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Adjuvant endocrine therapy for premenopausal women with breast cancer: Patient adherence and physician prescribing practices in Mexico

Cynthia Villarreal-Garza [a, b, *, 1], Fernanda Mesa-Chavez [a, b, 1], Ana S. Ferrigno [a, b], Cynthia De la Garza-Ramos [a, b], Alan Fonseca [b, c], Karen Villanueva-Tamez [a], Jose Y. Campos-Salgado [c], Marlid Cruz-Ramos [b, c], David O. Rodriguez-Gomez [a], Sandy Ruiz-Cruz [c], Paula Cabrera-Galeana [c]

[a] Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, Batallon de San Patricio 112, San Pedro Garza Garcia, Nuevo Leon, 66278, Mexico
[b] Joven & Fuerte: Programa para la Atencion e Investigacion de Mujeres Jovenes con Cancer de Mama en Mexico, Holbein 227, Int 210AB, Cd. de los Deportes, Mexico City, 03720, Mexico
[c] Departamento de Tumores Mamarios e Investigacion, Instituto Nacional de Cancerologia, San Fernando 22, Belisario Dominguez Secc 16, Tlalpan, Mexico City, 14080, Mexico

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ABSTRACT

Background: In resource-constrained settings, data regarding breast cancer patients' adherence to endocrine therapy (ET) and physicians' prescribing practices is limited. This study aims to decrease this knowledge gap in a real-world clinical practice.
Methods: Premenopausal women with stage 0-III hormone-sensitive breast cancer and receiving adjuvant ET during the past 1–5 years were identified in three Mexican referral centers. Participants' self-reported ET compliance, clinicopathologic characteristics, ET-related knowledge and beliefs, experienced adverse effects, social support, and patient-physician relationships were evaluated. Physician ET prescribing practices were compared with the gold standard according to international and national guidelines to assess clinicians' adherence to standard-of-care prescription.
Results: In total, 95/132 (72%) and 35/132 (27%) participants reported complete and acceptable adherence, respectively. Incomplete adherence was mainly attributed to forgetfulness, adverse effects, and unwillingness to take ET. Being employed/studying ($p = 0.042$), worrying about long-term ET use ($p = 0.031$), and experiencing >7 ET-related symptoms ($p = 0.018$) were associated with incomplete adherence. Guideline-endorsed regimens were prescribed in 84/132 (64%) patients, while the rest should have undergone ovarian function suppression (OFS) but instead received tamoxifen monotherapy.
Conclusions: Premenopausal Mexican women self-report remarkably high rates of adequate ET adherence. However, a considerable proportion misses ≥1 doses/month, usually because of forgetfulness. Notably, only 64% receive standard-of-care ET due to suboptimal prescription of OFS. Interventions that remind patients to take their ET, refine physicians' knowledge on the importance of OFS in high-risk patients, and increase access to OFS could prove pivotal to enhance optimal ET implementation and adherence, which could translate into improved patient outcomes.

1. Introduction

Hormone receptor-positive (HR+) tumors account for approximately 70% of all breast cancer (BC) cases [1,2]. To decrease HR+ BC recurrence risk, current guidelines by the American Society of Clinical Oncology, European School of Oncology-European Society

* Corresponding author. Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, Batallon de San Patricio 112, 14th Floor, Real de San Agustin, San Pedro Garza Garcia, Nuevo Leon, 66278, Mexico.
E-mail addresses: cynthia.villarreal@tecsalud.mx, cynthiavg@gmail.com (C. Villarreal-Garza), drafernandamesa@gmail.com (F. Mesa-Chavez).
[1] These authors contributed equally to this work.

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for Medical Oncology, and National Comprehensive Cancer Network recommend adjuvant endocrine therapy (ET) with tamoxifen or aromatase inhibitors (AI) for 5–10 years, with or without ovarian function suppression (OFS) [3–6]. Moreover, results from the SOFT-TEXT trials have proved that ET with OFS improves both disease-free survival and overall survival in premenopausal patients [7–10].

