Let's Pause to Talk About Birth Control and Menopause in Solid Organ Transplant

UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

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March 24th, 2022

Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Krystal Heinen:**
    - None
  - **CE mentor, Todd Larson:**
    - None
- Off-Label Uses of Medications
  - Antidepressants (including SSRIs and SNRIs)
  - Gabapentin
  - Vitamin E

Abbreviations

- ASCVD = atherosclerotic cardiovascular disease
- CV = cardiovascular
- CVD = cardiovascular disease
- DMPA = depot-medroxyprogesterone
- DVT = deep vein thrombosis
- EE = ethinyl estradiol
- ESRD = end stage renal disease
- FSH = follicle-stimulating hormone
- IUD = intrauterine device
- LH = luteinizing hormone
- OBGYN = obstetrician-gynecologist
- PCP = primary care provider
- PE = pulmonary embolism
- REMS = risk evaluation and mitigation strategies
- SNRI = serotonin–norepinephrine reuptake inhibitor
- SOT = solid organ transplant
- SSRI = selective serotonin reuptake inhibitor
- U.S. = United States of America
- VTE = venous thromboembolism

Pharmacy Technician Learning Objectives

1. Discuss barriers to contraceptive use
2. Distinguish between monophasic and multiphasic contraceptives
3. Recognize therapies for contraception and menopause

Pharmacist Learning Objectives

1. Select appropriate contraception therapies based on safety and efficacy
2. Propose a safe and effective contraceptive therapy plan for a solid organ transplant patient
3. Design a pharmaceutical or alternative therapy regimen for menopausal symptoms in a solid organ transplant recipient

Solid Organ Transplant Recipients

- **Women of reproductive age make up ~15% of the adult renal transplant recipients in the US**
  - Avoid pregnancy until graft function is stable
  - Pregnancies are higher risk
- **~24% of renal transplant recipients are women above the age of 50**
  - Higher risks of VTE, cancer, and bone disease

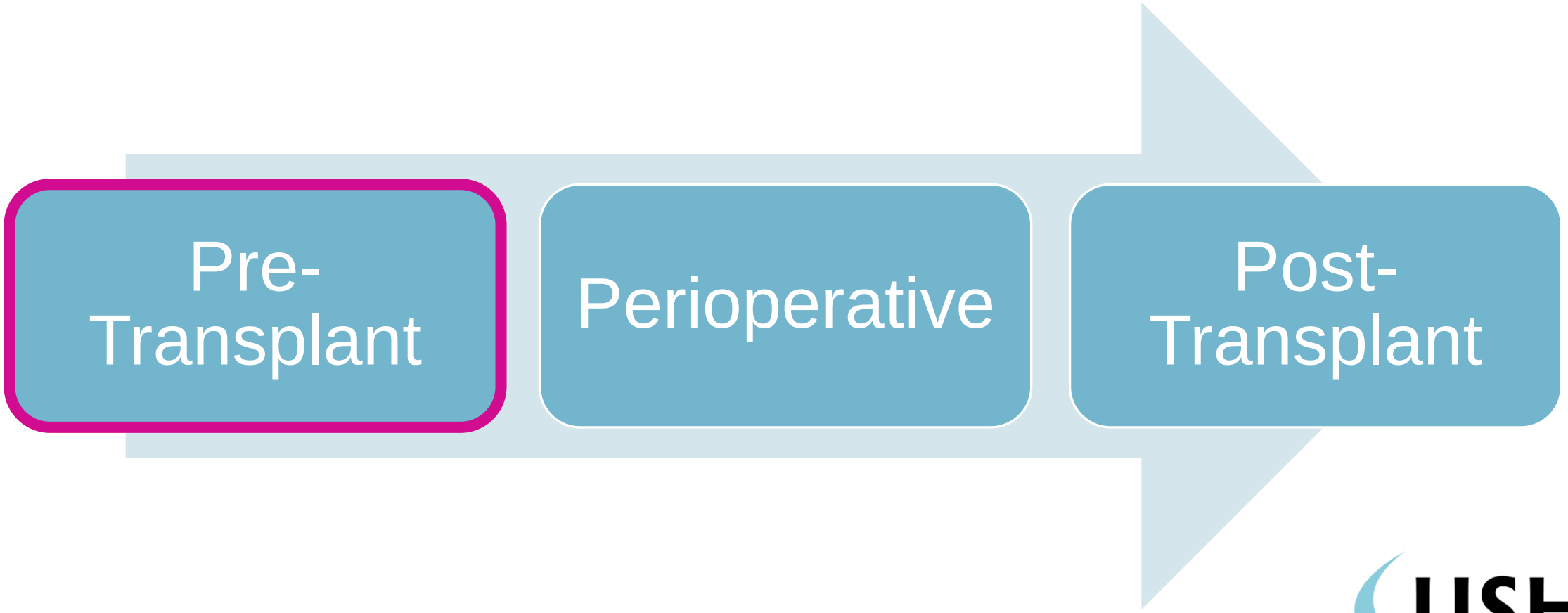
Due to the physiologic changes after transplant and the need for chronic immunosuppression, these patients have unique risks to consider



