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Male soy food intake was not associated with in vitro fertilization outcomes among their partners attending a fertility center

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Abstract

Male factor etiology may be a contributing factor in up to 60% of infertility cases. Dietary intake of phytoestrogens has been related to abnormal semen quality and hormone levels. However, its effect on couple fecundity is still unclear.

Intake of soy products was assessed in 184 men from couples undergoing infertility treatment with in vitro fertilization (IVF). Couples were recruited between February 2007 and May 2014 and prospectively followed to document treatment outcomes including fertilization, implantation, clinical pregnancy and live birth. Multivariate generalized linear mixed models with random intercepts, binomial distribution and logit link function were used to examine this relation while accounting for repeated treatment cycles and adjusting for potential confounders.

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CONFLICT OF INTEREST: Dr. Myriam Afeiche was at the Harvard School of Public Health when this work was conducted. Now, she is at the Nestle Research Center.

Male partner's intake of soy foods and soy isoflavones was unrelated to fertilization rates, the proportions of poor quality embryos, accelerated or slow embryo cleavage rate, and implantation, clinical pregnancy and live birth. The adjusted live birth rates per initiated cycle (95% CI) for partners of men in increasing categories of soy food intake were 0.36 (0.28 to 0.45), 0.42 (0.29 to 0.56), 0.36 (0.24 to 0.51), and 0.37 (0.24 to 0.52), respectively.

Soy food intake in men was not related to clinical outcomes among couples presenting at an infertility clinic. Data on the relation between phytoestrogens and male reproductive potential remains scarce and additional research is needed to clarify its role in human reproduction.

Keywords

soy intake; IVF; ICSI; male reproductive health; epidemiology

INTRODUCTION

Infertility is a common condition, affecting 15–30% of couples who try to become pregnant (Hull 1987). Among couples who undergo medical evaluation for their difficulties conceiving, male factor etiology is identified in as many as 58% of the couples (Thonneau et al. 1991). Although few modifiable risk factors for poor semen quality or male factor infertility are known (Hauser 2006, Sermondade et al. 2012), increasing evidence suggests that diet may be an important determinant of male reproductive potential (Wong et al. 2000). One dietary factor that has received particular attention in regards to its potential reproductive effects is intake of phytoestrogens. Phytoestrogens are a group of non-steroidal polyphenols found in a variety of plants and dietary products, particularly soy and soy-based foods and supplements (Xu et al. 2000). These compounds exert weak estrogenic activity as partial agonists of the estradiol receptor (ER) (Lee et al. 2003, Mueller et al. 2003, Pearce et al. 2003, Rickard et al. 2003). Their potential reproductive effects were initially described in sheep. A syndrome characterized by feminization of castrated sexually immature males, squamous metaplasia of the urethra and genitals, development of perianal cul-de-sac cysts communicating with the urethra, mammary hyperplasia, galactorrhea, and decreased fertility, was linked to the introduction of phytoestrogen-rich clover pastures (Bennetts 1946, Bennetts et al. 1946, Meyer 1970).

While deleterious effects of phytoestrogens on reproduction have been described in other mammalian species (Kyselova et al. 2003, Mei et al. 2011, Seppen 2012), it is less clear whether the same is true in humans. We previously reported that women's intake of soy foods was positively related to the probability of having a live birth during in vitro fertilization treatment among 315 women presenting an infertility clinic in Massachusetts (Vanegas et al. 2015). In men, soy supplementation leads to small changes in the hormonal milieu (Habito et al. 2000, Nagata et al. 2001). In addition, we and others have previously reported that intake (Chavarro et al. 2008) and urinary levels (Xia et al. 2013) of isoflavones (a type of phytoestrogens found primarily in soy) are related to lower sperm concentration. However, this inverse relation has not been observed in other studies (Mitchell et al. 2001). Moreover, only one study to date has evaluated whether phytoestrogens impact couple fecundity, rather than semen quality. Specifically, Mumford and colleagues found that

urinary levels of two classes of phytoestrogens (isoflavones and lignans) in the male partner were unrelated to fecundity after adjusting for urinary phytoestrogen levels in the female partner (Mumford et al. 2014). To further understand how phytoestrogens may impact male fertility, we evaluated the association of men's soy food intake and in vitro fertilization (IVF) outcomes among subfertile couples attending a fertility center.