Despite the well-documented benefits of ET, previous studies have found suboptimal adherence to this treatment in 31–73% of BC patients [11–15]. ET nonadherence can be particularly high among premenopausal women, with early interruption rates of up to 42% [8,14,16,17]. The high percentage of inadequate adherence to ET in this group is multifactorial, potentially associated with age-specific adverse effects, lack of understandable information about ET, poor-quality patient-physician relationships, and inadequate social support [16,18]. Moreover, the increasing use of OFS in young patients may lead to even lower adherence rates due to the high frequency of adverse effects related to this treatment strategy. Suboptimal adherence may hinder the benefits of adjuvant ET; this behavior has been associated with inferior levels of quality of life, higher medical costs and, most importantly, increased risk of BC recurrence and all-cause mortality [14,17,19–22].

In addition to patients' adherence, another aspect that warrants consideration when exploring the current use of ET is physicians' prescribing practices. Although clinical practice guidelines provide recommendations for treatment decisions, physicians must ultimately tailor ET prescriptions for each patient and the selection of the best strategy may be challenging in certain cases [23,24]. Factors beyond disease characteristics and recurrence risk must be taken into account, including patient preferences, comorbidities, fertility considerations, and financial limitations to access particular treatment modalities. Moreover, guideline uptake and adherence have been reported to be suboptimal, mainly due to physicians' lack of awareness of the current gold standard or resistance to change their practice [25–27]. These factors could contribute to variability in treatment selection, which may result in the underutilization of standard-of-care ET regimens and prevent patients from obtaining the full benefits of the optimal treatment modality.

In resource-constrained settings such as Mexico, there is limited data on premenopausal patients' compliance with ET, as well as the factors that influence suboptimal adherence. Likewise, there is no information in the literature regarding physicians' adherence to guideline-endorsed ET strategies. Thus, this study aims to compare the ET prescribed to premenopausal BC patients with the definite treatment taken by patients to characterize compliance behaviors and detect areas that may be targeted to promote optimal adherence. Patients' ET-related knowledge and beliefs, social support, experienced adverse effects, and perceived patient-physician relationships are explored. A comparison between physician practices and the gold-standard ET according to international and national guidelines is also made with the intent of evaluating clinicians' adherence to standard-of-care ET prescription in a real-world clinical setting.

2. Methods

2.1. Study design

This cross-sectional study was carried out between September 2019 and February 2020. Eligible patients were premenopausal women with stage 0-III HR+ BC, aged ≤50 years at diagnosis, who were currently receiving adjuvant ET that had been prescribed 1–5 years prior to inclusion. Patients were consecutively identified and invited to participate during their follow-up consultations in the medical or surgical oncology departments of three BC referral centers in Nuevo Leon and Mexico City, with public and private healthcare coverage representation.

Upon recruitment, patients completed an initial survey with the aid of a clinical researcher to ascertain their awareness regarding their prescribed ET (specific medications, OFS use, planned treatment duration, and regimen modifications). Participants then independently answered a questionnaire exploring sociodemographic characteristics, attitudes towards ET, self-reported adherence, experienced adverse effects, as well as their perception of their patient-physician relationship. Patients' self-reported compliance to ET during the last month was documented, defining complete and acceptable adherence as taking the medication 100% and ≥80% of days, respectively, in accordance with previous reports [12,20,21,28]. Treatment interruption was defined as ET discontinuation for ≥2 consecutive months [29,30]. This questionnaire was constructed based on selected questions from previously published surveys evaluating ET adherence and associated factors [12,16,31–34]. An initial version of the questionnaire was piloted with 10 patients to ensure all items were understandable and appropriate modifications were made according to patients' feedback.

