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ORIGINAL STUDY

A prospective controlled study of sexual function and sexually related personal distress up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy

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Abstract

Objective: Premenopausal risk-reducing bilateral salpingo-oophorectomy (RRBSO) may impair sexual function, but the nature and degree of impairment and impact of estrogen therapy on sexual function and sexually related personal distress after RRBSO are uncertain.

Methods: Prospective observational study of 73 premenopausal women at elevated risk of ovarian cancer planning RRBSO and 68 premenopausal controls at population risk of ovarian cancer. Participants completed the Female Sexual Function Index and the Female Sexual Distress Scale-Revised. Change from baseline in sexual function following RRBSO was compared with controls at 12 months according to estrogen therapy use.

Results: Baseline sexual function domains did not differ between controls and those who underwent RRBSO and subsequently initiated (56.2%) or did not initiate (43.8%) estrogen therapy. At 12 months, sexual desire and satisfaction were unchanged in the RRBSO group compared with controls. After RRBSO, nonestrogen therapy users demonstrated significant impairment in sexual arousal (β-coefficient (95% confidence interval) −2.53 (−4.86 to −0.19), $P < 0.03$), lubrication (−3.40 (−5.84 to −0.96), $P < 0.006$), orgasm (−1.64 (−3.23 to −0.06), $P < 0.04$), and pain (−2.70 (−4.59 to 0.82), $P < 0.005$) compared with controls. Although sexually related personal distress may have been more likely after RRBSO, irrespective of estrogen therapy use, there was insufficient data to formally test this effect.

Conclusions: The findings suggest premenopausal RRBSO adversely affects several aspects of sexual function which may be mitigated by the use of estrogen therapy. Further research is needed to understand the effects of RRBSO on sexual function and sexually related personal distress, and the potential for estrogen therapy to mitigate against any adverse effects.

Key Words: Hormone therapy – Risk-reducing bilateral salpingo-oophorectomy – Sexual distress – Sexual function – Surgical menopause.

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Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is recommended for women with pathogenic gene variants associated with a significant increase in ovarian cancer risk. This is the only intervention proven to reduce morbidity and mortality from ovarian cancer, and also improves overall survival.[1,2] RRBSO is recommended to be performed before the age of 40-45 in women with pathogenic gene variants which increase their risk of ovarian cancer.[3] Hence, RRBSO in premenopausal women will induce immediate surgical menopause with consequent adverse health implications. These include the acute onset of menopausal symptoms, development of vulvovaginal atrophy (VVA), accelerated bone loss, and increased risk of cardiovascular disease.[4,5]

Several prospective, cross-sectional, and retrospective studies have reported high rates of sexual dysfunction following RRBSO.[6-8] The possibility of a decline in sexual function may deter high-risk women from potentially life-saving surgery[9] and conversely lead some women to regret their decision for RRBSO.[10] A prospective study with published follow-ups at 12 months and 3.5 years reported a reduction in sexual pleasure and an increase in sexual discomfort after RRBSO, with mixed effects in terms of alleviation of symptoms with estrogen therapy (ET) use postsurgery.[11,12] A consistent limitation of these and other previous studies is that high-risk women undergoing RRBSO were compared with those undergoing ovarian cancer screening where potential awareness of their increased cancer risk might affect sexual function.[12] Use of ET, with a progestogen for women who retain their uterus, reduces vasomotor and vaginal symptoms and may protect against bone loss and cardiovascular disease.[13,14] However, the effects of ET on sexual function after RRBSO are uncertain.[11-13,15] In addition, previous studies have not measured factors known to substantially influence sexual function, such as change in partner status during follow-up and the route of ET delivery.[16,17] Furthermore, sexual function is not static and sexual dysfunction is common.[16] To determine whether changes in sexual function are attributable to RRBSO or simply reflect fluctuation in sexual function, a comparator group of women at population risk of ovarian cancer is needed to assess the effects of RRBSO.

The aim of this study was to prospectively evaluate sexual function and sexually related personal distress after RRBSO in high-risk premenopausal women according to postsurgical ET use in comparison with community-based controls at 12 months postsurgery to inform the ongoing care of younger women considering RRBSO.

