Baseline Estradiol Levels in Postmenopausal Women

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Introduction

- Estradiol (E2) is a key female reproductive steroidal hormone
- Reduced serum E2 levels are associated with menopausal symptoms such as vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA)[1]
  - Menopause-related symptoms can negatively affect a woman's quality of life[2-4]
  - Exogenous E2 administration may be used to treat menopausal symptoms[5]
- Normal postmenopausal E2 levels have been suggested as <10 pg/mL;[6] however, a generally accepted normal range for E2 determined from a well-defined population of postmenopausal women using an accurate, standardized, analytical method is still needed

Objective

To report data from a pooled analysis of serum estradiol levels from a large cohort of generally healthy postmenopausal women and assess the normal range of serum E2 levels based on various demographic parameters

Methods

Phase 3 Trials

- Two large, randomized, placebo-controlled, phase 3 clinical trials evaluated the efficacy and safety of two estradiol containing therapies for VMS or VVA
  - The REPLENISH trial showed that an oral capsule containing E2 and progesterone (TX-001HR) improved moderate to severe VMS in postmenopausal women with a uterus[7]
  - The REJOICE trial demonstrated that vaginal E2 inserts (TX-004HR) were effective in treating moderate to severe dyspareunia associated with menopausal VVA[8]
- Postmenopausal women enrolled in the REPLENISH trial (NCT01942668) were seeking treatment for VMS, were 40−65 years, had a body mass index (BMI) ≤34 kg/m^2, and had a uterus
- Postmenopausal women enrolled in the REJOICE trial (NCT02253173) were seeking treatment for self-identified moderate to severe VVA, were age 40−75 years, and had a BMI ≤38 kg/m^2

Estradiol Measurement

- In both trials, serum E2 levels were measured using gas chromatography/tandem mass spectrometry at baseline[9,10]
  - Lower limit of quantification (LLOQ): 2.0 pg/mL
  - Sensitivities for E2 on the LLOQ samples:
    - For precision: 4.83%
    - For accuracy: –8.00%
- Mean E2 levels were summarized descriptively by factors that might impact endogenous E2 levels (**Table 1**)

Table 1. Stratification parameters for estradiol analyses

Parameters	Subgroups
Age	40 to <45, 45 to <50, 50 to <55, 60 to <65, 65 to <70, or ≥70 years
Body weight	40 to <60, 60 to <80, 80 to <100, or ≥100 kg
BMI	<25, 25 to <30, or ≥30 kg/m^2
Race	White, African American, Asian or other/unknown
Smoking status	Smoker or nonsmoker
Alcohol intake	Yes or no
Number of pregnancies	0, 1 to 3, or ≥4
Number of live births	0 to 1, 2 to 3, or ≥4

Results

Phase 3 Studies

- Mean E2 levels at baseline were available from a total of 1905 postmenopausal women **(Table 2)**
  - Women in the VMS study (n=1835) had a mean age of 54.6 years (range, 40–66)[9]
  - Women in the VVA study (n=72) had a mean age of 58.5 years (range, 41–75)[10]

Table 2. Demographic and baseline characteristics

Characteristic, n (%)	Postmenopausal population (n=1905)
Age, years	
40 to <45	19 (1.0)
45 to <50	185 (9.7)
50 to <55	741 (38.9)
55 to <60	686 (36.0)
60 to <65	239 (12.5)
65 to <70	30 (1.6)
70+	5 (0.3)
Race	
White	1267 (66.5)
African American	593 (31.1)
Asian	12 (0.6)
Other	33 (1.7)
Weight, kg	
40 to <60	327 (17.2)
60 to <80	1053 (55.3)
80 to <100	501 (26.3)
100+	24 (1.3)

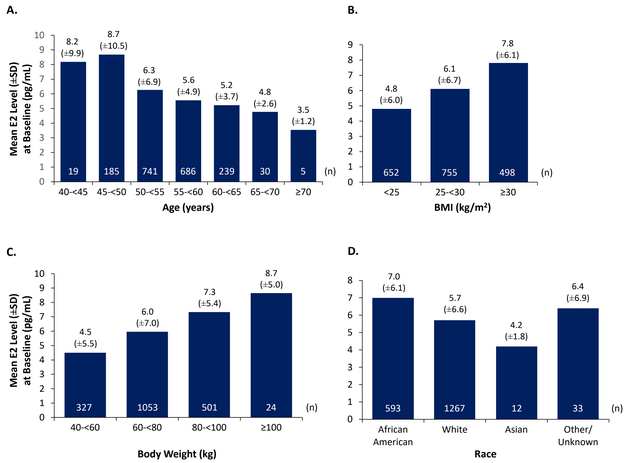
Characteristic, n (%)	Postmenopausal population (n=1905)
BMI, kg/m^2	
<25	652 (34.2)
25 to <30	755 (39.6)
30+	498 (26.1)
Number of pregnancies	
0	158 (8.3)
1–3	749 (39.3)
4+	998 (52.4)
Alcohol intake	
Yes	1220 (64.0)
No	685 (36.0)
Smoking	
Smoker	463 (24.3)
Nonsmoker	1442 (75.7)
Number of live births	
0–1	667 (35.0)
2–3	1001 (52.5)
4+	237 (12.4)

BMI, body mass index.