MATERIAL AND METHODS

Study population

Study participants were men enrolled in the EARTH Study, an ongoing prospective cohort established to identify environmental and nutritional determinants of fertility (Hauser et al. 2006). Couples planning to use their own gametes for infertility treatment who were within eligible age ranges (male partner 18–51 years, female partners 18–45 years) were approached by a study nurse and invited to participate in the study. Joint participation as a couple is encouraged but not required. Approximately 60% of those contacted by the research nurses participated in the study. Among 392 men who joined during the study period, 317 had data on pre-treatment soy-food intake, and the female partners of 182 of them had completed at least one in vitro fertilization (IVF) treatment cycle between November 2004 and May 2014, representing the study population for this analysis.

Ethical approval

The study was approved by the Human Subjects Committees of the Massachusetts General Hospital and the Harvard School of Public Health. Written informed consent was obtained from all participants.

Dietary assessment

At enrollment, height and weight were measured by a trained research nurse to calculate body mass index (BMI) (kg/m²) 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. Completion of this questionnaire took, on average, 30 minutes. The questionnaire included a section querying the frequency of consumption of 15 soy-based foods (Chun et al. 2009, Frankenfeld et al. 2003, Frankenfeld et al. 2002, Kirk et al. 1999). Men 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. The 15 food items included in the soy food questionnaire were tofu, tempeh, soy sausages, soy burgers, soy packages, miso soup, soy milk, soy yogurt, tofu cream, soy beans, soy nuts, soy drinks, soy protein and soy bars. 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 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 (United States Department of Agriculture 2007). Intakes of total isoflavones (daidzein, genistein and glycitein) were estimated by summing the isoflavone contribution of all food items in the questionnaire. A

more comprehensive dietary assessment was later added to the study with the introduction of a previously validated food frequency questionnaire (Rimm et al. 1992) which asked participants to report how often, on average, they consumed specified amounts of 131 food items during the previous year. From this questionnaire we estimated dietary pattern adherence scores (Gaskins et al. 2012).

Clinical management and assessment of outcomes—Women underwent one of three controlled ovarian stimulation IVF treatment protocols on day 3 of induced menses after completing a cycle of oral contraceptives: 1) luteal phase GnRH-agonist protocol, 2) GnRH-antagonist protocol, or 3) follicular phase GnRH-agonist/Flare protocol. Lupron dose was reduced at, or shortly after, the start of ovarian stimulation with FSH/hMG in the luteal phase GnRH-agonist protocol. FSH/hMG and GnRH-agonist or GnRH-antagonist was continued to the day of trigger with Human Chorionic Gonadotropin (hCG), 36 h before oocyte retrieval. Throughout the monitoring phase of the subject's IVF treatment cycle, estradiol levels were obtained (Elecsys Estradiol II reagent kit, Roche Diagnostics). Oocyte retrieval was completed when follicle dimensions on transvaginal ultrasound reached 16–18 mm and the estradiol level reached at least 500 pg/mL.

Embryologists determined the total number of oocytes retrieved per cycle and classified them as germinal vesicle, metaphase I, metaphase II (MII) or degenerated. Oocytes underwent either conventional IVF or intracytoplasmic sperm injection (ICSI) as clinically specified. Oocytes were checked for fertilization and graded as either normally fertilized or abnormally fertilized; two pronuclei or one or three pronuclei respectively. The resulting embryos were assessed for quality according to their morphological characteristics on day 3 and assigned a score between 1 (best) and 5 (worst), with grades 3, 4 and 5 considered poor quality. Embryo cleavage rate was measured as the sum of the number of cells in the embryo on day 3. Embryos that had reached 6–8 cells were considered to be cleaving at a normal rate, embryos with 5 cells or fewer were considered to be slow cleaving, and embryos with 9 or more cells were considered to have accelerated cleavage. In women who underwent an embryo transfer, clinical outcomes were measured. Successful implantation was defined as an elevation in plasma β -hCG levels above 6 IU/L after embryo transfer. An elevation in β -hCG with the confirmation of an intrauterine pregnancy by ultrasound was considered clinical pregnancy. Live birth was defined as the birth of a neonate on or after 24 weeks gestation.