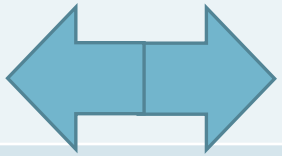
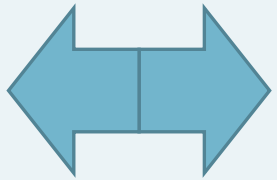

Hart A, et al. OPTN/SRTR 2019 Annual Data Report: Kidney. Am J Transplant. 2021;21 Suppl 2:21-137.

Kidneys: Facts, Function & Diseases. livescience.com. https://www.livescience.com/52047-kidneys.html. Published 2022. Accessed February 13, 2022. 2018 Viral Hepatitis Surveillance Report | CDC. Cdc.gov. https://www.cdc.gov/hepatitis/statistics/2018surveillance/index.htm. Published 2022. Accessed February 13, 2022. Gaea Marelle Miranda M. Structure and Function of the Heart. News-Medical.net. https://www.news-medical.net/health/Structure-and-Function-of-the-Heart.aspx. Published 2022. Accessed February 13, 2022. Facts, Function and Diseases. livescience.com. https://www.livescience.com/52250-lung.html. Published 2022. Accessed February 13, 2022.

Contraception



Female Reproductive Hormones

	Estrogen	Progesterone
Role in Reproduction	1. Causes maturation and release of the egg 2. Builds up uterine lining	1. Inhibits shedding of uterine lining 2. Prepares the uterine lining for attachment of the egg 3. Prevents the body from ovulating
CV Risk		
Risk of Cancer	 Endometrial and breast cancer	  *Synthetic progestins increase this risk
Risk of Osteoporosis		

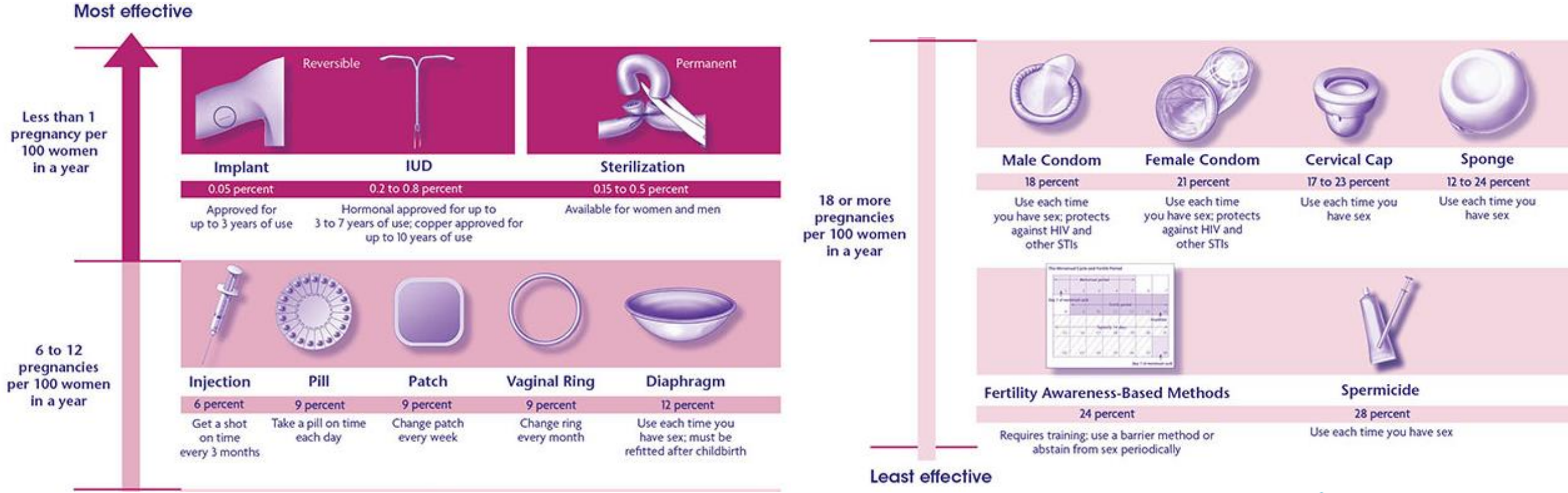
Manson JE, et al. The Women's Health Initiative trials of menopausal hormone therapy: lessons learned. *Menopause*. 2020;27(8):918-928. .

