

# How Do Postmenopausal Women Describe Breast Pain and Breakthrough Bleeding Associated With Hormonal Treatments for Menopausal Symptoms: Qualitative Interviews With Postmenopausal Women in the USA, China, Mexico, and Italy

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## BACKGROUND

- Estrogen plus progestin therapy (EPT) represents the current standard of care for postmenopausal women with a uterus for the treatment of symptoms associated with menopause
- While estrogens have shown success for treating climacteric symptoms, the presence of progestin is necessary to prevent endometrial proliferation
- Progestins contained in EPT are associated with side effects such as breast pain/tenderness and vaginal bleeding/spotting<sup>1</sup>
- Vaginal bleeding/spotting and breast pain/tenderness are the most common reasons women permanently discontinue EPT and explain some of the observed decreases in overall quality of life scores when starting EPT<sup>2</sup>
- Clinical trials to evaluate hormonal treatments for menopausal symptoms should employ valid and reliable measures to assess these tolerability symptoms
- Such symptoms are best measured by direct patient report, since clinicians can only evaluate them by asking the patients themselves

## OBJECTIVE

- The objective of this study was to conduct qualitative interviews with postmenopausal women to better understand the patient experience of breast sensations and vaginal bleeding symptoms associated with EPT and the language patients use to describe them to inform the development of new measurement tools for these symptoms

## METHODS

### Study Sample

- 59 postmenopausal women taking EPT (aged 40-63 years) were interviewed in the USA (n = 14), China (n = 15), Mexico (n = 15), and Italy (n = 15; Table 1)

Table 1. Study Sample Characteristics

	USA (n = 14)	China (n = 15)	Mexico (n = 15)	Italy (n = 15)
Age of interviewee, y				
Mean	52	51	52	46
Min, Max	41, 61	41, 58	47, 63	40, 54
Any children, n (%)				
Yes	11 (79)	15 (100)	13 (87)	11 (73)
No	3 (21)	0	2 (13)	4 (27)
Highest education level, n (%) <sup>a</sup>				
Junior high	0	0	0	1 (7)
High school diploma or GED	5 (36)	6 (40)	3 (20)	6 (40)
Some years of college	4 (29)	0	2 (13)	0
Junior college degree	0	8 (53)	0	0
Certificate program	0	0	3 (20)	1 (7)
University/professional degree	5 (36)	1 (7)	6 (40)	7 (47)
Secretarial skills education	0	0	1 (7)	0
Work status, n (%)				
Working full- or part-time	12 (86)	7 (47)	14 (93)	14 (93)
Looking for work	1 (7)	0	0	0
Full-time homemaker	1 (7)	0	1 (7)	1 (7)
Retired	0	8 (53)	0	0

GED, general educational development.  
<sup>a</sup>Percentages may not total 100% due to rounding.

- Table 2 lists the licensed pharmacological treatments for menopausal symptoms being taken by the women during the study
- All women had experienced breast pain and/or vaginal bleeding/spotting due to EPT in the 4 weeks prior to the interview, with 47 women experiencing both symptoms

Table 2. Current Pharmacological Treatments for Menopausal Symptoms

Treatment, n (%)	USA (n = 14)	China (n = 15)	Mexico (n = 15)	Italy (n = 15)
CE (generic)	–	–	1 (7)	–
Prempro (CE & MPA)	3 (21)	–	–	–
Premarin (CE)	7 (50)	4 (27)	1 (7)	–
Sixdin (CE)	–	–	1 (7)	–
Estradiol – oral (generic)	2 (14)	6 (40)	–	1 (7)
Activella (estradiol & norethindrone)	1 (7)	–	–	–
EstroGel (estradiol topical)	1 (7)	–	–	–
Angeliq (estradiol & drospirenone)	–	–	7 (47)	5 (33)
Femoston (estradiol & dydrogesterone)	–	–	–	6 (40)
Estraderm (estradiol patch)	–	–	–	1 (7)
Qlaira (estradiol valerate & dienogest)	–	–	–	1 (7)
Binodian depot injection (dehydroepiandrosterone enanthate & estradiol valerate)	–	–	1 (7)	–
Climene (cyproterone acetate micronized & estradiol valerate micronized)	–	–	2 (13)	–
Totelle Continuo (estradiol hemihydrate & trimegestone)	–	–	1 (7)	–
Tibolone (generic)	–	–	1 (7)	–
Livial (tibolone)	–	3 (20)	1 (7)	–
Progesterone (generic)	–	3 (20)	–	–
Prometrium (progesterone)	–	–	–	1 (7)
Paroxetine (generic)	1 (7)	–	–	–
Dydrogesterone (generic)	–	–	–	1 (7)
Norethisterone (generic)	–	1 (7)	–	–
EPT (brand unknown)	–	–	–	1 (7)
Unspecified	–	–	–	3 (20)

CE, conjugated estrogens; MPA, medroxyprogesterone acetate; EPT, estrogen plus progestin therapy.

