S-11.

Perimenopausal stage influences the prevalence of nighttime insomnia symptoms

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Objective: Perimenopause is the transition from reproductive to non-reproductive years in a women's life. During the early perimenopausal stage women begin to report sleep disturbances which are a conduit for additional health issues. This study addresses the importance of metabolic and cardiovascular risk among women suffering from insomnia. Empiric evidence consistently suggests a predisposition to insomnia in women; yet, there is a paucity of research that addresses insomnia in perimenopausal (PM) women as they transition to menopause. Our recent study reported that 31% to 42% of perimenopausal women (N=3302) had nighttime insomnia symptoms meeting the DSM-V nighttime criteria for insomnia disorder. The purpose of this study aimed to identify a stage of perimenopause when insomnia symptoms become more prevalent during the transition to menopause. This study examined the trajectory of insomnia symptoms in PM women through the transition to menopause while controlling for perimenopausal stage and number of years in each stage prior to menopause. Progression to menopause naturally and/or surgically was addressed. **Design:** A secondary analysis of 10 years of data, collected annually, from the Study of Women's Health across the Nation (SWAN) was completed, using the DSM-V criteria for insomnia disorder for nighttime impairment (any 1 insomnia symptom reported ≥ 3 per week). Descriptive analysis and repeated measures logistic regression between group and within group evaluation of change in nighttime insomnia symptoms over time were used to identify if perimenopausal stage (early vs. late), years per stage and surgical menopause (SM) in annually measured nighttime insomnia symptoms (sleep latency, wake after sleep onset, awakenings, sleep quality) influenced an insomnia disorder. **Results:** Participants (N=3302) were middle aged (45.9 + 2.69 years) diverse (African American 28%; Caucasian 50%; Asian 10%; Hispanic 12%) women, including 187 (6%) women who were identified as pre-perimenopausal or perimenopausal at baseline data collection. There is a significant difference among the perimenopausal stage groups with respect to the development of insomnia (p=0.003), with adjustment for baseline menopausal status, visit, and individual baseline sleep measures. Women that remained in the early stage were 0.82 times less likely to develop insomnia than those who progress from early to late to post-menopausal (95% CI 0.70, 0.96, p=0.015), 0.48 times less likely than those who progress from early to late to surgical menopause (95% CI 0.25, 0.94, p=0.034), 0.79 times less likely than those who progress from early to post-menopausal (95% CI 0.67, 0.93, p=0.005), and 0.65 times less likely than those who progress from early to surgical menopause (95% CI 0.51, 0.83, p<0.001). Those who progress from early to late perimenopause are 0.70 times less likely to develop insomnia disorder than those who progress from early to surgical menopause (95% CI 0.53, 0.94, p=0.016). Those who progress from early to late to post-menopausal are 0.769 times less likely to develop insomnia disorder than those who progress from early to surgical menopause (95% CI 0.63, 0.98, p=0.036). At the end of the 10 year data period women that progressed from early to late perimenopause were 3 times more likely to experience nighttime insomnia symptoms at the end of the follow-up period than at the beginning (95% CI 1.84, 5.06, p<0.001). **Conclusion:** Perimenopause predisposes women to develop nighttime insomnia symptoms with perimenopausal stage impacting the development of insomnia. Natural progression to menopause when compared to surgical progression also is protective against insomnia disorder development. Anticipatory guidance for PM women is needed to address an insomnia disorder. Providers need to routinely screen for an insomnia disorder in this high risk group. Interventions, including behavioral approaches, are needed.

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S-12.

Postmenopausal Women with Greater Paracardial Fat Have More Coronary Artery Calcification than Premenopausal Women: The Study of Women's Health Across the Nation (SWAN) Cardiovascular Fat Ancillary Study