Baseline Serum Estradiol Levels

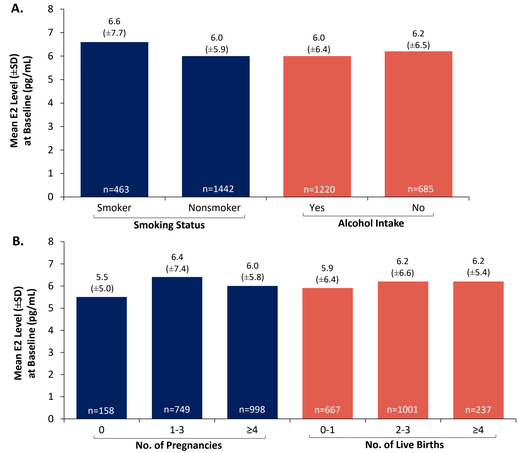
- Overall mean E2 levels at baseline were 5.6–6.5 pg/mL in the VMS population and 3.6–4.9 pg/mL in the VVA population
- Mean E2 levels varied when analyzed by age, BMI, weight, and race (**Figure 1**); mean E2 levels:
  - Were lower with increasing age, ranging from 8.2 pg/mL in women 40 to <45 years to 3.5 pg/mL in women ≥70 years of age
  - Were higher with increasing BMI from 4.8 pg/mL for BMI <25 kg/m^2 to 7.8 pg/mL for BMI ≥30 kg/m^2
  - Increased with increasing weight, ranging from 4.5 pg/mL for women 40 to 60 kg to 8.7 pg/mL for those ≥100 kg
  - Varied depending on race: African American women had the highest E2 levels, followed by White and Asian women
- No interaction between race and BMI was observed; African American race and increased BMI were both independently associated with higher estradiol levels

Figure 1. Mean E2 level at baseline stratified by (A) age, (B) BMI, (C) weight, and (D) race



- Smoking, alcohol use, and numbers of pregnancies or live births did not appear to influence E2 levels at baseline **(Figure 2)**

Figure 2. Mean E2 level at baseline stratified by (A) smoking status and alcohol intake and (B) number of pregnancies and live births



Conclusions

- The overall mean E2 levels for postmenopausal women were 3.6–6.5 pg/mL
- Stratification of E2 concentrations by demographic characteristics showed that serum E2 decreased with older age, lower BMI and lower weight, and was highest in African American women and lowest in Asian women
- Smoking status, alcohol intake, number of pregnancies or number of live births did not appear to influence baseline serum E2 levels
- The results may assist in explaining the potential differences in response to hormonal therapies in postmenopausal women, particularly those experiencing VMS and VVA

Disclosures

- GDC consults to multiple pharmaceutical companies including but not limited to TherapeuticsMD and has stock options from TherapeuticsMD. JHL consults for Allergan, Bayer Healthcare, Pfizer, AMAG, Ferring, and TherapeuticsMD and has received research support (paid to UH Cleveland Medical Center) from AbbVie, Allergan, Bayer Healthcare, Ferring, Femasys, and Palatin Technologies. JAS has served (past year, or current) as a consultant/advisor to AbbVie, Allergan plc, AMAG, Amgen, Ascend Therapeutics, Bayer Healthcare, CEEK Enterprises, Covance, Dare Bioscience, Duchesnay, Hologic, KaNDy/NeRRe Therapeutics, Mitsubishi Tanage, ObsEva SA, Palatin Technologies, Sanofi SA, Shionogi, Sprout, and TherapeuticsMD; has received (past year, or current) grant/research support from AbbVie, Agile Therapeutics, Allergan plc, Bayer Healthcare, Endoceutics, GTx, Ipsen, Myovant Sciences, New England Research Institute, ObsEva SA, Palatin Technologies, Symbio Research, TherapeuticsMD, and Viveve Medical; has also served (past year, or current) on the speaker's bureaus of AbbVie, AMAG, Duchesnay, Novo Nordisk, Shionogi, and TherapeuticsMD and is a stockholder (direct purchase) in Sermonix Pharmaceuticals. SG, BB, and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
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