Published in final edited form as:

Fertil Steril. 2015 March ; 103(3): 749–755.e2. doi:10.1016/j.fertnstert.2014.12.104.

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

Jose C. Vanegas, M.D.^a, Myriam C. Afeiche, PhD^f, Audrey J. Gaskins, ScD^{b,c}, Lidia Mínguez-Alarcón, PhD^f, Paige L. Williams, PhD^d, Diane L. Wright, DL PhD^e, Thomas L. Toth, M.D.^e, Russ Hauser, M.D., ScD^{c,e,f}, and Jorge E. Chavarro, M.D., ScD^{b,c,g,*}

^aSchool of Medicine, Pontificia Universidad Javeriana (Bogota DC), Colombia

^bDepartment of Nutrition, Harvard School of Public Health, Boston, MA

^cDepartment of Epidemiology, Harvard School of Public Health, Boston

^dDepartment of Biostatistics, Harvard School of Public Health, Boston

^eVincent Obstetrics and Gynecology, Massachusetts General Hospital and Harvard Medical School, Boston

^fDepartment of Environmental Health, Harvard School of Public Health, Boston

^gChanning Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston

Abstract

Objective—To study the relation of dietary phytoestrogens intake and clinical outcomes of women undergoing infertility treatment with assisted reproductive technology (ART).

Design—Prospective cohort study.

Setting—Fertility center in an academic hospital.

Participants—315 women who collectively underwent 520 ART cycles between 2007 and 2013.

Interventions—None

Outcomes—Primary outcomes were implantation, clinical pregnancy and live birth rates per initiated cycle.

Results—Soy isoflavones intake was positively related to live birth rates in ART. Compared to 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 isoflavone intake were 1.32

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*Correspondence: Jorge E. Chavarro M.D., ScD. Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115, jchavarr@hsph.harvard.edu.

Present address: Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115.

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(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.

Conclusions—Dietary soy intake was positively related to the probability of having a live birth during infertility treatment with ART.

Keywords

Cohort studies; Isoflavones; Phytoestrogens; Soy foods; Reproductive Techniques; Assisted

Introduction

Phytoestrogens are a group of pharmacologically active non-steroidal 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 (ER) with, varying affinity for each receptor subtype but generally exert weak estrogenic activity (2–5). These compounds first gained prominence in the reproductive literature in the late 1940's, 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 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 previous 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 these trials was more than 100 times higher than typical intakes in Western populations (19) and more than 10 times higher than those among Asians (20). A previous study by Mumford and collaborators 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 pre-treatment 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, MA). All women who meet age eligibility requirements (18–46 years) are approached by study personnel to participate in the EARTH study. Approximately 60% of those contacted by the research nurses participated in the study. From 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 all participants.

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 foods 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 9 possible frequencies of intake ranging from never or less than once per month to twice or more per day, and 3 possible usual serving sizes: medium (the specified serving size), small (less than specified) and large (more than 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 isoflavones 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 patterns scores (25).

Clinical management and assessment of outcomes

Women underwent a cycle of oral contraceptives pretreatment for 2–5 weeks to suppress ovulation prior to their ART cycle, 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 using 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 = 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. Human chorionic gonadotropin (hCG) was administered approximately 36 hr before the scheduled egg-retrieval procedure to induce ovulation. Details of egg retrieval have been previously described (26).

Couples underwent ART with 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 morphological quality (1 for best and up 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 on or after 24 weeks gestation. All clinical information was abstracted from electronic medical records.

Statistical analysis

Women were divided into four categories of soy and isoflavones intake: those who did not eat soy foods served as reference and the remaining women were divided into tertiles of intake. Descriptive statistics were calculated for demographic, dietary and reproductive characteristics according to categories of soy food intake. We used multivariable generalized linear mixed models with random intercepts to account for multiple IVF cycles per woman to evaluate the association of soy food intake with ART outcomes. Poisson distribution and log link function were specified for oocyte counts and binomial distribution and logit link function were specified for fertilization, embryo quality, and clinical outcomes. Tests for trend were conducted across categories using a variable with the median dietary soy intake in each category as a continuous variable in the regression models. Outcomes of women reporting any intake of soy foods or isoflavones were also compared to those of women reporting no intake in these models. Confounding was evaluated through directed acyclic graphs based on prior knowledge and descriptive statistics in the study population. In this evaluation we identified an association between soy intake and initial treatment protocol that was interpreted as a proxy for an unmeasured confounder. Hence, we decided to include treatment protocol and infertility diagnosis (the main determinant of treatment protocol) as covariates in our models. The final multivariable models included terms for age, BMI, infertility diagnosis, treatment protocol and race. To assess the possibility of residual confounding by dietary factors previously related to treatment outcomes in this population (folic acid and B12) (24), by overall food choices as captured in data-derived dietary patterns (27), and by male-partner intake of soy foods, we conducted sensitivity analyses where further adjustment for these factors was performed in the subgroup of women for whom these additional data was available. In these analyses the two dietary patterns identified using principal components analysis were a “Prudent pattern”, characterized by