Data on each patient's clinicopathological characteristics, prescribed oncological treatment, and premenopausal status were collected directly from their medical records by the research team. Subsequently, two BC oncologists independently determined the gold-standard ET regimen for each patient according to international and national guidelines, as well as local guidelines [3–5,35]. OFS plus tamoxifen/AI was considered standard-of-care when patients: were <35 years old, had lymph node involvement, or had ≥2 high-risk characteristics such as tumor size >2 cm, high histologic grade, or high Ki67 [3–5,35,36]. Given that the indication for adding OFS is inconclusive in some cases, when patients were >35 years, had node-negative disease and only one of the above-mentioned high-risk features, either OFS-including regimens or tamoxifen monotherapy was considered appropriate.

2.2. Statistical analysis

Descriptive statistics were used to analyze participants' sociodemographic and clinicopathologic characteristics, prescribed ET, self-reported adherence and attitudes to ET, adverse effects, and perceived patient-physician relationship. Absolute and relative frequencies were used for categorical variables, and medians and ranges, for continuous variables.

Chi-squared and Fisher's exact tests were used to explore associations between nonadherence and patients' sociodemographic characteristics, prescribed ET, attitudes towards ET, experienced adverse effects, or perception of the patient-physician relationship. Associations between the prescription of the gold-standard ET and physicians' specialty, and GnRH analogs (GnRHa) prescription according to their healthcare coverage were also assessed using these methods. A two-tailed p-value <0.05 was considered significant. Statistical analysis was performed using SPSS Statistics, version 27 (IBM Corp).

3. Results

3.1. Patient characteristics

Of 186 patients who met inclusion criteria, 132 (71%) agreed to participate and were analyzed. Median age was 45 years (range: 25–52) at study entry and 42 years (range: 23–49) at BC diagnosis. Most patients had completed at least high school (65%), were unemployed/housewives (60%), were in a relationship (78%), and had

public healthcare insurance (82%) (Table 1).

Regarding BC diagnosis and treatment, 102 (77%) patients presented with stage II (39%) and III (39%) disease; 105 (80%) had HR+/HER2- BC; 102 (77%) had received chemotherapy; and 22 (17%) had been or were being treated with anti-HER2 therapy. ET consisted of tamoxifen monotherapy in 93 (71%) cases; AI plus OFS with GnRHa or oophorectomy in 29 (22%); and tamoxifen plus OFS with GnRHa or oophorectomy in 10 (8%). Ninety-two (70%) patients were prescribed ET by a medical oncologist; the remaining 40 (30%), by a surgical oncologist. At the time of the survey, participants had received ET for 1–2 (35%), 2–3 (28%), or 3–5 (37%) years.

3.2. Patient attitudes and adherence to ET

Overall, 130 (98%) patients self-reported ≥80% adherence to ET. All 28 (100%) patients who were prescribed GnRHa claimed complete adherence to these agents. Regarding oral ET, 124 (94%) patients initially reported complete adherence: 95/103 to tamoxifen and 29/29 to AI. Nonetheless, when asked specifically about the number of missed doses of oral ET during the last 31 days, 28 of them acknowledged missing 1–6 doses and 1 declared not taking the oral ET altogether in the last month. Therefore, 95 (72%) patients had complete adherence, 35 (27%) acceptable adherence, and 2 (2%) inadequate adherence. Additionally, 3 (2%) patients had interrupted their oral ET for ≥2 months at some point, but none declared having suspended it definitely. Complete adherence rates did not differ significantly according to treatment with tamoxifen monotherapy or other ET strategies (69% vs. 79%; $p = 0.213$). Among those who did not take oral ET every day (n = 37), the most cited reasons were forgetfulness ($n = 28$, 76%), adverse effects ($n = 7$, 19%), and unwillingness to take the medication ($n = 4$, 11%). Table 2 details patients' answers to items exploring ET adherence.