Statistical analysis

Men were divided into four categories of soy food and soy isoflavone intake. Men reporting no soy food intake were considered as the reference group. The remaining men were divided into tertiles of increasing soy food and soy isoflavone intake. The association of pre-treatment soy food intake with baseline characteristics was evaluated using Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables. Correlation between male and female partners soy intake was evaluated using Spearman correlation coefficients. To evaluate the association between pre-treatment soy intake and treatment outcomes while accounting for multiple treatment cycles per couple, we used multivariate generalized linear mixed models with random intercepts, a binomial distribution and logit

link function. Tests for linear trends (Rosner 2000) were conducted using the median values of each category of intake as a continuous variable. In order to allow presentation of results on the scale in which variables were originally measured, regression coefficients for results were back-transformed and population marginal means (Searle et al. 1980) accounting for all covariates in the model were computed. Confounding was assessed using descriptive statistics from our study population through the use of directed acyclic graphs (DAGs) (Weng et al. 2009), taking into account prior knowledge on biological relevance. Models were adjusted for age (continuous), BMI (continuous), race (Asian and other), smoking status (never and ever), infertility diagnosis (male factor and other), and treatment protocol type (Luteal phase agonist, GnRH antagonist and Follicular phase GnRH-agonist treatment (protocol flare). We considered that an overall association was present when a statistically significant linear trend across quartiles was present. All tests were two-tailed and the level of statistical significance was set at 0.05. Statistical analyses were performed with SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

Our study population consisted of 182 men whose female partners underwent a total of 324 IVF cycles (282 fresh cycles). The mean (SD) age and BMI were 36.7 (4.6) years and 27.0 (3.8) kg/m², respectively. Most men (85%) were white/Caucasian and the largest minority group was Asian men (8%). Their female partners were, on average, 35.2 years of age and had a BMI of 23.9 kg/m². Men's soy and isoflavone intakes were highly variable with median (25th, 75th percentile) intakes of 0.04 (0, 0.21) serv/day and 0.40 (0, 4.3) mg/day. Men with higher soy intake were slightly leaner than men who did not consume soy foods (Table 1). Also, as expected, men's soy intake was positively related to their partner's soy intake ($r_s=0.30$, $p<.0001$). Other baseline characteristics were unrelated to soy intake.

Men's intakes of soy foods and soy isoflavones were each unrelated to fertilization rates (Table 2). The fertilization rates (95% CI) for partners of men who did not consume soy foods and those who did were 0.72 (0.60–0.76) and 0.70 (0.66–0.74), respectively. Results were similar when IVF and ICSI cycles were examined separately (Table II). Compared with men who did not consume soy foods, the proportions of accelerated cleaving embryos were higher in the top quartile of men's pre-treatment soy food or soy isoflavone intake; however, when the model was adjusted for female partner's soy food intake, the proportions of poor quality, accelerated cleaving or slow cleaving embryos were unrelated to men's pre-treatment soy food or soy isoflavone intake (Supplementary Table 1).

We also examined the relation of men's pre-treatment soy food and soy isoflavone intake with implantation, clinical pregnancy and live births (Figure 1). Male partner intake of soy foods prior to treatment was also unrelated to these outcomes. The adjusted live birth rates per initiated cycle (95% CI) for men who did not and who did consume soy foods were 0.37 (0.28 to 0.46) and 0.41 (0.33 to 0.50), respectively. Results were unchanged with further adjustment for female partner's soy food intake (Supplementary Table 1) or men's total energy intake and scores reflecting overall food choices (Supplementary Table 2).

DISCUSSION

In this cohort of men from subfertile couples presenting to a fertility clinic, men's intake of soy foods and soy isoflavones was unrelated to treatment outcomes. Specifically, pre-treatment soy intake was unrelated to fertilization rate, embryo quality, implantation, clinical pregnancy or live births. The mean (SD) of men's isoflavones intake was 5.6 (13.24) mg/day being 0 and 107.84 mg/day the minimum and maximum of isoflavones intake in this study population. This average of intake was comparable to that of men in the general US population (Chun et al. 2009) and was similar to that previously related with lower sperm concentration in the same study population (Chavarro et al. 2008). While these findings appear to be inconsistent with previous reports of an inverse relationship between soy intake and semen quality (Nagata et al. 2001, Xia et al. 2013), they are consistent with a previous report showing no association between male partner urinary phytoestrogen levels and fecundity among couples without a history of infertility (Mumford et al. 2014). They are also consistent with previous findings showing that lifestyle factors associated with semen quality do not always relate to infertility treatment outcomes (Gaskins et al. 2014).