METHODS

Participants

Study participants were classified as ''exposed'' or ''nonexposed.'' Exposed were premenopausal women planning RRBSO because of elevated risk of ovarian cancer due to confirmed pathogenic gene variants in *BRCA1/2, BRIP1, RAD51C* or Lynch syndrome or family history (RRBSO group). Nonexposed (called controls) were premenopausal women at population risk of ovarian cancer with intact ovaries. All participants resided in the Australian states of Victoria and New South Wales, or in Philadelphia, PA. Recruitment to the study has been described in detail elsewhere.[18] In brief, premenopausal women planning to undergo RRBSO were referred to the study by clinicians and family cancer clinics. RRBSO participants were required to be at elevated risk of developing ovarian cancer. Control participants were recruited through advertisements, social media, university and hospital newsletters, and by referral from RRBSO participants. Eligible participants were aged 18 to 50 years with regular menstrual cycles if nonhysterectomised, with no vasomotor symptoms, a serum FSH $\leq$ 15 IU/L, and serum estradiol $>$ 100 pmol/L. Women were excluded if they had been pregnant, lactating or taking antiestrogen therapy in the 3 months prior to enrollment, had undiagnosed vaginal bleeding, or were unable to complete the English-language questionnaires or unable to provide informed consent. Control participants were excluded if they were planning to undergo oophorectomy or become pregnant in the next 2 years. For the present analysis, participants were excluded if they reported a change in partner status between baseline and 12 months as this substantially influences sexual function,[16] or if they were using systemic combined hormonal contraception or androgen therapy at baseline or at 12 months. Control participants at elevated risk of ovarian cancer were also excluded for this analysis.

The study was approved by the Human Ethics Research Committees of the Peter MacCallum Cancer Centre, Melbourne, Australia (IRB # HREC/12/PMCC/24), the Prince of Wales Hospital, Sydney, Australia (IRB # HREC/13/POWH/61), the Royal Prince Alfred Hospital, Sydney, Australia (IRB # X14/0396), and the University of Pennsylvania, Philadelphia, PA

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Clinical Trials Registration: Australian and New Zealand Clinical Trials Registry (anzctr.org.au); Identifier #: ACTRN12615000082505; URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363554&isReview=true.

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(IRB #: CTSRMC/UPCC/01813). All participants provided written informed consent prior to any data collection.

Data collection and questionnaires used

Demographic information, medical, surgical and gynecological history, systemic and topical hormone therapy (HT), and hormonal contraceptive use were documented at clinic visits at baseline and 12 months. Other factors known to influence sexual function in premenopausal Australian women, including depression, anxiety, psychotropic medication, and partner status, were also documented.[16] The decision to use ET and dose were agreed between the participants and their treating doctor. All participants completed the Female Sexual Function Index (FSFI).[19] This questionnaire comprises six validated domains of sexual function reported for the past month: desire, arousal, lubrication, orgasm, satisfaction, and pain during intercourse. The FSFI has been validated in both well women and cancer survivors.[20] Sexually related personal distress was determined by the Female Sexual Distress Scale-Revised (FSDS-R).[21] This questionnaire also uses a 30-day recall period. Each of the 13 items are rated using a 5-point scale (0-4; total score range 0-52). A score of 11 or above indicates sexually related personal distress with high reliability, discriminative ability, and construct validity.[21]

Sample size and statistical analyses

The overall study sample size was based on the available data pertaining to the proportion of premenopausal women likely to have a total FSFI score below 26.55, which has been used in previous studies as an indicator of female sexual dysfunction.[18,22,23] It was estimated that 105 women planning a RRBSO and 105 premenopausal controls would provide 80% power ($\alpha = 0.05$) to detect an increase in the proportion of women with a FSFI score < 26.55 at follow-up from 24% in both groups at baseline to 34% in the RRBSO group, allowing for 15% loss to follow-up. This estimate assumed that the proportion of women with a baseline FSFI score < 26.55 would not differ between the study groups, and that the control group would have stable sexual function.[18]

Calculation of the total FSFI score requires completion of all items in the questionnaire. It also assumes participants have a heterosexual partner, and that sexual activity includes penetration. To include unpartnered women and women not having penetrative sex, as well as women who did not complete every domain of the FSFI, the total score could not be used in the present analysis. The original power calculation did not allow for the analysis of the group who underwent RRBSO according to ET use. For the between-group differences examined, this study would only have been adequately powered for a large difference in the FSFI domain scores in the order of six units. All women who completed at least the FSFI desire domain, which comprises the first two questions, were included in the analysis. All participants included in each FSFI domain analysis completed all items for that domain at baseline and follow-up.