ET-related adverse effects were reported by 130 (98%) patients, mainly hot flashes (82%), arthralgias (62%), fatigue (60%), vaginal dryness (58%), insomnia (56%), and headache (51%). A median of 7 (range: 0–13) types of ET-related adverse effects was reported by a given patient at any time. Complete adherence was significantly different between patients who had experienced ≤7 types of side effects and those who reported >7 (80% vs. 61%; $p = 0.018$). As disclosed in Table 3, a significant association was found between the type of ET and a higher frequency of hot flashes ($p = 0.029$), fluid retention ($p = 0.026$), decreased libido ($p = 0.003$), vaginal dryness ($p = 0.002$), and dyspareunia ($p = 0.001$). A higher proportion of patients who received tamoxifen plus OFS or AI plus OFS experienced hot flashes and fluid retention than those with tamoxifen monotherapy, while a greater rate of those treated with AI plus OFS experienced the latter three symptoms. Twenty (15%) patients did not recall their physician having explained the possible adverse effects of ET. Of the 98 patients who reported current side effects, 75 (77%) claimed their physician had taken measures to reduce these symptoms.

As for participants' awareness and beliefs concerning ET, 19 (14%) did not know their cancer had to be treated with ET, yet 128 (97%) believed ET reduced their BC recurrence risk. Fifty-two (39%) patients were worried about the long-term use of ET, mainly due to fear of experiencing harmful effects ($n = 13$, 10%), intensified or long-standing adverse effects in general ($n = 11$, 8%), decreased bone mineral density/osteoporosis ($n = 7$, 5%), increased endometrial cancer risk ($n = 3$, 2%), and vascular complications ($n = 3$, 2%). Patients who did not report any concern regarding the long-term use of ET more commonly claimed complete adherence to this treatment (79% vs. 62%; $p = 0.031$).

General aspects of patient-physician communication were also assessed. Overall, 127 (96%) patients considered that they had a good patient-physician relationship. Nearly all ($n = 130$, 98%)

Table 1
Patients' sociodemographic and clinicopathologic characteristics.

Characteristic	N = 132 (100%)
Age at ET initiation	
<35 years	15 (11.4)
≥35 years	117 (88.6)
Educational attainment	
<High school	46 (34.8)
≥High school	86 (65.2)
Occupation	
Unemployed/Housewife	79 (59.8)
Employed/Student	53 (40.2)
Relationship status	
Partnered	103 (78.0)
Unpartnered	29 (22.0)
Perceived partner support regarding ET	
I always have my partner's support	79 (59.8)
I sometimes have my partner's support	17 (12.9)
Most of the time, I do not have my partner's support	2 (1.5)
I definitely do not have my partner's support	5 (3.8)
I do not have a partner	29 (22.0)
Social support network	
Yes	96 (72.7)
No	36 (27.3)
Number of children	
0	18 (13.6)
1–2	68 (51.5)
≥3	46 (34.8)
Medical affiliation	
Public insurance	108 (81.8)
Private insurance	24 (18.2)
Treating center	
Instituto Nacional de Cancerologia, Mexico City	62 (47.0)
Hospital San Jose, Nuevo Leon	46 (34.8)
Hospital Zambrano Hellion, Nuevo Leon	24 (18.2)
ET coverage	
Complete coverage by public health insurance	101 (76.5)
Complete coverage by private health insurance	13 (9.8)
Complete coverage by the patient	14 (10.6)
Partial coverage by the patient	4 (3.0)
Perceived financial status	
Enough money for extra expenses	13 (9.8)
Little money for extra expenses	37 (28.0)
Money only to cover necessary expenses	47 (35.6)
Not enough money to cover necessary expenses	35 (26.5)
Clinical stage	
0	5 (3.8)
I	25 (18.9)
II	51 (38.6)
III	51 (38.6)
Tumor size	
Tis	5 (3.8)
T1	39 (29.5)
≥T2	88 (66.7)
Nodal status	
N0	47 (35.6)
≥N1	85 (64.4)
Breast cancer subtype	
HR+/HER2-	105 (79.5)
HR+/HER2+	25 (18.9)
HR+/HER2 unknown	2 (1.5)
Histological grade	
1	22 (16.7)
2	51 (38.6)
3	29 (22.0)
Not documented	30 (22.7)
Ki67	
<20%	46 (34.8)
≥20%	59 (44.7)
Not documented	27 (20.5)
ET	
Tamoxifen	93 (70.5)
AI + OFS	29 (22.0)
Tamoxifen + OFS	10 (7.6)
Time since ET initiation	
1–2 years	46 (34.8)
2–3 years	37 (28.0)

Table 1 (*continued*)

Characteristic	N = 132 (100%)
3–4 years	25 (18.9)
4–5 years	24 (18.2)

ET: endocrine therapy; HR: hormone receptor; AI: aromatase inhibitor; OFS: ovarian function suppression.

