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# Indication Deviation in Women's Health

Off-Label Drug Use from Conception to Menopause

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## Learning Objectives

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- ✓ **RECOGNIZE** diverse instances of off-label drug use in women's health, spanning pre-conception to menopause
- ✓ **DISCUSS** risks and advantages associated with off-label drug utilization during various reproductive stages
- ✓ **IDENTIFY** the pharmacist's role in advocating for safe and informed off-label drug use for women's health

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## Disclosures

- Dr. Giara has no relationships with ineligible companies.
- I will be discussing off-label use of drugs (obviously).
- Note that this activity will employ the terms "woman/women" to align with the biological expectations of ovulation.


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## Women's Health in 3 Phases




**Adolescence & Young Adulthood**

- Polycystic ovary syndrome (PCOS)
- Endometriosis



**Childbearing Years**

- Infertility/conception
- Pregnancy




**Menopause & Beyond**

- Vasomotor symptoms
- Genitourinary syndrome of menopause (GSM)

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## Adolescence & Young Adulthood

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## QUESTION 1

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Which of the following can be treated through off-label use of metformin?

- A) Hirsutism of PCOS
- B) PCOS with BMI  $\geq 25$  kg/m<sup>2</sup>
- C) Endometriosis

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## The Menstrual Cycle

- **MYTH:** Every woman's menstrual cycle is 28-days long
  - Only true for about 13% of women
  - Cycle length varies from 21 to 40 days
- Hormones regulate the process, splitting the cycle into 3 phases
  - **Follicle-stimulating hormone (FSH):** recruits follicles in the ovaries for growth and development
  - **Luteinizing hormone (LH):** triggers egg release from the ovary
  - **Gonadotropin-releasing hormone (GnRH):** stimulates pituitary gland to produce FSH and LH

Bull JR, et al. NPJ Digit Med. 2019;2:83.

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## Polycystic Ovary Syndrome (PCOS)

- Affects 1 in 10 women of childbearing age
- Etiology is complex, but PCOS largely depends on hormone imbalance
- Development of cysts (small, fluid-filled sacs) in the ovaries
- Patients experience
  - Irregular menstrual cycles
  - Hirsutism (up to 70% of patients)
  - Acne on the face, chest, and upper back
  - Thinning hair or hair loss on the scalp
  - Weight gain or difficulty losing weight
  - Skin darkening and skin tags

OASH. Polycystic ovary syndrome. Accessed November 10, 2023. <https://www.womenshealth.gov/a-z-topics/polycystic-ovary-syndrome>

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## PCOS Pathophysiology

- **Hormonal Imbalance in the HPO Axis**
  - Abnormal GnRH pulse frequency and amplitude → excess LH production
  - Stimulates the ovaries to produce more androgen, contributing to hyperandrogenemia
- **Follicular Growth Impairment**
  - Altered levels of LH, FSH, and other factors impair follicle growth
  - Leads to follicular arrest, ovulatory dysfunction, and presence of multiple small ovarian follicles
- **Hyperandrogenemia and Hyperinsulinemia**
  - Increased androgen (testosterone) and insulin levels
  - Often exacerbate each other

HPO, hypothalamic-pituitary-ovarian; Liao B, et al. Front Endocrinol (Lausanne). 2021;12:967422.

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## Off-Label: PCOS

**Primary goal of treatment:** improve the endocrine profile by ↓ weight, improving insulin resistance, and ↓ androgen levels

**Combined hormonal contraceptives (CHCs):**

- First-line for patients not trying to conceive
- Suppress ovarian hyperandrogenism to address irregular menstrual cycles, hirsutism, and acne
- CHC choice can be based on administration preference and minimizing adverse effects (AEs) to ensure adherence
  - No clinical advantage to using high dose ethinyl estradiol (≥ 30 mcg) for hirsutism
  - Consider higher weight and cardiovascular risk factors

Hoeger KM, et al. J Clin Endocrinol Metab. 2021;106(3):e1071-e1083; Steinberg Weiss M, et al. Fertil Steril. 2021;115(2):474-482; Teede HJ, et al. J Clin Endocrinol Metab. 2023;108(10):2447-2469.

