cycles, representing the study population for this analysis. There were no differences in baseline demographic and reproductive characteristics between the women who completed this questionnaire and women who did not. The study was approved by the Human Subject Committees of the Harvard School of Public Health and the Massachusetts General Hospital; written informed consent was obtained from every participant.

Baseline Characteristics and Dietary Assessment

At enrollment, height and weight were measured by a trained research nurse to calculate body mass index (BMI; kg/m^2), and a brief nurse-administered questionnaire was used to collect data on demographics, medical history, and lifestyle. Participants also completed a detailed take-home questionnaire with additional questions on lifestyle factors, reproductive health, and medical history. This questionnaire included a short food questionnaire containing 15 soy-based food questions. Women were asked to report how often, on average, they consumed each of these 15 foods during the preceding 3 months and to describe the usual serving size for each food in relation to a specified "medium" serving size (4 oz.). There were nine possible frequencies of intake, ranging from never or less than once per month to twice or more per day, and three possible usual serving sizes: medium (the specified serving size), small (less than the specified), and large (more than the specified). The isoflavone content of each food and specified portion size was obtained from a database developed by the United States Department of Agriculture (22). Total isoflavone intake was estimated by summing the isoflavone content of each food in the questionnaire weighted by each individual's intake. We also included a more detailed dietary assessment added in 2007 using a previously validated food frequency questionnaire (23) which asked participants to report how often, on average, they consumed specified amounts of 131 food items during the previous year to obtain intakes of nutrients previously related to treatment outcome in this cohort (24) and dietary pattern scores (25).

Clinical Management and Assessment of Outcomes

Women underwent a cycle of oral contraceptives pretreatment for 2–5 weeks to suppress ovulation before their ART cycles, unless contraindicated. On day 3 of induced menses, patients began controlled ovarian stimulation. Patients underwent one of three stimulation protocols as clinically indicated: 1) luteal-phase GnRH agonist protocol with the use of low-, regular-, or high-dose leuprolide with pituitary desensitization beginning in the luteal phase; 2) follicular-phase GnRH-agonist/flare protocol, in which leuprolide started on day 2 of the follicular phase at 20 units and decreased to 5 units on day 5; or 3) GnRH-antagonist protocol in which GnRH-antagonist began when the lead follicle reached 14 mm in size and/or estradiol levels were $\geq$1,000 pg/mL. Patients were monitored during gonadotropin stimulation for serum estradiol, follicle size measurements and counts, and endometrial thickness through 2 days before egg retrieval. hCG was administered ~36 hours before the scheduled egg retrieval procedure to induce ovulation. Details of egg retrieval have been previously described (26).

Couples underwent ART with the use of conventional in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) as clinically indicated. Embryologists classified oocytes as germinal vesicle, metaphase I, metaphase II (MII), or degenerated. Embryologists determined fertilization rate 17–20 hours after insemination as the number of oocytes with two pronuclei divided by the number of MII oocytes inseminated or injected. The resulting embryos were monitored for cell number and morphologic quality (1 for best to 5 for worst) on days 2 and 3. We defined successful implantation as a serum β-hCG level >6 mIU/mL typically measured 17 days (range 15–20 days) after egg retrieval, clinical pregnancy as the presence of an intrauterine pregnancy confirmed by ultrasound, and live birth as the birth of a neonate at or after 24 weeks' gestation. All clinical information was abstracted from electronic medical records.