Table 2
Patients' adherence to ET.

Questions and answers	N = 132 (100%)
Do you take your oral ET every day?	
Yes	124 (93.9)
No	8 (6.1)
How many doses of your oral ET have you missed in the last month (31 days)?	
0 (100% adherent)	95 (72.0)
1–6 (80–99% adherent)	35 (26.5)
7–31 (<80% adherent)	2 (1.5)
What were the main reasons you did not take your oral ET every day? * **(n=37)**	
I forgot to take it	28 (75.7)
It makes me experience side effects	7 (18.9)
I did not want to take it	4 (10.8)
It reminds me that I have an illness	3 (8.1)
It was not available in the drugstore	3 (8.1)
I lack financial resources/healthcare coverage to obtain it	3 (8.1)
Have you interrupted your oral ET for ≥2 months?	
Yes	3 (2.3)
No	129 (97.7)

ET: endocrine therapy.
*More than one answer allowed.

participants indicated that their physician had explained why ET was a necessary part of their treatment. Yet, 6 (5%) reported that the information had not been understandable, 17 (13%) considered they had not received sufficient information, 11 (8%) believed their physician had not dedicated enough time to explain ET to them, and 16 (12%) claimed their physician had not given them the opportunity to ask questions regarding ET.

The only sociodemographic characteristic associated with ET adherence was occupation, as unemployed patients were more likely to report daily compliance than students/employees (78% vs. 62%; $p = 0.042$). No significant differences in adherence were found according to other variables, including age, educational level, number of children, relationship status, perceived partner support, social support network, perceived financial status, type of ET, specialty of the prescribing physician, time taking ET, insurance coverage of ET, clinical stage, node involvement, reception of chemotherapy, treatment with anti-HER2 therapy, specific adverse effects, or perception of the patient-physician relationship (Table 4).

3.3. Physician ET prescribing practices

According to national and international guidelines on the treatment of choice for each particular case, 96 (73%) patients should have undergone OFS as part of their ET regimen, while the remaining 36 (27%) could have been treated with tamoxifen monotherapy. The gold standard was recommended in 84 (64%) cases; the remaining 48 (36%) should have undergone OFS but instead were prescribed tamoxifen only. Of note, all patients who received AI also underwent OFS. Guideline-endorsed ET was recommended to 61/92 (66%) patients who were treated by medical oncologists and to 23/40 (58%) of those treated by surgical oncologists (p=0.334). Reasons for which physicians did not prescribe OFS when it was part of the treatment of choice were only documented in 8/48 (17%) of such cases: physicians' consideration that OFS was not a necessary part of the patient's ET ($n = 5$) and patients' lack of financial resources to afford OFS ($n = 3$).

When gold-standard ET included OFS, GnRHa were covered by patients' health insurance in 65/96 (68%) cases; the remaining 31/96 (32%) were required to pay out-of-pocket. Overall, 30/65 (46%) who had insurance coverage were prescribed this treatment modality, compared to 9/31 (29%) who had to obtain GnRHa outside of their insurance plan ($p = 0.110$). In 10 (8%) patients, all ≤41 years, oophorectomy was recommended as an OFS alternative due to their limited financial access to GnRHa, yet only five of them had undergone the procedure by the time of their inclusion to this study. Of note, oophorectomy is frequently paid out-of-pocket by patients but represents a smaller expense when compared to prolonged GnRHa treatment in our setting.

4. Discussion

This study identified a remarkably high self-reported adherence to adjuvant ET among premenopausal BC patients in Mexico. However, the findings also suggest that guideline-endorsed ET is prescribed to a suboptimal proportion of patients in this population.