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## Off-Label: PCOS

**Metformin:**

- Insulin sensitization therapy; metabolic and reproductive benefits in PCOS
  - weight reduction
  - decreased plasma insulin and lipid levels
  - decreased blood pressure
  - decreased androgen plasma levels
  - restoration of a normal menstrual cyclicity and ovulation
- Consider for patients with BMI ≥ 25 kg/m<sup>2</sup>
  - May also be useful for adolescents at risk of or with PCOS for cycle regulation
- **Dosing:** 500 mg once daily, titrate every 1–2 weeks to max. 2.5 grams in adults, 2 grams in adolescents

BMI, body mass index; ER, extended-release; Frazzelli F, et al. Gynecol Endocrinol. 2017;33(1):39-42; Teede HJ, et al. J Clin Endocrinol Metab. 2023;108(10):2447-2469.

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## Off-Label: PCOS

**Anti-obesity agents:**

- Use in combination with lifestyle modifications
- GLP-1 receptor agonists (e.g., liraglutide, semaglutide)
- Orlistat 120 mg three times daily (gastric lipase inhibitor)

**Anti-androgen agents:**

- Consider for patients with hirsutism with suboptimal response to CHCs after 6 months
- Must be used with reliable contraception in whenever pregnancy is possible due to teratogenic risks
- Spironolactone 25–100 mg daily

GLP-1, glucagon-like peptide-1; Teede HJ, et al. J Clin Endocrinol Metab. 2023;108(10):2447-2469.

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## Off-Label: PCOS


**Additional Considerations:**

- CHCs are preferred for hirsutism and irregular menstrual cycles
- Metformin is preferred for metabolic indications
  - Can be considered for irregular menses when CHCs are contraindicated, not tolerated, or refused
  - Does not impact hirsutism
- Combination of CHCs and metformin is most beneficial for adults in high metabolic risk groups:
  - BMI > 30 kg/m<sup>2</sup>
  - Diabetes risk factors
  - Impaired glucose tolerance
  - High-risk ethnic groups

Teede HJ, et al. J Clin Endocrinol Metab. 2023;108(1):2447-2469.

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## Endometriosis



- Affects 1 in 10 women of childbearing age
- Inflammatory entity causing endometrial tissue growth outside the uterus
  - Estrogen-dependent process
- Wide range of symptoms
  - Chronic pelvic pain
  - Dysmenorrhea
  - Dyspareunia
  - Dysuria
  - Dyschezia
  - Infertility
  - Fatigue

Kalatzopoulos DR, et al. BMC Womens Health. 2021;21(1):397.

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## Off-Label: Endometriosis

**Primary goal of treatment:**  
alleviate endometriosis-associated pain

- Pain relievers
  - NSAIDs are considered symptomatic first-line treatment
  - Do not address the underlying cause of endometriosis
- Progestin-only contraceptives
  - Medroxyprogesterone acetate SC or IM every 3 months
  - Levonorgestrel IUD
- Combined hormonal contraceptives

IM, intramuscularly; IUD, intrauterine device; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneously. Kalatzopoulos DR, et al. BMC Womens Health. 2021;21(1):397.

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# Childbearing Years

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## QUESTION 2

**Which of the following is TRUE about off-label medication use during pregnancy?**

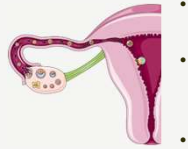
A) All drugs have sufficient efficacy and safety data to support their use during pregnancy

B) About three-quarters of pregnant women use medications for off-label uses during pregnancy

C) Providers should use the letter-based FDA rating system to aid in shared clinical decision-making

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## Infertility and Conception



- Most common causes of infertility in women are ovulation problems (e.g., PCOS), endometriosis, pelvic adhesions, and tubal disease
- Medications are used off-label for two major purposes
  - Induce ovulation
  - Aid in other aspects of the assisted reproduction process (IUI or IVF)
- Assisted reproduction is basically trial-and-error, creating lots of room for off-label drug use

IUI, intrauterine insemination; IVF, in-vitro fertilization. Kalatzopoulos DR, et al. BMC Womens Health. 2021;21(1):397.