Most of the existing literature on the potential reproductive effects of phytoestrogens on male reproduction focuses on their relation with reproductive hormone levels and semen quality. Specifically, two randomized dietary interventions examined the effect of soy products on male hormones (Habito et al. 2000, Nagata et al. 2001). Habito and coworkers found higher levels of testosterone/estradiol ratio in the meat diet group compared with men in the tofu diet group, and higher levels of SHBG and lower free androgen index value in the tofu diet group compared with the meat diet group (Habito et al. 2000). Similarly, Nagata and colleagues showed that a consumption of more than 400 mL of soy milk per day seemed to decrease estrone levels compared with no intake of soy milk (Nagata et al. 2001). In addition, we and others have previously reported associations between soy intake and semen quality. In a previous cross-sectional analysis among men from the EARTH cohort (Chavarro et al. 2008) we found that men consuming soy foods twice or more per week or more frequently had $41 \times 10^6/\text{mL}$ fewer sperm than men who did not consume soy foods. Soy food intake was unrelated to sperm motility, morphology or ejaculate volume, however (Chavarro et al. 2008). Similarly, Xia and collaborators reported an inverse relation between urinary phytoestrogen levels and sperm concentration, total count and motility, as well as a positive association with odds of idiopathic male infertility among Chinese men (Xia et al. 2013). On the other hand, isoflavone intake was positively related to sperm count and motility and inversely related to sperm DNA damage in a case-control study (Song et al. 2006), while isoflavone intake was unrelated to semen quality parameters and reproductive hormones in a separate study of young men (Mitchell et al. 2001). Clearly, whether soy isoflavones or other phytoestrogens have an impact on semen quality remains an open question.

No previous studies have evaluated the relation between men's pre-treatment soy intake and infertility treatment outcomes. The most comparable study examined the association between concentrations of male and female urinary phytoestrogens (isoflavones and lignans) and time to pregnancy in a population-based cohort of 501 couples without a history of infertility who were attempting to conceive (Mumford et al. 2014). In crude analyses, the

median male partner urinary levels of O-desmethyldaidzein (O-DMA; an intestinal bacterial metabolite of daidzein) were higher in couples who became pregnant than in couples who did not (28nmol/L vs 10nmol/L). However, and in agreement with our findings, male urinary phytoestrogen concentrations were unrelated to time to pregnancy. The fecundability odds ratios (95% CI) associated with a 1 unit increase in log-urinary isoflavones were 1.01 (0.92–1.12) for genistein, 1.02 (0.92–1.13) for daidzein, 1.03 (0.95–1.12) for O-DMA, and 0.99 (0.87–1.13) for equal. It is also important to point out that the lack of association with treatment outcomes is not necessarily inconsistent with an inverse association with sperm concentration. In fact, we have encountered this situation before. Specifically, we found that physical activity was positively related to sperm counts in two independent populations (Gaskins et al. 2014, Gaskins et al. 2013) but unrelated to infertility treatment outcomes (Gaskins et al. 2014). A possible explanation for this apparent disconnect is that in the setting of infertility treatment the semen quality parameter that is more strongly manipulated is sperm concentration. As a result, any links between low sperm concentration, or its determinants, with decreased fertility are minimized with infertility treatment.

The present study has some limitations. First, due to the design of this study, it may not be possible to extrapolate the findings to the general population of couples conceiving without medical intervention. However, men in this study are comparable to men attending other fertility clinics, so our findings could be applicable to other men seeking fertility treatment. In addition, as is the case of all studies based on diet questionnaires, measurement error and misclassification of intake are a major concern. Nevertheless, similar questionnaires have been found to correlate well with biological markers of intake (Vioque et al. 2013, Willett et al. 1985). Moreover, because soy food intake and diet were assessed prior to the initiation of infertility treatment it is this unlikely that error was related to treatment outcome. Therefore, the expected effect of this type of error is that the association between soy intake and treatment outcomes is actually stronger than that observed in this study. Strengths of this study include its prospective design which minimizes the risk of reverse causation, and the comprehensive adjustment of possible confounding variables thanks to the standardized assessment of a wide range of participant characteristics because of the complete follow-up of our study sample. Our study was also adequately powered to detect clinically relevant difference of 19% in live birth rates between men in the top and bottom categories of intake. Lastly, the couple-based approach allowed us to examine the relation of male soy intake to clinical outcomes rather than surrogate markers of fertility such as semen quality or reproductive hormone levels.