Descriptive statistics are expressed as frequencies, proportions, and medians (interquartile range [IQR]). Differences in the characteristics of participants between the RRBSO and control groups were compared using chi-square tests or two-sample test of proportions for any ET use at 12 months in the control and RRBSO groups.

For the analyses investigating the impact of RRBSO and ET on sexual function, participants who underwent RRBSO were divided into three groups according to ET use at 12 months: nonuse of systemic ET, oral ET use with/without a progestogen, and transdermal ET use with/without a progestogen or tibolone. Tibolone use was combined with the transdermal group as unlike oral estrogen, tibolone does not increase sex hormone binding globulin (SHBG),[24] and in a double-blind study its effects on sexual function in postmenopausal women were not different from the effects of transdermal ET.[25]

Differences in both the baseline and change in FSFI domain scores between the RRBSO and control groups were compared using linear regression models. Due to non-normality of the distribution of some domain scores at baseline, we incorporated bootstrapping with 1,000 replications for inference. These outcomes are reported as β-coefficients with 95% bootstrap bias-corrected confidence intervals (hereafter referred to as CIs). All statistical tests were two-sided, and we considered a P value of less than 0.05 to be statistically significant. All analyses were conducted using Stata (version 15.0).

RESULTS

Of the 194 study participants who completed the baseline and 12 month visits (RRBSO group $n = 95$, control group $n = 99$), 141 participants met the eligibility criteria for this analysis (RRBSO group $n = 73$, control group $n = 68$) (Fig. 1). All women in the RRBSO group had a bilateral oophorectomy between baseline and 12 months and all controls retained their ovaries. The mean age (standard deviation) of the women who had a RRBSO and controls were 42.2 (4.2) and 41.9 (5.2) respectively, and the groups were similar in terms of age categories ($P = 0.6$), body mass index (BMI) categories ($P = 0.8$), and ethnicity ($P = 0.1$) (Table 1). Controls were more likely to be educated beyond high school (94.1% vs 61.6%, $P < 0.001$). The groups did not differ with respect to partner status, whether they were sexually active, or factors known to affect sexual function including depression, anxiety, or reported psychotropic medication use at baseline and at 12 months[16] (data not shown).

None of the participants were using systemic ET at baseline, and none of the controls reported systemic ET use at baseline or 12 months. Amongst the RRSBO group 23 participants had undergone either a unilateral or bilateral mastectomy prior to recruitment including 7 as treatment for breast cancer, and 7 as risk-reducing bilateral mastectomy between baseline and 12 months. In the RRBSO group, oral ET ± progestogen use was reported by 17 participants, transdermal ET ± progestogen use was reported by 21 participants, and 3 participants were taking tibolone. Only one woman taking tibolone and one woman using transdermal ET were also using vaginal estradiol. The proportions of RRBSO non-ET users, oral ET users, and transdermal ET/tibolone users