The vast majority (98%) of participants reported ≥80% adherence to oral ET. These results are in agreement with those documented in several other studies including both pre- and postmenopausal BC patients, where 88–99% had adequate self-reported adherence to tamoxifen or AI [12,37–39]. Moreover, this proportion compares favorably to other studies evaluating young

Table 3
Patient-reported side effects according to the type of ET.

Side effects	Tamoxifen monotherapy (n = 93)	Tamoxifen + OFS (n = 10)	AI + OFS (n = 29)	*p*-value
Hot flashes	70 (75.3)	10 (100)	27 (93.1)	**0.029**
Arthralgias	53 (57.0)	6 (60.0)	21 (72.4)	0.332
Fatigue	51 (54.8)	5 (50.0)	22 (75.9)	0.110
Menstrual cycle alterations	47 (50.5)	5 (50.0)	13 (44.8)	0.865
Insomnia	46 (49.5)	7 (70.0)	20 (69.0)	0.114
Vaginal dryness	45 (48.4)	6 (60.0)	25 (86.2)	**0.002**
Headache	41 (44.1)	7 (70.0)	18 (62.1)	0.101
Weight gain	41 (44.1)	4 (40.0)	14 (48.3)	0.881
Decreased libido	39 (41.9)	3 (30.0)	22 (75.9)	**0.003**
Vision problems	39 (41.9)	4 (40.0)	12 (41.4)	0.992
Anxiety or nervousness	38 (40.9)	6 (60.0)	16 (55.2)	0.253
Dyspareunia	30 (32.3)	2 (20.0)	20 (69.0)	**0.001**
Gastrointestinal symptoms	23 (24.7)	5 (50.0)	13 (44.8)	0.050
Fluid retention	14 (15.1)	4 (40.0)	10 (34.5)	**0.026**

OFS: ovarian function suppression; AI: aromatase inhibitor.

Table 4
Factors associated with ET adherence.

Factor	Complete adherence (n = 95)	Incomplete adherence (n = 37)	*p*-value
Age at diagnosis			
≤40 years	43 (45.3)	17 (45.9)	
>40 years	52 (54.7)	20 (54.1)	0.944
Educational level			
<High school	32 (33.7)	14 (37.8)	
≥High school	63 (66.3)	23 (62.2)	0.653
Occupation			
Student/Employee	33 (34.7)	20 (54.1)	
Unemployed	62 (65.3)	17 (45.9)	**0.042**
Number of children			
0–2	63 (66.3)	23 (62.2)	
≥3	32 (33.7)	14 (37.8)	0.653
Relationship status			
Partnered	74 (77.9)	29 (78.4)	
Unpartnered	21 (22.1)	8 (21.6)	0.952
Perceived partner support regarding ET			
Always	57 (60.0)	22 (59.5)	
Not always/No partner	38 (40.0)	15 (40.5)	0.955
Social support network			
Yes	65 (68.4)	31 (83.8)	
No	30 (31.6)	6 (16.2)	0.075
Perceived financial status			
Enough or little money for extra expenses	35 (36.8)	15 (40.5)	
Money only to cover necessary expenses	37 (38.9)	10 (27.0)	
Not enough money to cover necessary expenses	23 (24.2)	12 (32.4)	0.399
Type of ET			
Tamoxifen monotherapy	64 (67.4)	29 (78.4)	
Tamoxifen + OFS	8 (8.4)	2 (5.4)	
AI + OFS	23 (24.2)	6 (16.2)	0.460
Prescribing physician			
Medical oncologist	66 (69.5)	26 (70.3)	
Surgical oncologist	29 (30.5)	11 (29.7)	0.929
Time since ET initiation			
1–2 years	37 (38.9)	9 (24.3)	
2–3 years	24 (25.3)	13 (35.1)	
>3 years	34 (35.8)	15 (40.5)	0.256
ET coverage			
Complete coverage by health insurance	83 (87.4)	31 (83.8)	
Partial or complete coverage by the patient	12 (12.6)	6 (16.2)	0.590
Clinical stage			
0-I	23 (24.2)	7 (18.9)	
II	38 (40.0)	13 (35.1)	
III	34 (35.8)	17 (45.9)	0.548
Node involvement			
Yes	61 (64.2)	24 (64.9)	
No	34 (35.8)	13 (35.1)	0.944
Chemotherapy			
Yes	73 (76.8)	29 (78.4)	
No	22 (23.2)	8 (21.6)	0.850
Anti-HER2 therapy			
Yes	15 (15.8)	7 (18.9)	
No	80 (84.2)	30 (81.1)	0.665
Number of ever-experienced adverse effects			
≤7	60 (63.2)	15 (40.5)	
>7	35 (36.8)	22 (59.5)	**0.018**
Worries or concerns regarding ET			
Yes	32 (33.7)	20 (54.1)	
No	63 (66.3)	17 (45.9)	**0.031**
Good patient-physician relationship			
Yes	92 (96.8)	35 (94.6)	
No	3 (3.2)	2 (5.4)	0.920