## Study Design

- Interviews began with open-ended questions about the participants' experiences of taking EPT, with follow-up probes to focus the discussion on the symptoms of breast pain/tenderness and vaginal bleeding/spotting due to EPT and any impact of these symptoms on health-related quality of life<sup>3</sup>
- All interviews were audio recorded, transcribed verbatim, and translated to English where necessary

## Analysis

- Thematic analysis<sup>4</sup> of verbatim transcripts was conducted to identify concepts describing the experiences of the participants using ATLAS.ti software<sup>5</sup>
- Items for new measurement tools were developed using this qualitative data at an international item generation meeting, with participants including interviewers from each country/language and clinical input from experts in menopause
- Interviews in non-English languages were analyzed in English, but the original language text was also retained, so that the exact terminology used in the original language was available during item generation

## RESULTS

- In all 4 countries, the breast sensations patients reported experiencing while taking EPT included 'pain and tenderness', 'breasts feeling swollen', and 'sensitivity of breasts and nipples to touch/contact'. Vaginal bleeding and spotting were commonly described in terms of frequency and severity. Both symptom groups impacted on psychological well-being, activities of daily living, and sex life<sup>3</sup>

### Breast Sensations Associated With Taking EPT

- The conceptual framework showing the 3 key breast sensations described by women are shown in Figure 1

