Indication Deviation in Women's Health

Off-Label Drug Use from Conception to Menopause

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Learning Objectives

- ✓ **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

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

A) Hirsutism of PCOS

B) PCOS with BMI ≥ 25 kg/m^2

C) Endometriosis

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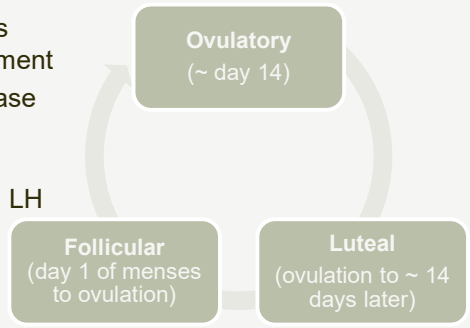
The Menstrual Cycle

- 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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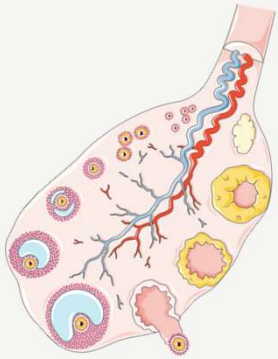
Polycystic Ovary Syndrome (PCOS)



- 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;12:667422.

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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^2
  - 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.
Fruzzetti 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^2
  - Diabetes risk factors
  - Impaired glucose tolerance
  - High-risk ethnic groups

Teede HJ, et al. *J Clin Endocrinol Metab*. 2023;108(10):2447-2469.

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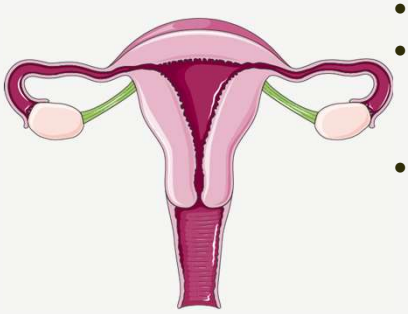
Endometriosis



- 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

Kalaitzopoulos 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.
Kalaitzopoulos 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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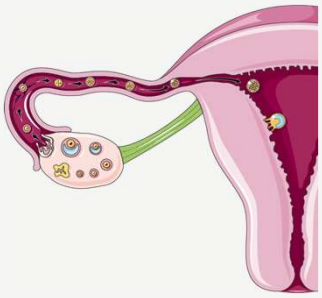
Infertility and Conception



- 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.
Kalaitzopoulos 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://advancedfertility.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** (cetrorelix, 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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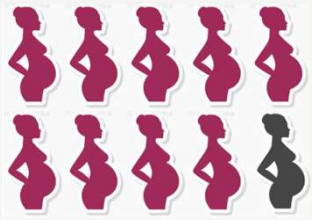
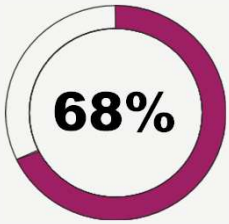
Medication Use in Pregnancy

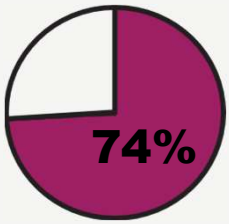
Less than 10% of drugs have sufficient maternal and fetal efficacy and safety information to support use during pregnancy



Use ≥ 1 medication during pregnancy



Use OTC and complementary medicines during pregnancy



Use medications off-label during pregnancy

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

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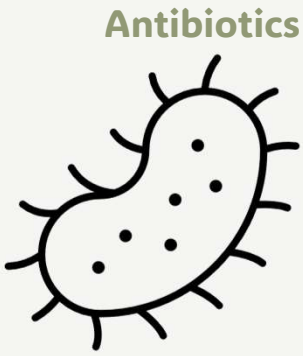

Common Medications Used During Pregnancy

GI, gastrointestinal.
Jin 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:
  1) Pregnancy, during labor, and delivery
  2) Lactation
  3) Females and males of reproductive potential

Jin 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?

A) Clonidine

B) Paroxetine

C) 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/flourish/entries/2023/04/preparing-for-menopause-understanding-the-signs-and-symptoms-in-all-three-stages; NIH. 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/flourish/entries/2023/04/preparing-for-menopause-understanding-the-signs-and-symptoms-in-all-three-stages

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Vasomotor Symptoms (VMS)

- Hot flushes (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 flushes 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

Umland EM, Falconieri 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

Angelous 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

Changes in External Genitalia:

•Loss of labial and vulval thickness

•Reduced pubic hair and subcutaneous fat of labia majora

•Reduced labia minora and hymenal remnants

Changes in Vaginal Health:

•Decreased collagen, elasticity, and blood flow

•Reduced vaginal discharge

•Dry and thin epithelium

•Change in vaginal microbiome and ↑ pH

Pelvic Floor and Vaginal Issues:

•Decreased pelvic floor strength and control

•Short and narrow vagina

•Prolapse

Angelous 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.
Angelous 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

Caretto 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

Caretto 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:

Vaginal probiotics	• May be most effective adjunct to vaginal estrogen • Daily for 5 days, then weekly for 10 weeks
Vitamin C (ascorbic acid)	• Used to acidify the urine to prevent bacterial growth • 1 to 3 grams 3 to 4 times daily
Cranberry	• Active compound associated with bladder health • 72 mg proanthocyanidin/day (20 oz cranberry juice)

SMX-TMP, sulfamethoxazole-trimethoprim.
Caretto 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/list-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?

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