ET: endocrine therapy; OFS: ovarian function suppression; AI: aromatase inhibitor.

and premenopausal BC patients that found a 70% ET adherence rate [40,41], and is slightly higher when compared to the SOFT-TEXT trials, where 75–89% of patients <35 years and 79–91% of those ≥35 years were adherent [36].

Furthermore, only 3 (2%) patients in this study reported an interruption of ET at any point during their treatment. This finding contrasts with those of two studies among women aged ≤40 in high-income countries, in which tamoxifen interruption occurred in 42% of patients during the first two years of treatment [16], and in 17–50% during the first five years of treatment [18].

As for GnRHa, all participants undergoing this treatment modality reported complete adherence. This optimal compliance compares favorably to the SOFT-TEXT trials, in which nonadherence to GnRHa ranged from 15 to 23% in women <35 years and from 8 to 17% in those ≥35 years [36]. In agreement with the present results, a recent report concluded that OFS in young patients was not

associated with lower ET adherence [41].

Previous reports have found a higher risk of nonadherence among younger women, particularly those aged <40 [14,15,17,42,43]. However, this study found an unexpectedly high proportion of adherent young patients. In line with what has been identified in other studies, possible contributors to this sample's high adherence rate include patients' awareness of the need for ET as part of their treatment and its central role in reducing their BC recurrence risk [44], their perception of having high-quality patient-physician relationships [31,38,44–46], and having received management for ET-related side effects in most cases [19].

Similar to previous studies, the most prevalent reasons for suboptimal adherence to ET in this population were forgetfulness, adverse effects, and unwillingness to take the medication [12,37,47,48]. Complete adherence was significantly more common in unemployed patients than in students/employees, who might have more daily activities to fulfill and may therefore be more likely to forget to take their medication. Likewise, complete adherence was more frequent among those who had no concerns regarding the long-term use of ET. Of note, patients' most common worries were related to the perceived harm of ET and fear of experiencing adverse effects, similar to what has been previously reported [19]. Therefore, devoting sufficient time to inform patients on the possible ET-related adverse effects, resolving questions or concerns raised during the office visit, offering take-home educational material to reinforce information, and ensuring that side effects are addressed might prove efficacious to decrease patients' worries regarding ET and thereby improve their adherence.

Interestingly, a significant association was found between the type of ET and certain adverse effects. The presence of these specific symptoms did not correlate with nonadherence. However, patients who had experienced more types of adverse effects had lower rates of complete adherence. In addition, it should be noted that most participants were in the first years of ET and, if not addressed appropriately, experiencing persistent burdensome adverse effects could lead to a higher risk of nonadherence over time [16,19,49,50].