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## Off-Label: Infertility

**Letrozole for inducing ovulation:**

- Mechanism of action: Nonsteroidal aromatase inhibitor
  - Aromatase converts androgens to estrogen, so letrozole suppresses estrogen production → pituitary gland releases FSH + LH → follicle development
- Dosing: 2.5 mg (some take 5 mg or 7.5 mg) once daily cycle days 5–9
  - Up to 80% of anovulatory women taking letrozole will ovulate
  - No official recommendation for a maximum number of cycles
- AEs: Arthralgia, asthenia, bone pain, dizziness, edema, flushing, headache, hot flashes, hypercholesterolemia, increased sweating
  - Generally better tolerated than clomiphene citrate

[No author]. Med Lett Drugs Ther. 2011;53(1376):86-88. Femara (letrozole) for infertility, ovulation problems and PCOS treatment. Accessed November 15, 2023. <https://advanceforinfertility.com/fertility-medications/femara-letrozole-treatment/>; Femara [prescribing information].

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## Off-Label: Infertility

**Assisted reproductive technology (ART):**

- Intrauterine insemination (IUI):** place sperm directly into a woman's uterus to increase the chances of fertilization
  - Often use ovulation-inducing drugs to ensure correct timing
- In vitro fertilization (IVF):** combine eggs and sperm outside the body in a laboratory to create embryos, which are transferred into the woman's uterus
- About 1.7% of all infants born in the U.S. annually are conceived using ART

Usadi RS, et al. Fertil Steril. 2015;103(3):583-594.

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## Off-Label: Infertility

- Aspirin**
  - Possible improved embryo implantation
- Blood thinners (enoxaparin)**
  - For patients with recurrent miscarriage caused by blood clotting problems (e.g., APS, thrombophilias)
- Dopamine agonists (bromocriptine, cabergoline)**
  - Treatment of infertility of pituitary origin; treatment of OHSS
- GnRH antagonists (cetorelix, ganirelix)**
  - Used to treat OHSS (excessive response to medications used to make eggs grow, especially injectable gonadotropins)
- Steroids (dexamethasone)**
  - Induce ovulation in clomiphene-resistant PCOS; before IVF embryo transfer
- Sildenafil**
  - Increase endometrial thickness in ART

APS, antiphospholipid syndrome; OHSS, ovarian hyperstimulation syndrome. Usadi RS, et al. Fertil Steril. 2015;103(3):583-594.

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## Medication Use in Pregnancy

- Concerns with medication use in pregnancy:
  - Potential harmful effects on fetal development
  - Birth defects, pregnancy loss, and long-term adverse health outcomes
- Thalidomide Tragedy of 1962 raised concerns about medication safety during pregnancy
  - Notable increase in severe birth defects linked to its use for pregnancy-related nausea and vomiting
- Impact on clinical trials
  - Pregnant women are often excluded due to safety concerns
  - Physiological changes in pregnancy affect pharmacokinetics
  - Consequently, evidence (usually insufficient) to support use typically only becomes available post-marketing

Gray SG, McGuire TM. J Pharm Pract Res. 2019;49(4):389-395.

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## Medication Use in Pregnancy

Less than 10% of drugs have sufficient maternal and fetal efficacy and safety information to support use during pregnancy

**Use ≥ 1 medication during pregnancy**

**Use OTC and complementary medicines during pregnancy: 68%**

**Use medications off-label during pregnancy: 74%**

OTC, over-the-counter. Gray SG, McGuire TM. J Pharm Pract Res. 2019;49(4):389-395.

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## Common Medications Used During Pregnancy

**GI medications**

**Analgesics**

**Antibiotics**

GI, gastrointestinal. Jif. J. JAMA. 2022;328(5):486.