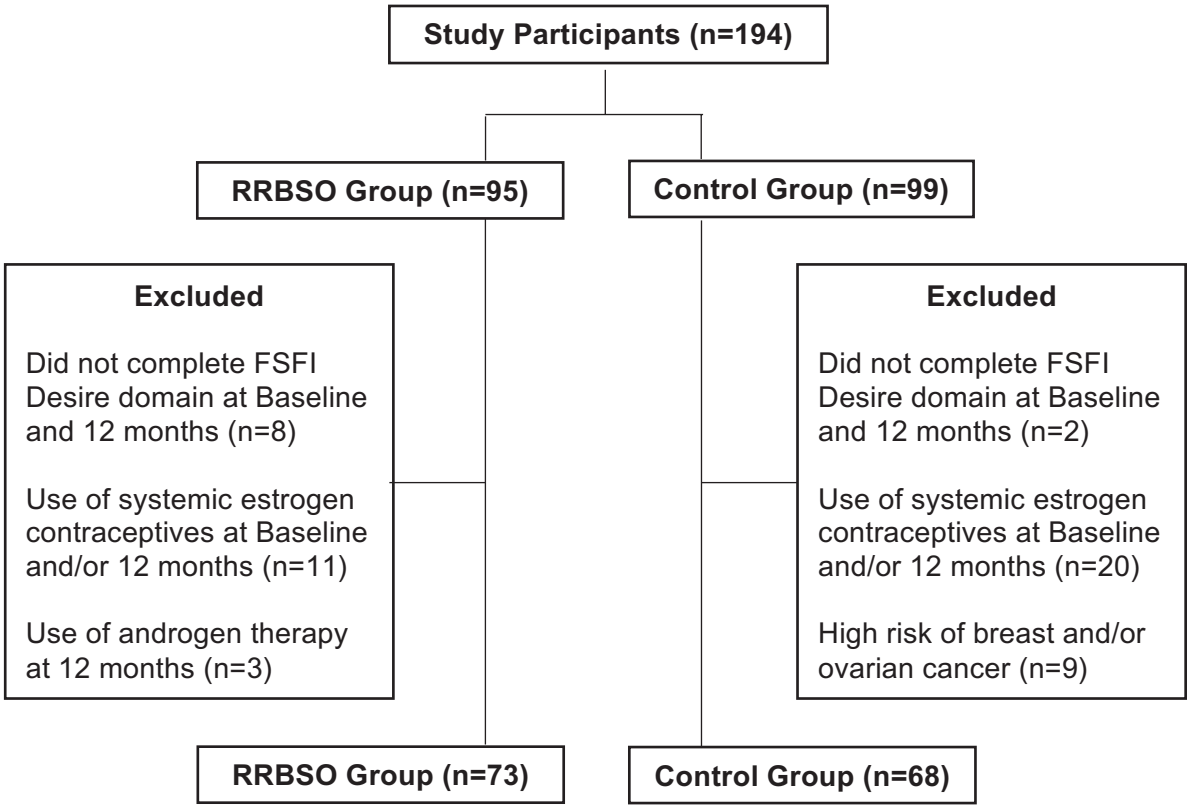

FIG. 1. Participant flowchart. Control, premenopausal women who retained their ovaries; FSFI, Female Sexual Function Index; RRBSO, premenopausal women who had risk-reducing bilateral salpingo-oophorectomy.

who had a mastectomy prior to ($n = 10$, 5, and 8, respectively), or during the study ($n = 3$, 1, and 3, respectively) were similar in each of the three RRBSO groups.

Change in sexual function following RRBSO

Participants who underwent RRBSO were evaluated according to their reported ET use at 12 months. At baseline, none of the FSFI domain scores differed between any RRBSO groups (no ET, oral ET, or transdermal ET/tibolone) and the control group (Table 2). There were no differences between the control group and any of the three RRBSO groups in the change in the FSFI desire or satisfaction domains over the 12-month follow-up period. However, there were significant differences between the control and RRBSO-no ET group, with negative β coefficients indicating lower scores, suggesting impaired function, in the RRBSO-no ET group for change in the domains of arousal ($P < 0.03$), lubrication ($P < 0.006$), orgasm ($P < 0.04$), and pain ($P < 0.005$) at 12 months. For the RRBSO-transdermal ET/tibolone group, compared with controls, reductions in the FSFI domain scores at 12 months approached statistical significance for the domains of arousal ($P < 0.06$), lubrication ($P < 0.07$), and orgasm ($P < 0.06$).

Change in sexually related personal distress after RRBSO

The proportion of participants in each group classified as having sexually related personal distress (FSDS-R score ≥ 11) at each time point was examined. Fewer participants in each of the RRBSO groups completed the FSDS-R at both time points than completed the FSFI. Over the 12-month follow-up period, most controls (73.5%) reported no change in sexually related personal distress compared with baseline (Table 3). More women in the RRBSO groups were classified as having sexually related personal distress at 12 months (23.1-27.6%) compared to controls (11.8%). However, the small numbers of participants precluded formal statistical testing.