intakes of fish, fruits, cruciferous vegetables, yellow vegetables, tomatoes, leafy green vegetables, and legumes, and a “Western pattern” characterized by high intakes of processed meat, high fat dairy, fries, refined grains, pizza, and mayonnaise. Higher pattern scores reflect closer adherence to each pattern. All analyses were conducted using the Statistical Analysis System Software package SAS 9.4 (SAS Institute Inc., Cary NC).

Results

We identified 315 women who underwent 520 ART cycles through June 2013. Most of the women were white (81%) and their mean (SD) age was 36 (4) years. Table 1 summarizes the baseline characteristics of the study population according to pre-fertility treatment intake of soy foods. Women with higher intakes of soy foods were more likely to be Asian, have healthier diets overall and their partners were also more likely to consume soy foods. There was a suggestion of greater use of luteal phase agonist protocols as the initial stimulation protocol for women with greater soy food intake. There were no significant differences in age, BMI, smoking status, primary infertility diagnosis, day 3 FSH serum levels, embryo transfer day or number of embryos transferred in the first treatment cycle across soy food intake categories. Similarly, soy food intake was unrelated to intake of folic acid or vitamin B12.

Soy food intake was not related to peak E2 levels, endometrial thickness, or yield of MII oocytes (Table 2). However, soy food intake was positively related to fertilization rate (Table 3). The fertilization rate was 6% higher in women who consumed soy foods compared to women who did not (77% vs 71%, $p=0.004$). When this relation was examined separately for IVF and ICSI cycles, it appeared to be slightly stronger for IVF cycles but there was no significant heterogeneity by cycle type (p , heterogeneity=0.11). Embryo quality and cleavage rate were not related to soy food intake (Supplemental Table 1).

We then examined the relation of soy food intake with clinical outcomes of ART cycles (Table 4). Clinical pregnancy and live birth rates per initiated cycle were higher among women reporting any intake of soy foods than those of women who did not consume soy. The age-adjusted clinical pregnancy rate was 11% (52% vs 41% $p=0.03$) higher and the age-adjusted live birth rate was 13% (44% vs 31% $p=0.007$) higher among soy food consumers than among the non-consumers. In multivariable-adjusted models, the odds of live birth were significantly higher among women in the highest category of soy food (0.34–1.02 servings/day) and isoflavones intake (7.56–27.89 mg/day) than those of women in the lowest category (Table 4). However, the tests for linear trend were not statistically significant. Excluding protocol and diagnosis from the regression models did not affect the results. In the model excluding these two terms, the multivariable-adjusted odds ratio from for live birth comparing women in the highest soy intake category to women who did not consume soy was 1.81 (1.06, 3.09).

We conducted sensitivity analyses aimed at addressing the possibility of residual confounding due to other dietary factors (Supplemental Table 2). In the subgroup of women for whom complete dietary information was available ($n=240$) further adjustment for dietary factors previously related to live birth rates in this cohort and for data-derived dietary

patterns did not change the association. Similarly, in the subgroup of women for whom there was data available on her male partner's soy food intake (n=93) adjustment for male intake of soy foods did not change the association between female soy intake and live births.

Discussion

We evaluated treatment outcomes of 315 women who underwent 520 cycles of ART in relation to dietary intake of soy foods and isoflavones. We found significant positive associations of soy intake with live births, clinical pregnancy and fertilization rates. Moreover, sensitivity analyses suggested little evidence for residual confounding by other dietary factors. These relations were observed at comparable intake levels to those of US adults in the general population. Specifically, mean total isoflavone intake among soy food consumers in this study was 3.4mg/day compared to 3.1mg/day for adult soy consumers in the general population (19). These findings suggest that the beneficial effects of soy foods intake on live birth and clinical pregnancy previously documented in randomized trials (17, 18) may also be observed at significantly lower intakes of these compounds.