In summary, male partner intake of soy foods was not related to infertility treatment outcomes in a prospective cohort study of couples seeking fertility care. These findings are consistent with a previous report among couples without a history of infertility attempting to become pregnant. However, they are at odds with previous reports suggesting a deleterious effect of soy food and soy isoflavones intake on semen quality. Despite these findings, data on the relation between phytoestrogens and male reproductive potential remains scarce and additional research is needed to clarify its role in human reproduction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Adjusted rates (95% CI) in clinical outcomes per initiated cycle according to men's soy food intake

Models are adjusted for men's age, BMI, race, smoking status, couple's infertility diagnosis, and female's ART protocol type. Test for trends were performed using the median level of soy food or isoflavone intake in each quartile 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.

Table 1
Demographic and reproductive characteristics of 182 men in the EARTH Study by quartile of soy food intake.

	G1 (n=73)	G2 (n=39)	G3 (n=37)	G4 (n=33)	P, trend [†]
Total soy intake, sv/day	0	0.1 (0, 0.1)	0.2 (0.2, 0.3)	1.0 (0.6, 1.4)	<0001
Isoflavones, mg/day	0	1.2 (0.5, 1.6)	4.1 (2.6, 5.5)	24.3 (13.7, 43.1)	<0001
Baseline characteristics					
Age (years)	37.1 (33.9, 40.4)	36.4 (33.0, 38.5)	36.7 (33.8, 40.4)	35.9 (33.2, 40.3)	0.62
Race/ethnicity, n (%)					0.52
White	66 (90.4)	33 (84.6)	30 (81.1)	26 (78.8)	
Black	0 (0)	1 (2.6)	0 (0)	0 (0)	
Asian	3 (4.0)	3 (7.7)	5 (13.5)	4 (12.1)	
Other	4 (5.3)	2 (5.1)	2 (5.4)	3 (9.1)	
BMI (kg/m ²)	27.5 (25.2, 29.5)	25.4 (23.1, 28.0)	26.9 (33.8, 40.4)	26.5 (23.7, 28.3)	0.07
Current smoker, n (%)					0.30
Never smoker	43 (58.9)	30 (76.9)	24 (64.9)	24 (72.7)	
Past smoker	23 (31.1)	7 (18.5)	9 (24.3)	9 (27.3)	
Current smoker	7 (9.5)	2 (5.1)	4 (10.8)	0 (0)	
Varicocele, n (%)	6 (8.2)	6 (15.4)	3 (8.1)	2 (6.1)	0.51
History of cryptorchidism, n (%)	6 (8.2)	5 (5.1)	0 (0)	1 (3.0)	0.28
Any reproductive surgery, n (%)	19 (26.0)	8 (20.5)	6 (16.2)	6 (18.2)	0.63
Men's dietary characteristics²					
Total fat (sat, mono, poly, trans), g/day	67.2 (52.9, 83.1)	76.7 (53.2, 97.7)	66.9 (57.1, 77.9)	73.4 (54.2, 85.5)	0.74
Total protein (animal and vegetal), g/day	76.5 (68.8, 101.1)	81.7 (64.9, 103.4)	76.7 (63.0, 93.4)	94.1 (68.8, 111.6)	0.52
Total carbohydrates, g/day	215.4 (183.0, 278.8)	248.4 (182.9, 308.7)	217.8 (184.6, 257.1)	263.4 (192.7, 324.9)	0.42
Total energy intake, kcal/day	1996.9 (1529.5, 2363.9)	1912.7 (1682.3, 2603.6)	1955.3 (1537.0, 2529.1)	2156.8 (1599.5, 2486.8)	0.73
Western Pattern score	-0.10 (-0.74, 0.26)	-0.36 (-0.66, 0.42)	-0.35 (-0.50, 0.34)	0.22 (-0.66, 1.57)	0.21
Prudent Pattern score	-0.04 (-0.71, 0.71)	-0.16 (-0.77, 0.64)	0.05 (-0.58, 0.89)	-0.26 (-0.53, 0.40)	0.57
Female partner characteristics					
Age (years)	35.0 (33.0, 39.0)	35.0 (32.0, 38.0)	36.0 (33.0, 39.0)	35.0 (32.0, 38.0)	0.95
BMI (kg/m ²)	23.2 (20.6, 26.6)	22.8 (21.1, 25.2)	22.2 (20.9, 25.6)	23.2 (21.3, 25.8)	0.96