DISCUSSION

In premenopausal women at high risk of ovarian cancer, RRBSO was associated with reductions in arousal, lubrication, and orgasm and increased dyspareunia, compared with similarly aged premenopausal women not at increased ovarian cancer risk who retained their ovaries. Whereas ET seemed to mitigate these adverse sexual effects, it did not seem to reduce the likelihood of sexually related personal distress 12 months postsurgery compared with controls. As the power of the study was limited and multiple comparisons were undertaken that may have resulted in chance findings, the observed between-group differences should be interpreted with caution.

We specifically chose not to use high-risk women planning to retain their ovaries as controls because they were likely to be younger or differ in their plans for future pregnancy from the RRBSO group, factors that may impact sexual function. Furthermore, we believe that a reference group of premenopausal women from the general population provides a more clinically

TABLE 1. *Characteristics of the study participants*

Characteristic	RRBSO group ($n = 73$) n (%)	Control group ($n = 68$) n (%)	P value[a]
Recruitment site			
The Royal Women's Hospital Melbourne	42 (57.5)	64 (94.1)	<0.001
Others	31 (42.5)	4 (5.9)	
Age in years at Baseline, mean (SD)	42.2 (4.2)	41.9 (5.2)	
30 to <40	22 (30.1)	23 (33.8)	0.6
≥40	51 (69.9)	45 (66.2)	
Body mass index (kg/m^2) at baseline			
Underweight (<18.5)	0 (0.0)	0 (0.0)	0.8
Normal (18.5-24.9)	31 (42.5)	29 (42.6)	
Overweight (25-29.9)	24 (32.9)	25 (36.8)	
Obese (≥30)	24 (24.6)	14 (20.6)	
Ethnicity			
European ancestry	57 (78.1)	60 (88.2)	0.1
Other[b]	16 (21.9)	8 (11.8)	
Education beyond high school			
Yes	45 (61.6)	64 (94.1)	<0.001
Relationship status at baseline			
Married/de-facto	63 (86.3)	56 (82.4)	0.5
Other[c]	10 (13.7)	12 (17.6)	
Smoking status at baseline			
Yes	5 (6.8)	2 (2.9)	0.3
Alcohol consumption at baseline			
Yes	64 (87.7)	65 (95.6)	0.09
Parity at baseline			
Non-parous	11 (15.1)	13 (19.1)	0.5
Parous	62 (84.9)	55 (80.9)	
Unilateral or bilateral mastectomy at baseline[d]			
Yes	23 (31.5)	0 (0.0)	<0.001
Prophylactic bilateral mastectomy between baseline and 12 mo			
Yes	7 (9.6)	0 (0.0)	0.009
Hysterectomy at baseline			
Yes	1 (1.4)	3 (4.4)	0.3
Progestogen only oral contraception at baseline			
Yes	1 (1.4)	0 (0.0)	0.3
Progestogen only oral contraception at 12 mo			
Yes	0 (0.0)	0 (0.0)	NA
Depo-medroxy progesterone acetate or contraceptive implant at baseline			
Yes	4 (5.5)	4 (5.9)	0.9
Depo-medroxy progesterone acetate or contraceptive implant at 12 mo			
Yes	0 (0.0)	2 (2.9)	0.1
LNG-IUD only in situ at baseline			
Yes	12 (16.4)	19 (27.9)	0.1
LNG-IUD only in situ on the 12 mo			
Yes	26 (35.6)	17 (25.0)	0.2
Systemic ET formulation baseline			
No use of ET	73 (100.0)	68 (100.0)	NA
Systemic ET formulation 12 mo			
No use of ET[e]	32 (43.8)	68 (100.0)	<0.001
Oral ET only	1 (1.4)	0 (0.0)	
Oral ET plus systemic progestogen	4 (5.5)	0 (0.0)	
Oral ET plus LNG-IUD	12 (16.4)	0 (0.0)	
Transdermal ET only	12 (16.4)	0 (0.0)	
Transdermal ET plus systemic progestogen	2 (2.8)	0 (0.0)	
Transdermal ET plus LNG-IUD[f]	7 (9.6)	0 (0.0)	
Tibolone[f]	3 (4.1)	0 (0.0)	
FSFI domain score at baseline, median (IQR)			
Desire	6.0 (2.0)	6.0 (1.0)	0.4
Arousal	16.0 (5.0)	16.0 (4.5)	0.7
Lubrication	19.0 (4.0)	19.0 (4.0)	0.3
Orgasm	13.0 (4.0)	13.0 (4.0)	0.9
Satisfaction	13.0 (6.0)	12.0 (4.0)	0.5
Pain	15.0 (4.0)	14.0 (4.0)	0.6
FSDS-R score at baseline, median (IQR)	5.0 (10.0)	6.5 (12.5)	
Classified as having sexually related distress			
Yes	16 (24.2)	25 (36.8)	0.2