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## Guidance for Providers

- The reality is that **most** drug use in pregnancy is off-label
  - Consider risk versus benefit based on available clinical data
- All FDA-approved prescribing information and OTC labeling includes information regarding safety of use during pregnancy and lactation
- Prior to 2015, the FDA used a letter-based system for pregnancy risk
  - Ranged from A (no risk in human studies) to X (evidence of fetal abnormalities in animals or humans)
- Transitioned to a Pregnancy and Lactation Labeling Rule, requiring an overview of safety for 3 categories:
  - Pregnancy, during labor, and delivery
  - Lactation
  - Females and males of reproductive potential

Am J JAMA. 2022;328(5):486.

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## Menopause & Beyond

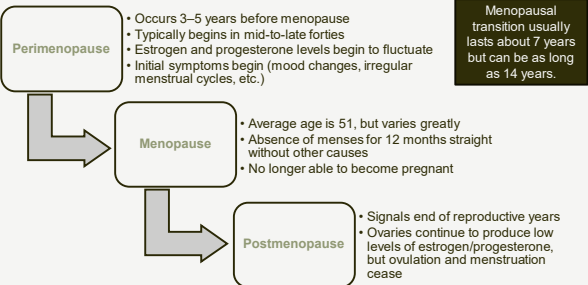
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## QUESTION 3

Which of the following drugs is used off-label to treat menopausal hot flashes?

- Clonidine
- Paroxetine
- Fezolinetant

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**Perimenopause**

- Occurs 3–5 years before menopause
- Typically begins in mid-to-late forties
- Estrogen and progesterone levels begin to fluctuate
- Initial symptoms begin (mood changes, irregular menstrual cycles, etc.)

**Menopausal transition usually lasts about 7 years but can be as long as 14 years.**

**Menopause**

- Average age is 51, but varies greatly
- Absence of menses for 12 months straight without other causes
- No longer able to become pregnant

**Postmenopause**

- Signals end of reproductive years
- Ovaries continue to produce low levels of estrogen/progesterone, but ovulation and menstruation cease

Ferris E. Preparing for Menopause: Understanding the Signs and Symptoms in all Three Stages. Accessed Nov. 16, 2023. <https://www.summahealth.org/fourish/articles/2023/04/preparing-for-menopause-understanding-the-signs-and-symptoms-in-all-three-stages>. NH. What is menopause? Accessed Nov. 16, 2023. <https://www.nia.nih.gov/health/menopause/what-menopause>

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## Common Menopausal Symptoms

Symptoms begin during perimenopause and dissipate over time:

- Hot flashes
- Insomnia or sleep disturbances
- Night sweats
- Elevated heart rate
- Mood changes (e.g., irritability, depression, anxiety)
- Vaginal dryness or discomfort during intercourse
- Urinary incontinence or frequent urination
- Decreased libido

Ferris E. Preparing for Menopause: Understanding the Signs and Symptoms in all Three Stages. Accessed November 16, 2023. <https://www.summahealth.org/fourish/articles/2023/04/preparing-for-menopause-understanding-the-signs-and-symptoms-in-all-three-stages>

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## Vasomotor Symptoms (VMS)

- Hot flashes (or flashes) and night sweats
  - Sudden sensation of extreme heat in the upper body, particularly the face, chest, and neck
  - Perspiration, flushing, chills, clamminess, anxiety, and possible heart palpitations
  - Last about 1 to 5 minutes
- Symptoms are debilitating and interfere with quality of life and sleep
  - 87% of women who have hot flashes have them daily
  - One-third experience more than 10 episodes daily
- Associated with increased blood pressure and clinical hypertension
- Up to 82% of women during and/or after the menopause transition
  - For about half of women, persists for 4 years after menopause
  - For 10% of women, lasts 12 years following menopause

Lee E, et al. Am J Physiol Heart Circ Physiol. 2022;323(6):H1270-H1280. ACOG. Obstet Gynecol. 2014;123(1):202-216.