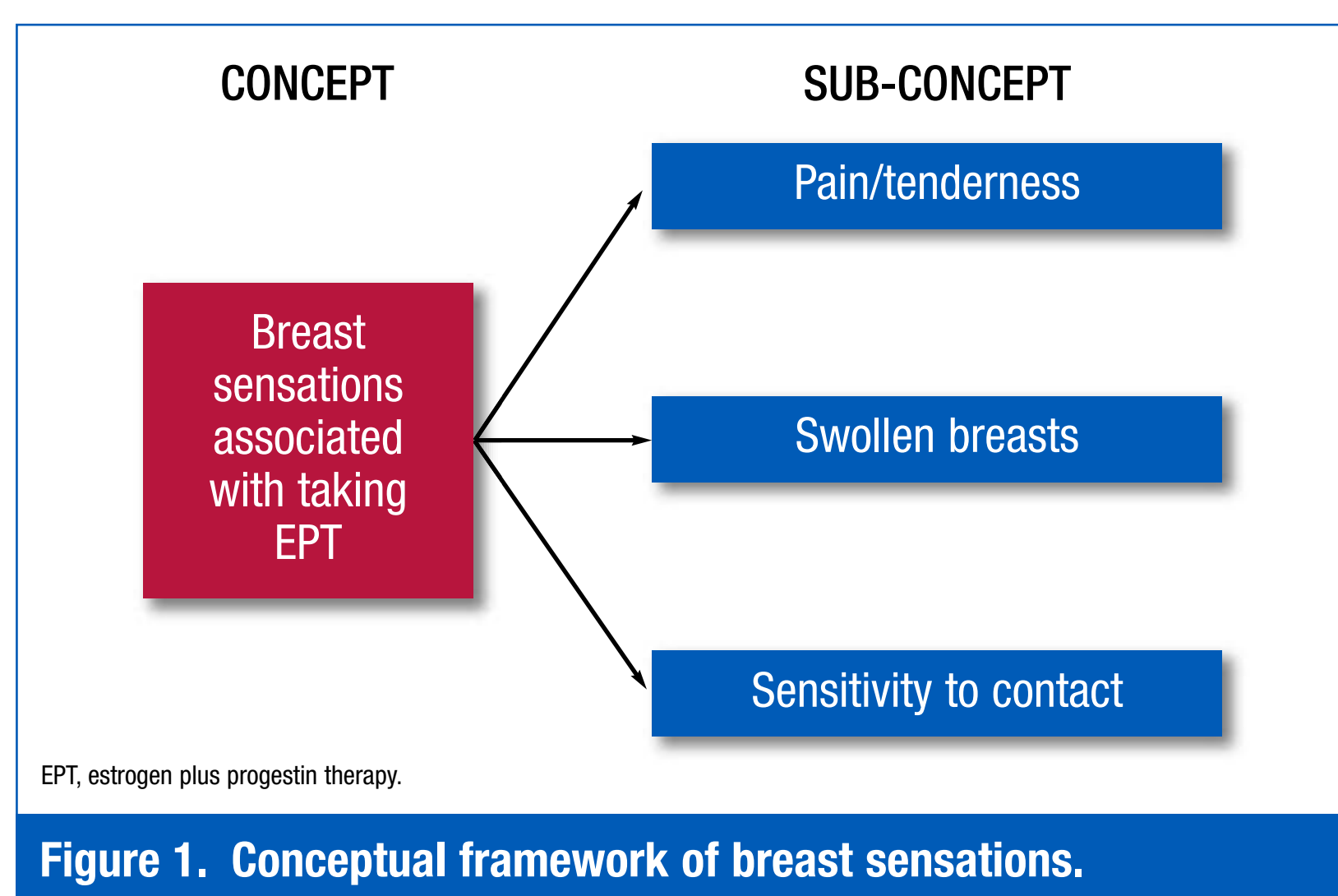


Figure 1. Conceptual framework of breast sensations.

### Pain/tenderness

Breast pain was reported by 53 patients across all 4 countries, and breast tenderness was experienced by 13 patients in the USA and China. There is no equivalent term for 'tenderness' in the Italian and Mexican Spanish languages; the nearest term literally translates back to US English as 'sensitivity' and conceptually as 'affectionate'

Severity of breast pain/tenderness was described by patients as 'light', 'mild', 'moderate', or 'severe'. For those women who used the term 'tenderness', the data suggested that this term was used to describe a mild sensation of pain and can therefore be considered to be part of a continuum of pain. Only 1 patient (in the USA) specifically stated that her experience of 'breast tenderness' was not painful. Therefore, tenderness was described as mild pain

When asked to describe their breast pain and/or tenderness, women spoke of a **dull ache**: "I felt there's some dull pain inside"; a **squeezing feeling**: "It's like they're being squished"; a **burning sensation**: "It just gets tender, sore and very warm up in here"; a **sharp pain**: "If I had to get a little bang... a stabbing pain"; or **tingling/prickling pain**: "It's like a little tingling, and it seems like the nipples are trying to push in, shrink"

However, there was not a great deal of consistency in what terms patients used, and each specific descriptor was only used by a relatively small subgroup of women, or by women in a particular country. For example, only women in the USA and Mexico described their pain as a 'burning' (n = 6) or 'tingling/prickling' (n = 4) sensation, and only women in the USA and China described their pain as 'squeezing/pinching' (n = 6)

### Swollen breasts

In addition to pain and tenderness, women described their breasts as feeling swollen: "Sometimes I can feel breast swelling." Other descriptors used to convey this feeling included breasts feeling 'heavy' or 'hard'

20 patients in all 4 countries discussed this symptom suggesting that it is an important sensation, in addition to pain and tenderness, for women taking EPT

### Sensitivity to contact

Women also described their breasts feeling sensitive when hugging, being touched, when washing, when clothes rubbed against them, or when they bumped into objects: "To the touch they're just sensitive. Sensitive like feeling like they're filled with water. And it's not enjoyable having them touched"

22 patients across all 4 countries described experiencing this sensation as part of their EPT experience

20 patients reported that their whole breast felt sensitive, while 2 reported that the sensitivity was around or on the nipple: "It's nipples, nipples are really sensitive, so sensitive that if I touch them, it bothers me; it is an excessive sensitivity that bothers"

### Frequency and duration of breast sensations

Frequency of breast pain/tenderness and sensitivity was described by patients as 'constant', 'daily', or 'occasionally'

Patients also talked about how long their breast sensations lasted, with statements ranging from 'less than 30 minutes' to 'up to 1 week'

### Triggers/exacerbating factors

Women described a number of things that could either trigger or make breast sensations worse. These included **touch**: "I had told her [doctor] once and again that they are untouchable... I simply couldn't tolerate it"; **movement**: "When I bend forward to tie my shoes"; **lying down**: "Mostly when I lay down, but as the day goes by it is as if it goes away, but then at night the pain returns again"; **clothing**: "I even don't wear a bra because, well, I can't stand it"; and **washing**: "I feel it more generally when I am taking a shower"

### Bleeding Symptoms Associated With Taking EPT

- The conceptual framework showing vaginal bleeding/spotting symptoms are shown in Figure 2