ET, estrogen therapy; FSDS-R, Female Sexual Distress Scale-Revised; FSFI, Female Sexual Function Index; IQR, interquartile range; LNG-IUD, levonorgestrel intra-uterine device; NA, not applicable; RRBSO, risk-reducing bilateral salpingo-oophorectomy.

[a] P value is based on test of proportion.

[b] Others include Eurasian, Euro-Caribbean, Latin-American, Asian, and Unknown.

[c] Others include boy/girlfriend, casual, and no partner.

[d] 15 prophylactic, 7 for breast cancer, and 1 unknown.

[e] None using vaginal estrogen.

[f] One woman using vaginal estrogen.

TABLE 2. *Change in sexual function following RRBSO according to estrogen therapy, compared with controls, over 12 months*

Study Group	Desire β (95%-CI) *P* value	Arousal β (95%-CI) *P* value	Lubrication β (95%-CI) *P* value	Orgasm β (95%-CI) *P* value	Satisfaction β (95%-CI) *P* value	Pain β (95%-CI) *P* value
FSFI domain at baseline compared with controls						
Control ($n = 68$)	0	0	0	0	0	0
RRBSO: No ET use ($n = 32$)	0.15 (−0.72 to 1.02) 0.7	0.05 (−2.25 to 2.36) 1.0	−0.27 (−2.76 to 2.22) 0.8	−0.39 (−2.24 to 1.46) 0.7	−0.41 (−2.14 to 1.31) 0.6	−0.24 (−2.59 to 2.11) 0.8
RRBSO: Oral ET ($n = 17$)	0.25 (−0.77 to 1.27) 0.6	−3.09 (−6.49 to 0.32) 0.08	−2.12 (−5.88 to 1.64) 0.3	−2.15 (−4.81 to 0.51) 0.1	−0.51 (−2.43 to 1.42) 0.6	0.07 (−3.09 to 3.23) 1.0
RRBSO: Transdermal ET or Tibolone[a] ($n = 24$)	0.20 (−0.96 to 0.57) 0.6	−0.27 (−2.36 to 1.82) 0.8	−0.15 (−2.99 to 2.70) 0.9	0.21 (−1.63 to 2.06) 0.8	0.21 (−1.48 to 1.90) 0.8	0.01 (−2.49 to 2.50) 1.0
Change in FSFI domain (12 mo baseline) compared with controls						
Control ($n = 68$)	0	0	0	0	0	0
RRBSO: No ET Use ($n = 32$)	−0.47 (−1.23 to 0.28) 0.2	−2.53 (−4.86 to −0.19) 0.03	−3.40 (−5.84 to −0.96) 0.006	−1.64 (−3.23 to −0.06) 0.04	−0.16 (−1.33 to 1.64) 0.8	−2.70 (−4.59 to 0.82) 0.005
RRBSO: Oral ET ($n = 17$)	−0.66 (−1.42 to 0.10) 0.09	−0.04 (−2.37 to 2.28) 1.0	−0.57 (−4.47 to 3.33) 0.8	−0.03 (−2.90 to 2.96) 1.0	−0.08 (−1.55 to 1.71) 0.5	−1.89 (−5.36 to 1.57) 0.3
RRBSO: Transdermal ET or Tibolone[a] ($n = 24$)	−0.29 (−0.93 to 0.36) 0.4	−3.71 (−6.43 to 0.08) 0.06	−3.46 (−7.15 to 0.23) 0.07	−2.87 (−7.88 to 0.14) 0.06	−1.56 (−3.21 to 0.90) 0.3	−1.46 (−4.46 to 1.55) 0.3