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Objective: Cardiovascular disease (CVD) risk increases after menopause. Volumes of cardiovascular (CV) fat, shown to be associated with subclinical CVD and CVD events, are significantly higher in postmenopausal than premenopausal women. Paracardial adipose tissue (PAT), the fat outside the pericardium, has been shown to be associated with lower levels and declines of estradiol hormone, suggesting this CV fat depot as a potential menopause-specific CVD risk factor. Whether associations between CV fat depots and subclinical CVD are stronger in postmenopausal women and could be explained or modified by endogenous estradiol levels are not known. Our specific objective was to evaluate separately the cross-sectional associations of PAT and epicardial adipose tissue (EAT), the fat within the pericardium, and coronary artery calcification (CAC) in midlife women. Effect modifications by menopausal status and endogenous estradiol levels were also assessed. **Design:** Women from the SWAN cardiovascular fat ancillary study at the Pittsburgh and Chicago sites were evaluated. Volumes of CV fat depots and CAC Agatston scores were measured using electron beam computed tomography scans. CAC was evaluated as both dichotomous (presence of CAC: CAC ≥10) and continuous (extent of any CAC: log (CAC>0)) measures. CV fat volumes were log transformed to achieve normality and both linear and logistic regression modeling were used as appropriate. Final models were adjusted for study site, race, age, menopausal status, log triglycerides, systolic blood pressure, body mass index residuals, smoking status, endogenous estradiol, cycle day of the blood draw, use of medications and use of hormone therapy (HT). **Results:** The study included 478 women (38% Black, 62% White; 58% pre-/early peri-, 10% late peri-, and 32% post-menopausal) aged 46–59 years (mean (SD): 51(2.9) years). About half of the participants (n=226(47%)) had CAC scores >0 and 20% had CAC scores≥10. Both EAT and PAT were significantly associated with presence and extent of CAC in final models, P values <0.05. In models adjusted for all covariates but not estradiol and HT use, associations between PAT and presence and extent of CAC were significantly modified by menopausal status (Interaction P values: 0.0008, 0.002, respectively); such that postmenopausal women with greater volumes of PAT were more likely to have CAC presence (OR(95%CI), per 1SD increase in log PAT: 2.11(1.05, 4.24), P=0.04) and greater extent of calcification (β(SE), per 1SD increase in log PAT: 0.54(0.21), P=0.01) when compared with pre-/early perimenopausal women. Additional adjustment for estradiol level and HT use attenuated these differences. Moreover, estradiol levels significantly modified the associations between PAT and CAC extent in final models, interaction P value: 0.006; such that in the upper PAT tertile, CAC extent was significantly higher than in the lower PAT tertiles (geometric mean CAC scores 13.9 vs. 3.9, respectively, P=0.039) mainly in women with estradiol levels within the lowest estradiol tertile (≤18.65pg/ml). **Conclusion:** In midlife women, CV fat was significantly associated with presence and extent of coronary calcification independently of traditional CVD risk factors. Associations between PAT and CAC measures were stronger in postmenopausal women and in women with lower levels of estradiol. These findings suggest that paracardial fat could be a menopause-specific CVD risk factor, supporting the need to monitor and target this risk factor for intervention as women transition through menopause.

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S-13.

Changes in sexual function among midlife women: "I'm older… and I'm wiser."

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Objective: Quantitative studies indicate that many aspects of sexual function decline during midlife. However, quantitative studies may fail to capture individual women's lived experience of sexual function during midlife. Qualitative approaches that allow women to speak their own words regarding their experiences can capture nuances and individual variations in women's lived experiences of sexual function during midlife. We gathered qualitative data among sexually active women aged 45-60 to explore (1) women's perceptions of changes in their sexual function over time; and (2) how midlife women respond to these changes. **Design:** Twenty interviews and three focus groups were conducted by a trained facilitator using an interview guide; sessions were audio-recorded and transcribed. We used a template organizing approach for data analysis. Codebook development by two investigators proceeded using an iterative process until a final codebook was agreed upon; the primary investigator then coded all data. A second investigator coded a randomly selected 10% of data and kappa scores were calculated for inter-coder reliability. Codes relating to changes in sexual function with aging were examined to identify key themes. **Results:** The mean age (N=39) was 58 (range 46-59); 53% were White, 36% were Black, and 10% were of another race. Thirteen percent were premenopausal, 44% were perimenopausal, and 28% were not sure. All but 2 women identified as heterosexual. Major themes emerged surrounding both negative and positive **changes** in sexual function, what women **attributed** these changes to, and how women **responded** to them. With regards to **changes** in sexual function, the most common *negative changes* were decreased frequency of sex, lower libido, vaginal dryness, and difficulty reaching orgasm. More women **attributed** these *negative changes* to psychosocial stressors, such as family and career, than biological factors such as menopause. For some women, partner issues, including partner health problems, relationship discord, and partner sexual dysfunction [including both erectile dysfunction (ED) and low libido] were a major source of negative sexual changes. In fact, there were several women who noted their libido was much higher than their male partner's. Among the women who reported *positive changes*, several women felt that while frequency of sexual activity had decreased, their satisfaction with sex had increased. They **attributed** these *positive changes* to higher self-confidence, increased self-knowledge, and better communication skills as they aged. When examining how women **responded** to negative changes, we identified 3 key themes: (1) indifference (small proportion of women); (2) distress (moderate proportion); and (3) adaptation (large proportion). Adaptations reported included use of vaginal lubricants, lengthening foreplay, incorporating other types of sex besides penetrative intercourse (oral and manual stimulation), trying other sexual positions, masturbating more, and encouraging use of ED treatments in their partners. Additionally, some women adapted by placing higher value on the emotional aspects of sex (such as emotional intimacy) than the physical aspects (such as achieving orgasm). **Conclusion:** Changes in sexual function, such as decreased responsiveness, vaginal dryness, lower libido, and difficulty reaching orgasm are common as women move through midlife. However, positive changes, such as increased satisfaction with sex, were also observed. Many women adapt to negative changes by modifying their expectations regarding sexual activity or changing sexual priorities in order to maintain or even increase overall sexual satisfaction. Providers who care for midlife women should ask about any changes in sexual function during routine visits. Providers should recognize that not all changes are attributable to biological changes and explore psychosocial and interpersonal factors, particularly partner sexual dysfunction or relationship discord. Providers should also recognize that women have a wide range of responses to changes in sexual function with aging, highlighting the importance of assessing not only physical sexual function, but also overall sexual satisfaction.