Forms of Contraception

Hormonal Combination	Progestin-Only	Non-Hormonal
• Pills • Skin patch • Vaginal ring	• Pills • Implant • Injection • IUD	Sterilization Barrier methods Copper IUD

Colquitt CW, et al. Contraceptive Methods. *J Pharm Pract*. 2017;30(1):130-135.

Efficacy

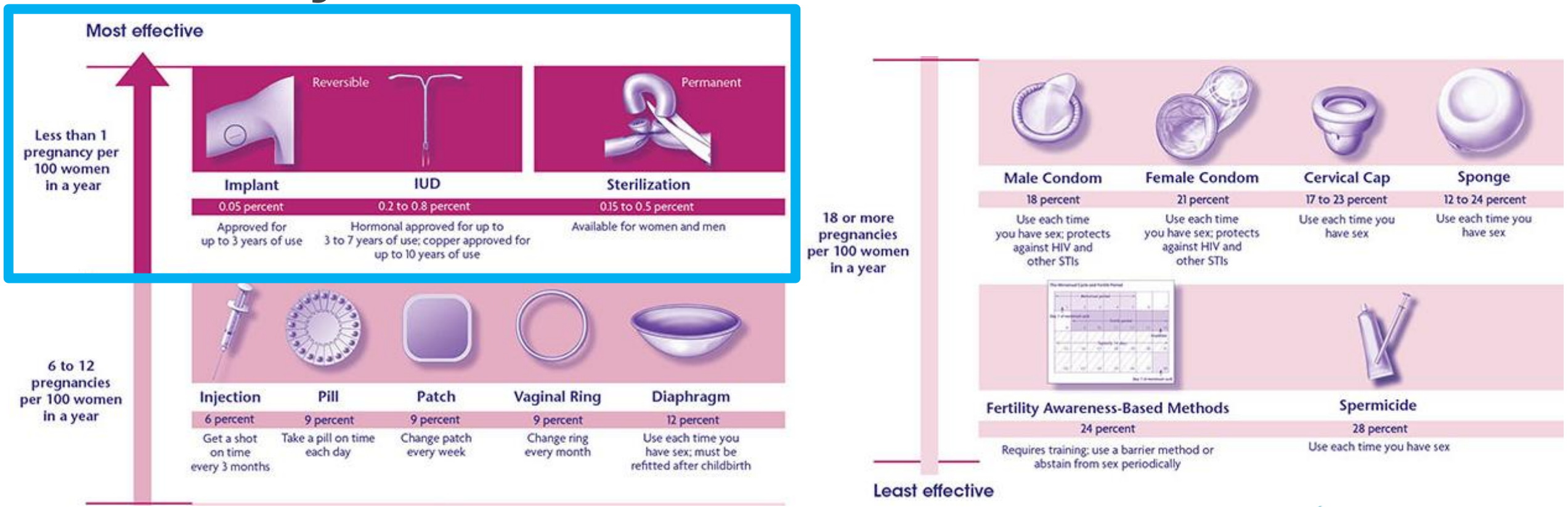


ACOG
The American College of Obstetricians and Gynecologists

USHP

Effectiveness of Birth Control Methods. ACOG.org. https://www.acog.org/womens-health/infographics/effectiveness-of-birth-control-methods. Published 2022. Accessed February 10, 2022.