β, bias-corrected beta-coefficient; CI, confidence interval; ET, estrogen therapy; FSFI, Female Sexual Function Index; RRBSO, risk-reducing bilateral salpingo-oophorectomy.
[a] $n = 3$.

relevant comparator group for premenopausal RRBSO. Importantly, prior to undergoing RRBSO the sexual profile of the high-risk women did not differ from controls, and at 12 months post-RRBSO there was no difference in sexual desire or sexual satisfaction compared with controls irrespective of ET use or nonuse. The lack of any impact of RRBSO on sexual desire and satisfaction contrasts with the findings of an earlier study that reported a reduction in sexual pleasure post-RRBSO in both ET users and nonusers.[12] The difference between the two studies may reside in the questionnaires used and the lack of a control group in the earlier study.[12] However, our findings suggest that sexual desire and satisfaction may be maintained after RRBSO, even in non-ET users.

The acute loss of ovarian sex steroid production which occurs following surgical menopause, substantially adversely affects the urogenital tract through direct tissue effects and by changing the vaginal microcirculation,[26] and reduces vaginal blood flow.[27,28] Consequently estrogen insufficiency results in vulvovaginal atrophy characterized by vaginal irritation, dryness and discomfort during sexual activity and impaired vasodilation that accompanies sexual stimulation.[29] Use of ET restores clitoral and vaginal blood flow which is important for sexual arousal, lubrication and orgasm.[29] Hence, it would be expected that ET use would maintain lubrication, comfort with vaginal intercourse, arousal and orgasm compared with controls as seen in the oral ET group. However, because the oral ET group was the smallest comparator, the null findings in the ET group compared with controls should not be interpreted to mean that ET prevents changes in sexual function after RRBSO.

Compared to controls, we observed declines in sexual arousal, lubrication, orgasm, and pain at 12 months after RRSBO in non-ET users. Women and clinicians considering use of ET after premenopausal RRBSO should be aware that ET may confer specific benefits in these domains of sexual function. Previous studies have suggested that transdermal ET has a more favorable effect on sexual arousal compared to oral ET.[17] In this study we were unable to determine whether specific ET modes of delivery were superior in maintaining these aspects of sexual function, potentially due to limited sample size and variations in ET dose used. However, a true benefit of oral ET over transdermal ET/tibolone cannot be excluded.

It is noteworthy that only two women, one taking tibolone and one using transdermal ET, reported vaginal estrogen use post RRBSO. Low-dose vaginal ET is highly effective for the treatment of vulvovaginal atrophy, is inexpensive, and has an excellent safety profile,[30] yet as highlighted by our findings, is often forgotten as a treatment option and therefore remains under prescribed.

The overall prevalence of sexually related personal distress in all the study groups was lower than has previously been reported for premenopausal Australian women at baseline and follow-up.[16] The majority of study participants had no change in sexually related personal distress over the course of the study. Yet, irrespective of ET use, RRBSO participants appeared more likely to have become newly classified as having sexually related personal distress at 12 months compared with controls,

TABLE 3. *Change in sexually related distress after RRBSO according to estrogen therapy, and in controls, over 12 months*

Study group	Baseline		12 mo		Change in distress status		
	Not distressed[a] *n* (%)	Distressed *n* (%)	Not distressed *n* (%)	Distressed *n* (%)	No change	Became distressed	Became not distressed
Control ($n = 68$)	43 (63.2)	25 (36.8)	45 (66.2)	23 (33.8)	50 (73.5)	8 (11.8)	10 (14.7)
RRBSO: No ET Use ($n = 29$)	23 (79.3)	6 (20.7)	19 (65.5)	10 (34.5)	17 (58.6)	8 (27.6)	4 (13.8)
RRBSO: Oral ET ($n = 13$)	9 (69.2)	4 (30.8)	6 (46.2)	7 (53.8)	10 (76.9)	3 (23.1)	0 (0)
RRBSO: Transdermal ET or Tibolone[b] ($n = 22$)	16 (72.7)	6 (27.3)	11 (50)	11 (50)	15 (68.2)	6 (27.3)	1 (4.5)

ET, estrogen therapy; RRBSO, risk reducing bilateral salpingo-oophorectomy.
[a]Score of < 11 on the Female Sexual Distress Scale-Revised (FSDS-R) questionnaire.
[b]$n = 3$.

although we were unable to establish this statistically. We have previously reported the main risk factors for nonspecific sexually related distress include psychotropic medication use, being sexually inactive and undergoing infertility treatment.[16] In the present study, the included number of women was too small for formal statistical testing to be undertaken, including examination of factors that might be associated with this change. Further research is needed to establish whether RRBSO increases the risk of sexually related personal distress and the main determinants of this effect.