Our results are in agreement with those of two previous randomized trials of phytoestrogen supplementation among women undergoing treatment for infertility. Shahin and colleagues randomized 147 women with unexplained infertility to a timed intercourse cycle with clomiphene citrate (CC) and a phytoestrogen supplement (120mg/d during cycle days 1–12) or timed intercourse with CC alone (17). In an analysis excluding women who failed ovarian stimulation with CC, the clinical pregnancy rate was significantly higher among the women who received phytoestrogens (36.7%) than among women who did not (13.6%) (17). Similarly, Unfer and collaborators randomized 213 women undergoing infertility treatment using IVF to receive a daily isoflavone supplement (1,500mg/d) or placebo as part of a luteal phase support protocol (18). In this trial the ongoing pregnancy/delivery rate among women receiving isoflavone supplementation was nearly double that of women receiving placebo (30.3% vs. 16.2%) (18). Nevertheless, our results and those of these two trials stand in contrast to the findings from a prospective cohort study of pregnancy planners. Mumford and collaborators found no relation between urinary isoflavones and fecundity among couples trying to become pregnant (21). It is possible that these divergent results are due to differences in fertility potential between subjects included in these studies. By design, prospective time to pregnancy studies include a mix of highly fecund couples and couples with diminished fecundity from the outset. In contrast, couples with diminished fecundity are, also by design, highly over-represented in studies among individuals seeking infertility treatment. It is possible that isoflavones and other phytoestrogens have no effect among highly fecund individuals but may be helpful in circumstances of diminished fecundity. While this hypothesis is consistent with the existing literature it should be further evaluated.

The mechanism through which dietary isoflavones, or other dietary phytoestrogens, could influence live birth rates in the setting of infertility treatment is not entirely clear. In the trial by Shahin and colleagues, phytoestrogen supplements increased endometrial thickness (17). Unfer and collaborators also documented an increase in endometrial thickness following isoflavone supplementation among women undergoing IUI (18). The findings from these trials suggest that the benefits of isoflavones could be related to estrogenic effect

of isoflavones on the endometrium thus improving implantation and embryo survival. However, we did not observe any association between intake of isoflavones from food sources and endometrial thickness. Nevertheless, it is important to point out that despite the vastly different doses of phytoestrogens in the previous trials and in the present study, the magnitude of the effects on clinical pregnancy and live birth rates are remarkably similar. Collectively, these findings suggest that the positive effect of isoflavones on live birth rates during infertility treatment may not be due to changes in endometrial thickness. Instead, these observed effects may be due to other, yet to be identified mechanisms. For example, we found that fertilization rate was higher among women who consumed soy products than among those who did not suggesting that improvements in gamete interactions may be responsible for the observed relations. Rodent models have also documented improved oocyte quality with dietary soy intake (28). An alternative interpretation consistent with our data includes a protective effect of phytoestrogens on pregnancy loss. Additional studies are needed to test this hypothesis. Our data also suggest that high dose supplement may not be necessary to obtain clinically relevant results. Additional research aimed at identify the mechanisms linking phytoestrogens to reproductive success and the lowest necessary doses needed for clinically relevant results are necessary.

Our study has some limitations. The most important one is the possibility of residual confounding due to other factors known or suspected to influence treatment outcomes that was not available in the entire study population. Nevertheless, sensitivity analyses in subgroups of women where complete dietary data of the participants and their partners was available suggest that additional adjustment for other dietary and partner factors has little influence on the observed association and would be unlikely to change the conclusions of the study. The consistency of our findings with those of two previous randomized trials lends further support to the interpretation that the observed relations were not due to residual confounding. As is the case of all studies using food frequency questionnaires, there is a possibility of measurement error. Specific concerns in this study include our inability to measure “hidden” isoflavone sources (e.g. products containing soy-protein enriched flour) and misclassification of diet due to actual changes of patient’s diet over time. However, this will most likely result in random misclassification of isoflavone intake and bias towards the null, therefore the expected effect of this type of error is that the association between soy intake and treatment outcome is actually stronger than that observed in this study. An additional limitation is that, by studying couples receiving treatment for infertility, our results may not be generalizable to women without known fertility problems. However, our results may still be generalizable to the hundreds of thousands of couples who undergo infertility treatment each year. Strengths of the study include its prospective design, which minimizes the risk of reverse causation, as well as its sample size and complete follow-up of participants, which allowed us to evaluate live births as the main study endpoint.