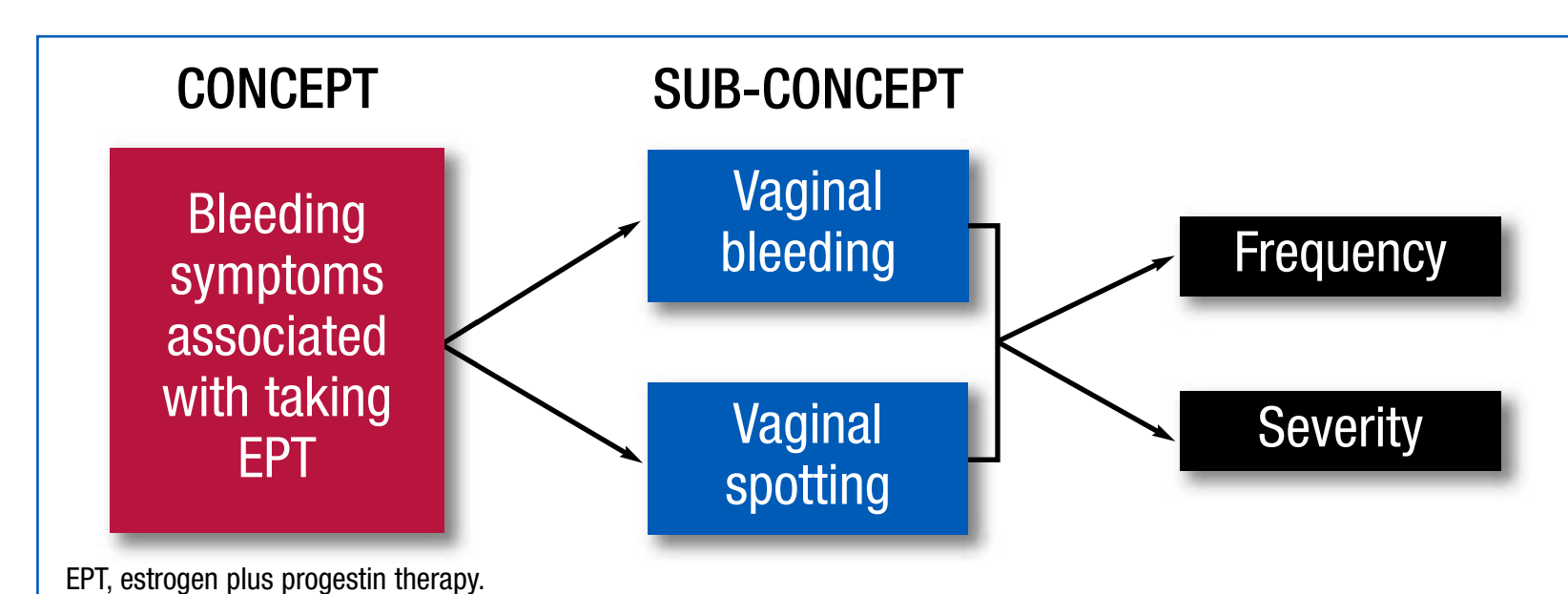


Figure 2. Conceptual framework of vaginal bleeding/spotting.

### Vaginal bleeding

Vaginal bleeding was described by 28 patients in all 4 countries

Severity: The main difference in the way women differentiated bleeding from spotting was in terms of severity and the amount of blood: "Bleeding is when you feel you have your period... Something more than a panty-liner to collect the blood. Something that actually saturates you, a saturation if you will"

Thus, bleeding was described by women as requiring the use of sanitary protection: "Bleeding is like you're going through a couple tampons a day"

Frequency: Women described experiencing bleeding 'daily', 'monthly', 'occasionally', or 'irregularly': "Sometimes I get it within a 2-week span of having it the last time. Sometimes it could be a 6-week span"

### Vaginal spotting

Vaginal spotting was described by 50 patients in all 4 countries

Severity: Women considered vaginal bleeding to be 'spotting' when bleeding was very light and when there were only small amounts of blood: "You might only get one little spot in your underwear, and then you might get 5 or 6," or "Spotting is where you could put a pad in and you would never fill the pad up"

Women would not necessarily use sanitary protection when spotting, although many wore panty-liners as this helped to feel 'clean' or 'fresh', or was a preventive measure to avoid staining underwear: "Since I always wear a panty-liner anyway, I just changed it, put a new one on and that's it, but it is just a preventive measure." As spotting is frequently defined as vaginal bleeding not requiring sanitary protection, this suggests that any definition should be updated to allow for the use of panty-liners

Frequency: Like bleeding, spotting could occur 'weekly', 'monthly', 'occasionally', and 'irregularly', and could last anywhere from 1 to 8 days: "It's scary. And it's like so sporadic. And you don't know if it's ever going to stop or if it's going to come again"

## CONCLUSIONS

- In-depth interviews with a geographically diverse sample elicited common descriptors for the breast sensations and vaginal bleeding symptoms associated with EPT and allowed items to be developed that are applicable across cultures, conceptually consistent, and easily translated
- Accurately capturing descriptors used by patients is critical to ensure new outcome tools have content validity

### References

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