Regarding physicians' ET prescribing practices, gold-standard treatment was only recommended in 64% of cases. This proportion displays considerable discrepancy in physicians' perceptions about the ET of choice for premenopausal women and demands further exploration. In the context of our population, a possible cause for this phenomenon may be physicians' consciousness of patients' limited access to expensive treatment with GnRHa for OFS, which are not routinely covered by Mexican public health insurance schemes. Similarly, oncologists in another Latin American study expressed that patients' ET schemes are prescribed according to their insurance plans, which sometimes limit the available treatment options [51]. Another reason may be that, besides medical oncologists, other specialists such as breast surgeons and gynecological oncologists also prescribe ET and provide follow-up to BC patients. Noteworthy, in a previous study, ET initiation was more likely among patients treated by a medical oncologist rather than a surgeon, suggesting that the former may be more aware of ET prescription recommendations [52]. Thus, the present finding that guideline-endorsed regimens were prescribed more frequently by medical than by surgical oncologists highlights the need to increase physicians' knowledge of national and international recommendations for ET in premenopausal patients.

This study has some limitations that should be considered. A selection bias cannot be excluded as nonadherent patients might be less likely to attend their medical appointments and be invited to participate in this study, possibly leading to an underestimation of the prevalence of nonadherence and its contributing factors. Moreover, the reasons why some patients refused to participate are unknown. Additionally, as a result of recall bias or social desirability bias, patient self-report can considerably overestimate adherence rates in comparison with other methods such as electronic pill caps, serum assessments or pharmacy records [39,53–55]. Nonetheless, these strategies were not feasible due to this study's multicentric nature and the participants' diverse healthcare insurance policies, which entailed different medication sources. Another limitation that should be taken into account is the use of a non-validated questionnaire, which hinders direct comparisons with other series. Moreover, a limited number of patients from only three centers were included, restricting the generalizability of results. Importantly, overall adherence for the total planned duration of ET cannot be determined as most participants had received ET for 1–3 years; however, no significant differences were found according to the time since ET initiation. Notwithstanding, among its main strengths, this study includes patients from major BC referral institutions in the country that offer services to the public and private healthcare sectors. Thereby, the results could provide valuable information regarding ET adherence and beliefs among Mexican patients. Furthermore, to our knowledge, this is one of the limited number of studies exploring premenopausal patients' ET adherence, and it is the first to assess physicians' prescribing practices in this population.

5. Conclusions

Premenopausal BC patients in Mexico self-report remarkably high rates of ET adherence. However, a considerable proportion misses $\geq$1 doses per month, particularly students and employees, patients concerned about the long-term duration of ET, and those who experienced more numerous adverse effects. Remarkably, standard-of-care ET prescription was suboptimal, presumably due to physicians' OFS prescription depending on patients' insurance and financial access to GnRHa; providers' limited awareness of guideline recommendations; and, potentially, ET prescription by surgeons instead of medical oncologists. Interventions aimed at improving patients' adherence and effectively managing adverse effects; strategies for refining physicians' knowledge on the importance of OFS in high-risk premenopausal BC patients; and initiatives for increasing access and coverage of GnRHa could enhance adherence to guideline-endorsed ET, which could translate into improved outcomes in this group of patients.

Author's contributions

Cynthia Villarreal-Garza, Fernanda Mesa-Chavez and Paula Cabrera-Galeana contributed to the study conception and design. Material preparation, data collection and analysis were performed by Fernanda Mesa-Chavez, Ana S Ferrigno, Cynthia De la Garza-Ramos, Karen Villanueva-Tamez, Alan Fonseca, Jose Y Campos-Salgado, Marlid Cruz-Ramos, David O Rodriguez-Gomez, and Sandy Ruiz-Cruz. The first draft of the manuscript was written by Cynthia Villarreal-Garza and Fernanda Mesa-Chavez and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Patient participation was in accordance with the ethical standards of the institutional research committee of Escuela de Medicina del Instituto Tecnologico y de Estudios Superiores de Monterrey (reference number: P000191-TXHOR-CS006) and Instituto Nacional de Cancerologia (reference number: INCAN/CI/0549/2019), as well as with the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

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Declaration of competing interest

The authors declare no competing interests.

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