	G1 (n=73)	G2 (n=39)	G3 (n=37)	G4 (n=33)	P, trend ¹
Median (IQR) or N (%)					
Current smoker, n (%)					0.62
Never smoker	53 (72.6)	30 (76.9)	27 (73.0)	21 (63.6)	
Past smoker	16 (21.9)	8 (20.5)	10 (27.0)	11 (33.3)	
Current smoker	4 (5.5)	1 (2.6)	0 (0)	1 (3.0)	
Total soy intake, sv/day	0.04 (0, 0.2)	0.1 (0, 0.2)	0.2 (0.1, 0.3)	0.3 (0.1, 0.5)	0.0001
Isoflavones, mg/day	0.54 (0, 3.98)	2.6 (0.5, 4.7)	3.2 (1.3, 8.0)	6.7 (1.8, 12.4)	<.0001
Couple and treatment characteristics					
Previous IUI, n (%)	32 (43.8)	19 (48.7)	19 (48.7)	10 (30.3)	0.37
Previous IVF, n (%)	20 (27.4)	11 (28.2)	9 (24.3)	3 (9.1)	0.18
Initial infertility diagnosis, n (%)					0.60
Male factor	26 (35.6)	13 (33.3)	11 (29.7)	11 (33.3)	
Female factor	18 (24.7)	13 (33.4)	16 (43.2)	12 (36.4)	
Diminished Ovarian Reserve	4 (5.5)	3 (7.7)	3 (8.1)	4 (12.1)	
Endometriosis	3 (4.1)	2 (5.1)	4 (10.8)	1 (3.0)	
Ovulation Disorders	5 (6.9)	5 (12.8)	5 (13.5)	1 (3.0)	
Tubal	6 (8.2)	2 (5.1)	4 (10.8)	4 (12.1)	
Uterine	0 (0)	1 (2.5)	0 (0)	2 (6.1)	
Unexplained	29 (39.7)	13 (33.3)	10 (27.0)	10 (30.3)	
Day 3 FSH Levels, IU/L	6.9 (6.0, 8.1)	6.5 (5.6, 8.1)	7.1 (6.1, 8.4)	7.4 (6.3, 8.7)	0.58
Initial female treatment protocol, n (%)					0.33
Luteal phase agonist ³	59 (78.7)	33 (84.6)	24 (64.9)	26 (78.8)	
Antagonist	6 (8.0)	4 (10.3)	8 (21.6)	5 (15.2)	
Flare ⁴	8 (11.0)	2 (5.1)	5 (13.5)	2 (6.1)	
Time between questionnaire completion and first ART cycle, day	95.0 (52.0, 173.0)	105.0 (46.0, 177.0)	113.0 (45.0, 214.0)	86.0 (60.0, 229.0)	0.86
Initial ICSI cycles, n (%) ⁵	35 (52.2)	16 (47.1)	17 (50.0)	15 (46.9)	0.95
Embryo Transfer Day					0.11
Day 2	4 (5.5)	2 (5.1)	2 (5.4)	1 (3.0)	
Day 3	26 (35.6)	19 (48.7)	22 (59.5)	20 (60.6)	
Day 5	31 (42.5)	13 (33.3)	10 (27.0)	9 (27.3)	
Number of Embryos Transferred					0.17

	G1 (n=73)	G2 (n=39)	G3 (n=37)	G4 (n=33)	P, trend ¹
	Median (IQR) or N (%)				
No embryos transferred	9 (12.3)	1 (2.6)	0 (0)	3 (9.1)	
1 embryo	15 (20.6)	6 (15.4)	6 (16.2)	2 (6.1)	
2 embryos	38 (52.1)	21 (53.9)	20 (54.1)	24 (72.7)	
3+ embryos	8 (11.0)	7 (17.9)	8 (21.6)	4 (12.1)	

¹ From Kruskal-Wallis test for continuous variables and chi-squared tests for categorical variables.