In the context of favorable effects of ET on sexual function, the safety of ET after RRBSO requires consideration. The highest quality data comes from a prospective observational study of women with a *BRCA1* gene pathogenic variant.[31] Overall ET was not associated with a greater risk of breast cancer during a 7.6 year follow-up, although post oophorectomy ET alone was associated with a small risk reduction in breast cancer, whereas ET plus systemic progestogen use was associated with an small increase in breast cancer risk.[31] Overall, the benefits of ET are thought to outweigh the risks for younger premenopausal women undergoing RRBSO.[32] However, overall uptake of ET is low in this population, potentially because the risks versus benefits of ET in high-risk women are not fully understood and safety concerns remain.[33]

Strengths of this study include the prospective design and the comparison of premenopausal women undergoing RRBSO with premenopausal controls of a similar age, providing a meaningful comparison group. Additional strengths include the use of validated questionnaires that assessed several domains of sexual function and sexually related personal distress, and detailed prospective data on the use of ET. The FSFI was selected as it is the most widely used validated sexual function questionnaire. The FSFI was initially developed and validated in monogamous, heterosexual women with sexual arousal disorder.[19] However, a total FSFI score cannot be generated for women who are unpartnered, are not heterosexual or who do not participate in penetrative sex. Nonetheless, the individual domains have been validated which enabled us to report findings for each of these.[19] To eliminate the impact of change in partner status on sexual function,[34] we restricted our analysis to participants who did not change their relationship status during the study. The decision to use and choice of ET was determined by each participant's clinical needs, personal medical history, and personal preference.

Our analysis included a number of different outcomes, hence multiple comparisons, which creates the possibility of chance findings. Such chance findings can include both significant and nonsignificant associations. Our findings should be interpreted as preliminary and all require confirmation in a larger study. A major challenge, which may be considered a potential limitation, was dealing with the complexity of sexual function and the unanticipated exclusion of study participants from the analysis, reducing study power. In addition, a clinical evaluation was not undertaken to ascertain the reasons for the development of sexually related personal distress after RRBSO. Future qualitative studies may inform the mechanisms driving this observation which may include relationship issues, negative sexual self-image, and exposure to physical, emotional, or sexual abuse.[35] We did not examine the impact of prior mastectomy on sexual function. However, we have previously observed that prior mastectomy +/− reconstruction did not increase the likelihood of impaired sexual function.[36] We also did not measure circulating androgens after RRBSO. However, we have recently shown that circulating androgen concentrations explain very little of the variation in sexual function in premenopausal women.[37] We also did not evaluate relationship satisfaction, which may predict ongoing sexual activity after RRBSO despite symptoms such as vaginal dryness.[38] We did not measure changes in cancer-related anxiety which may have impacted sexual function. The diversity of ET formulations used, with or without a range of progestogens, required pragmatic grouping of participants according to their ET use. In order not to exclude the three participants who used tibolone, they were included with transdermal ET as the effects of tibolone on sexual function in women with sexual dysfunction have been shown to be similar to an estradiol-norethisterone patch in a randomized placebo-controlled trial.[25]

CONCLUSIONS

Our results suggest RRBSO might adversely affect several aspects of sexual function, including arousal, orgasm, lubrication, and sexual pain, which appeared to be mitigated by ET use. Our findings highlight the importance of pre-RRBSO sexual counselling which many women report is inadequate.[10] However, larger studies are required to inform preoperative decision-making and postoperative care, specifically, the potential benefits of ET for sexual function after RRBSO. Further research is needed to understand the effects of

RRBSO on sexual function and the broader psychosocial factors that might influence sexually related personal distress, including sexual self-image and relationships. The potential benefits of vaginal estrogen for lubrication, arousal, and pain after RRBSO need to be established.

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