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## Off-Label: VMS

**SSRIs and SNRIs:**

- Paroxetine is FDA approved for VMS, but others are not
- RCTs support effectiveness for VMS in healthy, nondepressed women

**Clonidine:**

- Centrally acting alpha 2-agonist antihypertensive that shows modest benefit
  - Better than placebo, but less benefit compared to HRT
- Dose: 0.1 mg/day

**Gabapentin:**

- GABA analogue antiepileptic that shows benefit in several studies
  - 45% reduction in hot flush frequency and 54% reduction in symptom severity
- Dose: 600–900 mg/day

GABA, gamma aminobutyric acid; HRT, hormonal replacement therapy; RCT, randomized controlled trial. ACOG. Obstet Gynecol. 2014;123(1):202-216.

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## Off-Label: VMS

**Black cohosh:**

- Comes from roots and stems of a flowering plant native to North America
- Many active compounds (e.g., flavonoids, phytochemicals)
  - Mechanisms by which this helps VMS of menopause are unclear
- Trials assessing effectiveness for VMS are inconsistent
  - Two meta-analyses showed some benefit in treating VMS
  - One RCT showed similar efficacy to tibolone (HRT) at reducing symptoms
- Dose: (typical) 20–40 mg/day
- No known clinically relevant drug interactions
- Long-term effects are unknown
  - Potential for hepatotoxicity

Umbard EM, Falconeri L. Int J Womens Health. 2012;4:305-319.

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## Genitourinary Syndrome

- Genitourinary syndrome of menopause (GSM) is a chronic, progressive, vulvovaginal, sexual, and lower urinary tract condition
- Affects up to 70% of postmenopausal and 15% of premenopausal women
  - Often undiagnosed, as symptoms are mild and nonspecific in about half of postmenopausal women
- Decreased estrogen results in hormonal and anatomical changes in the genitourinary tract
- Greatly impacts quality of life, especially for sexually-active women

Angelus K, et al. Cureus. 2020;12(4):e7586.

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## GSM Pathophysiology

**Decreased estrogen results in hormonal and anatomical changes in the genitourinary tract**

<p><b>Changes in External Genitalia:</b></p> <ul style="list-style-type: none"> <li>Loss of labial and vulval thickness</li> <li>Reduced pubic hair and subcutaneous fat of labia majora</li> <li>Reduced labia minora and hymenal remnants</li> </ul>	<p><b>Changes in Vaginal Health:</b></p> <ul style="list-style-type: none"> <li>Decreased collagen, elasticity, and blood flow</li> <li>Reduced vaginal discharge</li> <li>Dry and thin epithelium</li> <li>Change in vaginal microbiome and ↑ pH</li> </ul>
<p><b>Pelvic Floor and Vaginal Issues:</b></p> <ul style="list-style-type: none"> <li>Decreased pelvic floor strength and control</li> <li>Short and narrow vagina</li> <li>Prolapse</li> </ul>	

Angelus K, et al. Cureus. 2020;12(4):e7586.

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## Symptoms of GSM

GENITAL	SEXUAL	URINARY
Vaginal dryness	Dyspareunia	Dysuria
Irritation/burning/itching	Reduced lubrication	Urinary urgency
Vaginal discharge	Post-coital bleeding	Stress/urgency incontinence
Thinning/graying pubic hair	Decreased libido/arousal	Recurrent UTI
Pelvic pain/pressure	Dysorgasmia	Urethral prolapse
Vaginal prolapse		Ischemia of vesical trigone

UTI, urinary tract infection. Angelus K, et al. Cureus. 2020;12(4):e7586.

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## Off-Label: GSM

**Primary Goal: Achieve relief of symptoms**

**Topical testosterone:**

- Vaginal estrogen or dehydroepiandrosterone (DHEA) are preferred
  - Helpful for those with history of estrogen-dependent breast cancer
- Used off-label for dyspareunia and vulvovaginal atrophy
  - Can help with proliferation of vaginal epithelium to improve vaginal tissue health
  - May also address hypoactive sexual desire
- Limited but promising data
- Dose: 150 or 300 mcg/day vaginally
  - Most studies reviewed only 4 weeks of use, so longer duration studies are needed

[No author]. Obstet Gynecol. 2021;138(6):950-960.