² n=144 men who filled out the FFQ.

³ Luteal phase GnRH-agonist protocol.

⁴ Follicular phase GnRH-agonist/Flare protocol.

⁵ n=167 (excludes 15 cycles cancelled due to poor response).

Table 2

Associations¹ between male (n=182) soy food and isoflavone intake with fertilization² rates and embryo quality among their partners (324 IVF cycles) from the EARTH Study.

Ranges	Fertilization Rate %, all cycles	Fertilization Rate %, IVF cycles	Fertilization Rate %, ICSI cycles	Poor quality embryos %	Accelerated embryo cleavage %	Slow embryo cleavage %
Soy foods (sv/day)						
(0)	0.72 (0.67, 0.76)	0.65 (0.56, 0.72)	0.74 (0.68, 0.79)	0.14 (0.10, 0.19)	0.20 (0.13, 0.31)	0.52 (0.35, 0.69)
(0.04–0.09)	0.69 (0.62, 0.75)	0.68 (0.58, 0.77)	0.72 (0.61, 0.80)	0.20 (0.13, 0.28)	0.22 (0.11, 0.39)	0.66 (0.40, 0.85)
(0.10–0.34)	0.74 (0.67, 0.79)	0.67 (0.55, 0.76)	0.80 (0.72, 0.86)	0.20 (0.13, 0.29)	0.24 (0.12, 0.42)	0.71 (0.45, 0.88)
(0.35–5.17)	0.67 (0.59, 0.74)	0.66 (0.54, 0.77)	0.68 (0.57, 0.77)	0.18 (0.12, 0.27)	0.42 (0.26, 0.61)*	0.49 (0.28, 0.70)
P-trend ³	0.32	0.96	0.33	0.60	0.02	0.49
Isoflavone (mg/day)						
(0)	0.72 (0.67, 0.76)	0.65 (0.56, 0.72)	0.74 (0.68, 0.79)	0.14 (0.10, 0.19)	0.20 (0.12, 0.31)	0.52 (0.35, 0.69)
(0.09–1.84)	0.7 (0.62, 0.76)	0.70 (0.58, 0.79)	0.71 (0.61, 0.79)	0.21 (0.14, 0.31)	0.25 (0.13, 0.42)	0.72 (0.47, 0.88)
(1.94–7.89)	0.71 (0.63, 0.77)	0.65 (0.55, 0.74)	0.80 (0.70, 0.88)	0.18 (0.12, 0.27)	0.19 (0.08, 0.36)	0.62 (0.34, 0.83)
(7.93–107.84)	0.70 (0.63, 0.76)	0.67 (0.56, 0.77)	0.72 (0.63, 0.80)	0.19 (0.12, 0.28)	0.42 (0.26, 0.6)*	0.50 (0.29, 0.71)
P-trend ³	0.81	0.84	0.84	0.54	0.02	0.46
Soy foods (sv/day)						
None (0)	0.72 (0.67, 0.76)	0.65 (0.56, 0.72)	0.74 (0.68, 0.79)	0.14 (0.10, 0.19)	0.21 (0.13, 0.32)	0.52 (0.35, 0.69)
Any (0.04–5.17)	0.70 (0.66, 0.74)	0.67 (0.61, 0.73)	0.74 (0.68, 0.79)	0.19 (0.15, 0.24)	0.29 (0.21, 0.39)	0.61 (0.47, 0.73)
P-trend ³	0.57	0.63	0.93	0.12	0.22	0.44

¹ Data are presented as predicted marginal means (95% CI) adjusted for age, BMI, race, smoking status, infertility diagnosis, and protocol type using the LSMEANS procedure. All analyses were run using generalized linear mixed models with random intercepts, binomial distribution, logit link function, and compound symmetry correlation structure.

² 89 men contributed 124 IVF (in vitro fertilization) cycles and 92 men contributed 145 ICSI (intra-cytoplasmic sperm injection) cycles.

³ Tests for trends were performed using the median level of soy food or isoflavone intake in each quartile as a continuous variable in each model.

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