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S-14.

TX-004HR Provides Robust Efficacy for Symptomatic Postmenopausal Vulvar and Vaginal Atrophy (VVA) while Providing Negligible to Very Low Systemic Absorption of Estradiol: Results of Clinical Phase 2 and 3 Trials

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Objective: Approximately 30M US women with symptomatic VVA remain untreated. This has been reported to be due in part to concerns about estrogen exposure and its perceived risks. TX-004HR (TherapeuticsMD, Inc., Boca Raton, FL) is an investigational, applicator-free, low-dose, vaginal softgel capsule containing solubilized 17β-estradiol (E2), designed to rapidly and effectively treat symptoms of VVA without increasing serum E2 levels while providing easy insertion and complete dissolution to minimize discharge. The current objective is to present data from the TX-004HR studies that demonstrate negligible to very low systemic E2 absorption with robust efficacy data. **Design:** The REJOICE Trial was a randomized, double-blind, placebo-controlled, phase 3 study of TX-004HR 4 μg, 10 μg, and 25 μg in postmenopausal women with a self-identified most bothersome symptom of moderate-to-severe dyspareunia. Treatments were self-administered once daily for 2 weeks then twice weekly for 10 weeks. Co-primary endpoints were change from baseline in vaginal superficial and parabasal cells, vaginal pH, and severity of dyspareunia at week 12 compared with placebo, and safety. Pharmacokinetic (PK) parameters were compared with placebo. Additionally, 2 single-dose, 2-way crossover, relative bioavailability trials compared the PK of TX-004HR with FDA/EMA approved vaginal E2 tablets (10 μg and 25 μg). Estradiol PK parameters evaluated in the 3 studies are reported here. **Results:** In the phase 3 trial, all doses of TX-004HR compared with placebo (MITT n=747) significantly improved the 4 co-primary endpoints at week 2 through week 12, as well as the secondary endpoints of vaginal dryness by week 6 and vulvar and/or vaginal itching or irritation by week 12 (except 4 μg, p=0.0503), and was well-tolerated with no treatment-related serious AEs reported. The phase 3 PK study (n=72) showed no difference in systemic E2 levels for 4 μg and 10 μg TX-004HR vs placebo, as measured by AUC and C_{avg} (Table 1). E2 AUC and C_{avg} with 25 μg TX-004HR was higher than placebo, but average concentrations remained within the normal postmenopausal range (Table 1). E2 levels at day 84 were similar to placebo indicating no systemic drug accumulation. SHBG concentrations did not change with treatment. The two phase 2 studies (n=36 for each) of TX-004HR 10 μg and 25 μg resulted in statistically significantly lower E2 absorption than an approved E2 tablet at identical doses, with 25 μg TX-004HR demonstrating AUC less than 1/3 that of the approved product (Table 2). **Conclusion:** With robust efficacy demonstrated as early as 2 weeks and up to 12 weeks at all 3 doses, TX-004HR 4 μg and 10 μg showed negligible systemic E2 absorption, while 25 μg resulted in very low systemic absorption of E2 in the phase 3 trial. TX-004HR 10 μg and 25 μg showed lower systemic E2 exposure than equivalent doses of an approved E2 tablet. The absence of clinically meaningful increases in E2 concentrations paired with data consistent with a lack of systemic effects (eg no increase in SHBG) suggests that TX-004 HR delivers excellent efficacy with negligible to very low systemic exposure and thus may warrant an adjustment of estrogen class labeling.

Sources of Funding: TherapeuticsMD

Table 1. Phase 3 study PK parameters for E2 (unadjusted mean±SD).

		$AUC_{0\text{-}24}$ (pg*hr/mL)			C_{avg} (pg/mL)		
Day	Dose (μg)	TX-004HR	Placebo	p-value	TX-004HR	Placebo	p-value
1	4	91.7±37.9	117±77.3	NS	3.92±1.46	4.86±3.22	NS
	10	138±75.2	117±77.3	NS	5.76±3.13	4.86±3.22	NS
	25	217±99.0	117±77.3	0.0021	9.06±4.13	4.86±3.22	0.0021
14	4	87.2±42.8	104±66.4	NS	3.63±1.78	4.34±2.77	NS
	10	110±54.6	104±66.4	NS	4.59±2.27	4.34±2.77	NS
	25	172±80.1	104±66.4	0.0108	7.15±3.34	4.34±2.77	0.0108

Table 2. Phase 2 studies PK parameters for E2 (baseline adjusted geometric mean).

	$AUC_{0\text{-}24}$ (pg*hr/mL)			C_{max} (pg/mL)		
Dose (μg)	TX-004HR	Vaginal Tablet	p-value	TX-004HR	Vaginal Tablet	p-value
10	49.62	132.92	<0.0001	14.38	20.38	0.0194
25	89.21	292.06	<0.0001	23.08	42.70	<0.0001