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## Off-Label: Recurrent UTI of GSM

**Recurrent UTI: ≥ 3 episodes in 12 months OR ≥ 2 episodes in 6 months**

- Lower estrogen levels cause changes in:
  - urogenital epithelium
  - urogenital microbiome
- Also associated with lower *Lactobacillus* presence and higher urogenital pH
- Most implicated pathogen is *Escherichia coli*, which is resistant to many antimicrobial agents

Careto M, et al. Maturitas. 2017;99:43-46.; Jung C, Brubaker L. Climacteric. 2019;22(3):242-249.

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## Off-Label: Recurrent UTI of GSM

**D-mannose:**

- Monosaccharide sugar that reduces adherence to the bladder mucosa
- Available OTC
- Dose: 2 grams dissolved in 200 mL water daily

**Methenamine:**

- Converts to formaldehyde in acidified urine to kill bacteria
- Prescription only
- Caution in renal and/or hepatic impairment
- Dose: 1 gram twice daily

Careto M, et al. Maturitas. 2017;99:43-46.; Jung C, Brubaker L. Climacteric. 2019;22(3):242-249.

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## Off-Label: Recurrent UTI of GSM

**Antibiotics:**

- Continuous – nitrofurantoin, SMX-TMP, trimethoprim, cephalexin, fosfomycin
- Post-coital – nitrofurantoin, SMX-TMP, cephalexin
- Effective but increased risk of antimicrobial resistance

**Other therapies with limited evidence:**

<b>Vaginal probiotics</b>	<ul style="list-style-type: none"> <li>May be most effective adjunct to vaginal estrogen</li> <li>Daily for 5 days, then weekly for 10 weeks</li> </ul>
<b>Vitamin C (ascorbic acid)</b>	<ul style="list-style-type: none"> <li>Used to acidify the urine to prevent bacterial growth</li> <li>1 to 3 grams 3 to 4 times daily</li> </ul>
<b>Cranberry</b>	<ul style="list-style-type: none"> <li>Active compound associated with bladder health</li> <li>72 mg proanthocyanidin/day (20 oz cranberry juice)</li> </ul>

SMX-TMP, sulfamethoxazole-trimethoprim.  
Careto M, et al. Maturitas. 2017;99:43-46.; Jung C, Brubaker L. Climacteric. 2019;22(3):242-249.

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## The Pharmacist's Role

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## Optimizing Off-Label Therapies


- Prioritize patient education, informed decision-making, and safety of off-label therapies
- Respect patient autonomy
  - Children as young as 5 years old can comprehend medication instructions and be involved in their own care
  - Use clear, non-judgmental language
- Assess for safety in pregnancy and lactation
  - Product labeling
  - LactMed from the National Library of Medicine
  - MotherToBaby (formerly the Organization of Teratology Information Specialists)



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## Pregnancy Exposure Registries

- Research studies that collect health information on exposure to drugs and vaccines during pregnancy
  - Effects on the woman, the developing fetus, and sometimes newborn infants
  - Pregnant women volunteer to share their experiences
- Sponsored by manufacturers or other researchers (not the FDA)
- Sometimes women can sign themselves up; sometimes must be an HCP
- Ask about what to expect:
  - How often will the registry contact you?
  - How will they keep your information private?
  - Who can you contact with questions?
  - How do you share the study results when the registry ends?
  - Do they also intend to collect information about your newborn baby?



FDA. List of pregnancy exposure registries. Accessed November 27, 2023. <https://www.fda.gov/science-research/womens-health-research/tdp-pregnancy-exposure-registries>

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Women's health is an essential part of global public health, and it deserves our dedicated attention, research, and care to ensure that all women receive the best possible treatment and support.

**Questions?**