In summary, we prospectively assessed the relation between pre-fertility treatment intakes of soy food in a cohort of women undergoing ART, and found that dietary soy intake was positively related to the probability of having a live birth. These findings are consistent with the results of previous trials of phytoestrogen supplementation. The results from this study provide further evidence that relatively minor modifications to diet could have major impact on human fertility and on infertility treatment outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: NIH grants ES022955, R01ES009718, R01ES000002, P30DK46200 and T32DK007703

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Table 1

Demographic and dietary characteristics of study participants according to pre-treatment intake of soy foods.

	Soy foods intake (groups)				p ^c
	G1 (No intake)	G2	G3	G4 (highest)	
N	104	73	67	71	
		Median (IQR) or N (%)			
Range, servings/day	0	0.07 (0.04-0.09)	0.16 (0.14-0.21)	0.50 (0.34-1.02)	<0.001
Isoflavones, mg/day	0	1.0 (0.5, 2.5)	3.3 (2.6, 7.5)	12.1 (7.6, 27.9)	<0.001
Baseline characteristics					
Age, years	36.6 (33.0, 39.0)	35.0 (32.0, 38.0)	36.0 (33.0, 39.0)	34.0 (32.0, 38.0)	0.28
Race/Ethnic group					0.001
White/Caucasian	86 (82.7)	57 (78.1)	56 (83.6)	56 (78.9)	
Asian	3 (2.9)	5 (6.9)	9 (13.4)	13 (18.3)	
Hispanic/Latino	9 (8.7)	9 (12.3)	2 (3.0)	2 (2.8)	
African American	6 (5.8)	2 (2.7)	0 (0.0)	0 (0.0)	
Body Mass Index, kg/m ²	23.5 (21.6, 26.6)	22.6 (20.9, 25.8)	23.0 (20.6, 25.7)	23.1 (21.2, 25.7)	0.17
Ever smoker	25 (24.0)	26 (35.6)	16 (23.9)	21 (29.6)	0.31
Dietary characteristics^a					
Folic acid intake mcg/day	1170.3 (8010.9, 1378.0)	1237.4 (836.9, 1459.0)	1249.8 (837.9, 1439.1)	990.2 (811.2, 1286.4)	0.19
Vitamin B12 Intake mcg/day	12.2 (9.2, 16.25)	12.2 (9.1, 16.3)	13.2 (10.0, 18.0)	11.8 (9.12, 16.5)	0.45
Prudent Pattern score	-0.49 (-0.84, 0.10)	-0.39 (-0.82, 0.35)	-0.05 (-0.49, 0.41)	0.20 (-0.36, 0.99)	<0.001
Western Pattern score	0.24 (-0.34, 0.80)	-0.15 (-0.73, 0.34)	-0.24 (-0.70, 0.50)	-0.27 (-0.81, 0.29)	0.008
Male partner Isoflavones, mg/day ^b	0	0.37 (0.0, 3.2)	1.22 (0.0, 2.9)	2.60 (0.0, 10.2)	<0.001
Baseline Reproductive characteristics					
Initial infertility diagnosis					0.90
Male factor	37 (35.6)	25 (34.3)	21 (31.3)	26 (36.6)	
Diminished ovarian reserve	9 (8.7)	10 (13.7)	7 (10.5)	4 (7.0)	
Tubal Disease	9 (8.7)	4 (5.5)	6 (9.0)	3 (4.2)	
Endometriosis	10 (9.6)	3 (4.1)	2 (3.0)	5 (7.0)	
Ovulatory	7 (6.7)	5 (6.9)	7 (10.5)	6 (8.5)	
Uterine	1 (1.0)	0 (0.0)	1 (1.5)	1 (1.4)	

	Soy foods intake (groups)				p ^c
	G1 (No intake)	G2	G3	G4 (highest)	
Unexplained	31 (29.8)	26 (35.61)	23 (34.3)	25 (35.2)	0.03
Initial treatment protocol					
Antagonist	14 (13.5)	3 (4.1)	8 (11.9)	5 (7.4)	
Flare ^d	11 (10.6)	12 (16.4)	14 (20.9)	4 (5.6)	
Luteal phase agonist ^f	79 (76.0)	58 (79.4)	45 (67.2)	62 (87.3)	0.46
Day 3 FSH, IU/L	6.8 (5.8, 8.1)	7.0 (6.2, 8.4)	6.9 (5.6, 8.3)	6.5 (5.6, 7.6)	
Embryo Transfer Day					
No embryos transferred	17 (16.3)	5 (6.8)	9 (13.4)	6 (8.4)	
Day 2	4 (3.8)	6 (8.2)	4 (5.9)	2 (2.8)	0.53
Day 3	52 (50.0)	31 (42.5)	33 (49.3)	34 (47.9)	
Day 5	25 (24.0)	27 (37.0)	17 (25.4)	23 (32.4)	
Egg Donor or Cryo Cycle	6 (5.8)	4 (5.5)	4 (6.0)	6 (8.5)	
Number of Embryos Transferred					0.53
No embryos transferred	17 (16.4)	5 (6.9)	9 (13.4)	7 (8.5)	
1 embryo	8 (7.7)	7 (9.6)	9 (13.4)	11 (15.5)	
2 embryos	52 (50.0)	48 (65.8)	34 (50.8)	38 (53.5)	
3+ embryos	21 (20.2)	9 (12.3)	11 (16.4)	9 (12.7)	0.46
Egg Donor or Cryo Cycle	6 (5.8)	4 (5.5)	4 (6.0)	6 (8.5)	

^aData from 240 patients for whom complete dietary data was available.

^bData from 93 patients for whom complete male partner soy intake information was available.

^cFrom Kruskal-Wallis Tests and Chi Square test for categorical variables.

^dFollicular phase GnRH-agonist/Flare protocol.

^fLuteal phase GnRH-agonist protocol.

Table 2

Soy food and isoflavone intake in relation to endometrial thickness and ovarian stimulation outcomes.

Endometrial Wall thickness, mm		E2 Trigger Levels, pmol/L	MII Oocytes, n
Groups of intake [range, servings/d]		Adjusted Mean ^a (95% confidence interval)	
Soy foods (servings/day)			
G1 [0]	10.00 (9.44, 10.56)	2077 (1853, 2301)	8.17 (7.192, 9.28)
G2 [0.04–0.13]	9.88 (9.26, 10.50)	2272 (2029, 2514)	8.02 (7.00, 9.20)
G3 [0.14–0.33]	9.99 (9.32, 10.66)	2120 (1853, 2387)	8.22 (7.08, 9.54)
G4 [0.34–1.02]	9.97 (9.30, 10.64)	2035 (1770, 2301)	7.60 (6.54, 8.83)
p, trend ^b	0.98	0.41	0.28
Isoflavone (mg/day)			
G1 [0]	10.00 (9.45, 10.55)	2087 (1865, 2309)	8.16 (7.18, 9.26)
G2 [0.54–2.63]	9.61 (8.97, 10.24)	2257 (2005, 2509)	8.41 (7.30, 9.68)
G3 [2.64–7.55]	10.38 (9.74, 11.02)	2219 (1963, 2474)	7.78 (6.73, 8.98)
G4 [7.56–27.89]	9.86 (9.20, 10.51)	1985 (1724, 2245)	7.60 (6.56, 8.81)
p, trend ^b	0.82	0.16	0.23

^aData are presented as predicted marginal means adjusted for age, BMI, infertility diagnosis, protocol type and race.

^bTest for trend were performed using the median level of soy or isoflavone in each group as a continuous variable in the model.

Table 3

Soy food and isoflavones intake in relation to fertilization rate in 302 women (409 cycles) from the EARTH study

Groups of intake [range, servings/d]	All cycles		IVF cycles		ICSI cycles	
	Adjusted Fertilization Rate <i>a</i> (95% confidence interval)					
Soy foods (servings/day)						
G1 [0]	0.70 (0.64, 0.76)		0.71 (0.62, 0.79)		0.64 (0.51, 0.76)	
G2 [0.04–0.13]	0.77 (0.71, 0.82) *		0.80 (0.72, 0.86) *		0.73 (0.60, 0.83)	
G3 [0.14–0.33]	0.77 (0.70, 0.82) *		0.79 (0.69, 0.86)		0.74 (0.61, 0.84) *	
G4 [0.34–1.02]	0.76 (0.69, 0.82) *		0.77 (0.66, 0.86)		0.71 (0.58, 0.81)	
p, trend ^b	0.16		0.45		0.27	
Isoflavone (mg/day)						
G1 [0]	0.70 (0.64, 0.76)		0.71 (0.62, 0.79)		0.65 (0.52, 0.76)	
G2 [0.54–2.63]	0.77 (0.71, 0.82) *		0.80 (0.72, 0.87) *		0.73 (0.61, 0.83)	
G3 [2.64–7.55]	0.78 (0.72, 0.83) *		0.79 (0.70, 0.86)		0.75 (0.63, 0.85) *	
G4 [7.56–27.89]	0.75 (0.68, 0.81)		0.77 (0.67, 0.85)		0.70 (0.57, 0.80)	
p, trend ^b	0.37		0.51		0.58	

^aData are presented as predicted marginal means adjusted for age, BMI, infertility diagnosis, protocol type and race.

^bTest for trend were performed using the median level of soy or isoflavone in each quartile as a continuous variable in the model

* Indicates a p-value < 0.05 comparing that group vs. first group.

144 women contributed 190 IVF cycles and 110 women contributed 218 ICSI cycles.

Abbreviations: IVF, in vitro fertilization; ICSI, intra-cytoplasmic sperm injection.

Table 4
Soy food and isoflavones intake in relation to clinical outcomes of women undergoing infertility treatment with assisted reproductive technologies in the EARTH study

Groups of intake [range, servings/d]	Implantation			Clinical pregnancy			Live birth		
	Age-adjusted OR (95% CI)	Adjusted OR (95% CI) ^a	Reference	Age-adjusted OR (95% CI)	Adjusted OR (95% CI) ^a	Reference	Age-adjusted OR (95% CI)	Adjusted OR (95% CI) ^a	Reference
Soy foods (servings/day)									
G1 [0]	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
G2 [0.04–0.13]	1.58 (0.96, 2.58)	1.53 (0.81, 2.24)	1.60 (0.98, 2.60)	1.43 (0.87, 2.34)	1.71 (1.02, 2.87)	1.55 (0.91, 2.62)			
G3 [0.14–0.33]	1.30 (0.78, 2.16)	1.25 (0.74, 2.10)	1.47 (0.89, 2.44)	1.40 (0.84, 2.34)	1.71 (1.00, 2.92)	1.61 (0.94, 2.78)			
G4 [0.34–1.02]	1.42 (0.87, 2.33)	1.35 (0.92, 2.54)	1.54 (0.94, 2.51)	1.50 (0.91, 2.47)	1.85 (1.10, 3.20)	1.79 (1.05, 3.04)			
p, trend ^b	0.33	0.30	0.19	0.20	0.06	0.07			
Isoflavone (mg/day)									
G1 [0]	Reference	Reference	Reference	Reference	Reference	Reference			
G2 [0.54–2.63]	1.34 (0.81, 2.22)	1.2 (0.74, 2.10)	1.41 (0.85, 2.33)	1.28 (0.77, 2.14)	1.44 (0.83, 2.44)	1.32 (0.76, 2.27)			
G3 [2.64–7.55]	1.60 (0.99, 2.59)	1.54 (0.95, 2.51)	1.73 (1.07, 2.79)	1.63 (1.01, 2.14)	2.00 (1.21, 3.32)	1.87 (1.12, 3.14)			
G4 [7.56–27.89]	1.34 (0.81, 2.22)	1.33 (0.80, 2.21)	1.46 (0.89, 2.41)	1.41 (0.85, 2.35)	1.85 (1.09, 3.13)	1.77 (1.03, 3.03)			
p, trend ^b	0.41	0.40	0.26	0.29	0.05	0.07			

^aData are presented as predicted odds ratios adjusted for age, BMI, infertility diagnosis, protocol type, folate and B12 intake, dietary patterns and race.

^bTest for trend were performed using the median level of soy in each group as a continuous variable in the model.

Implantation was defined 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 on or after 24 weeks gestation.