Efficacy



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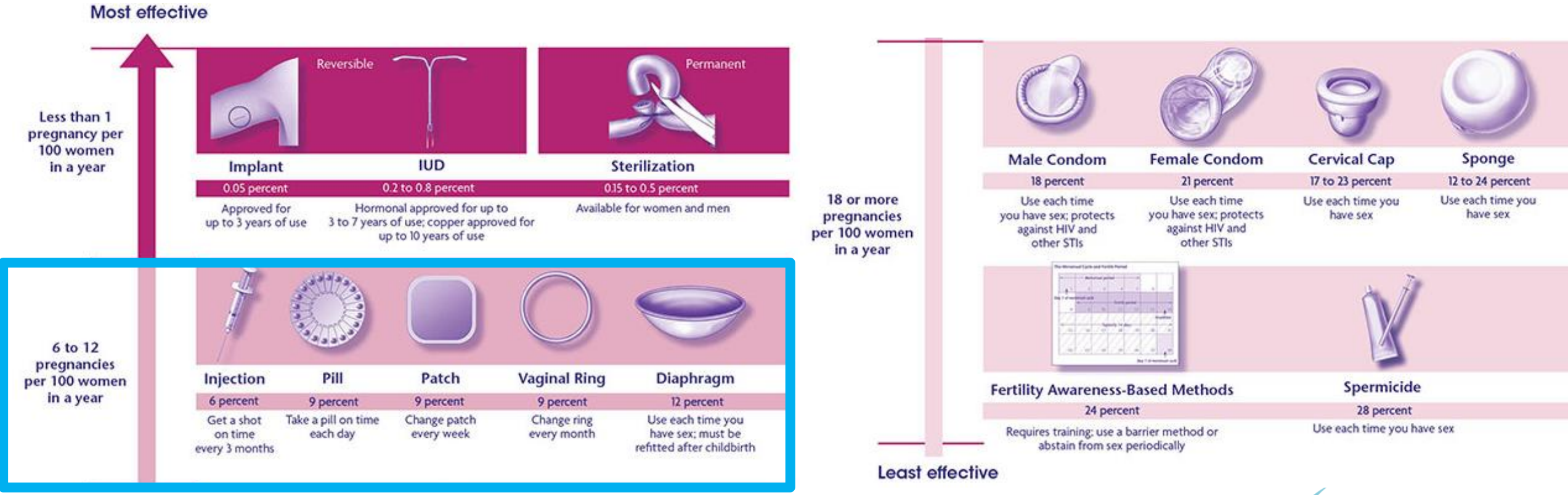

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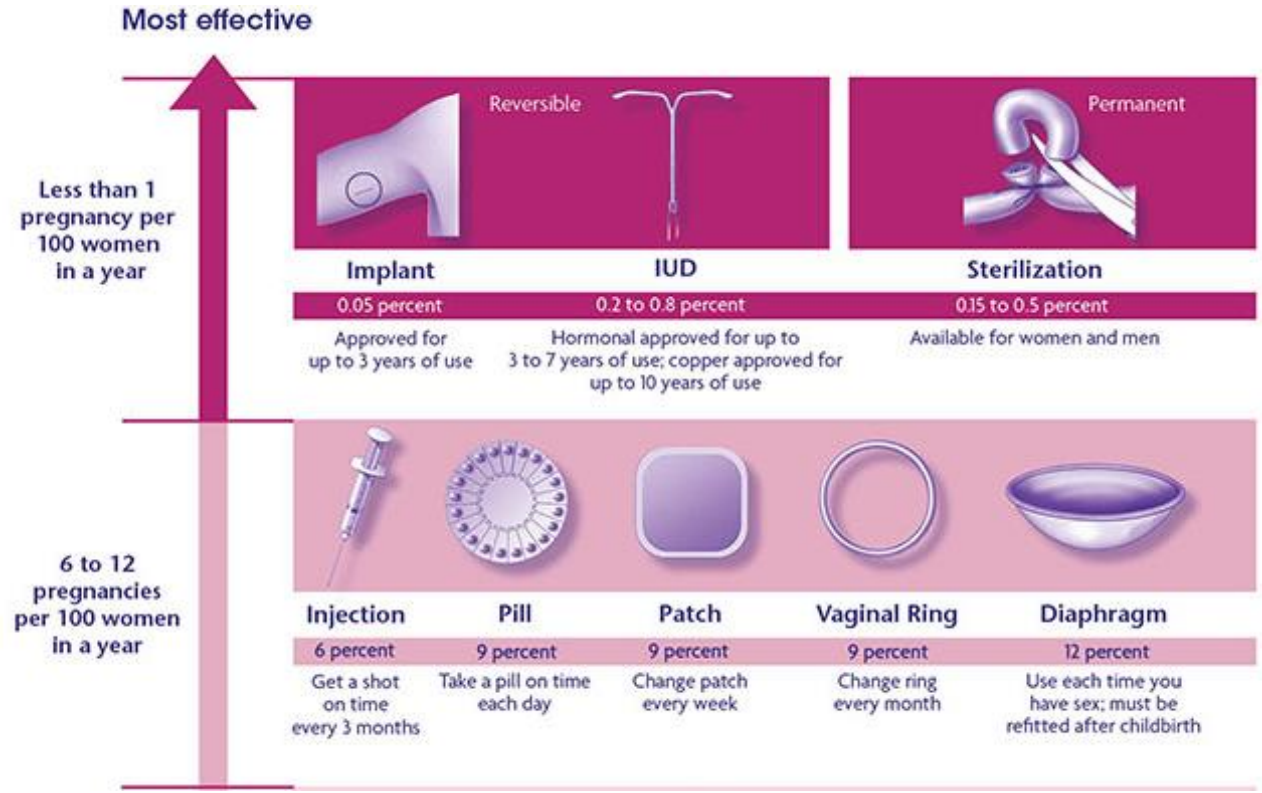

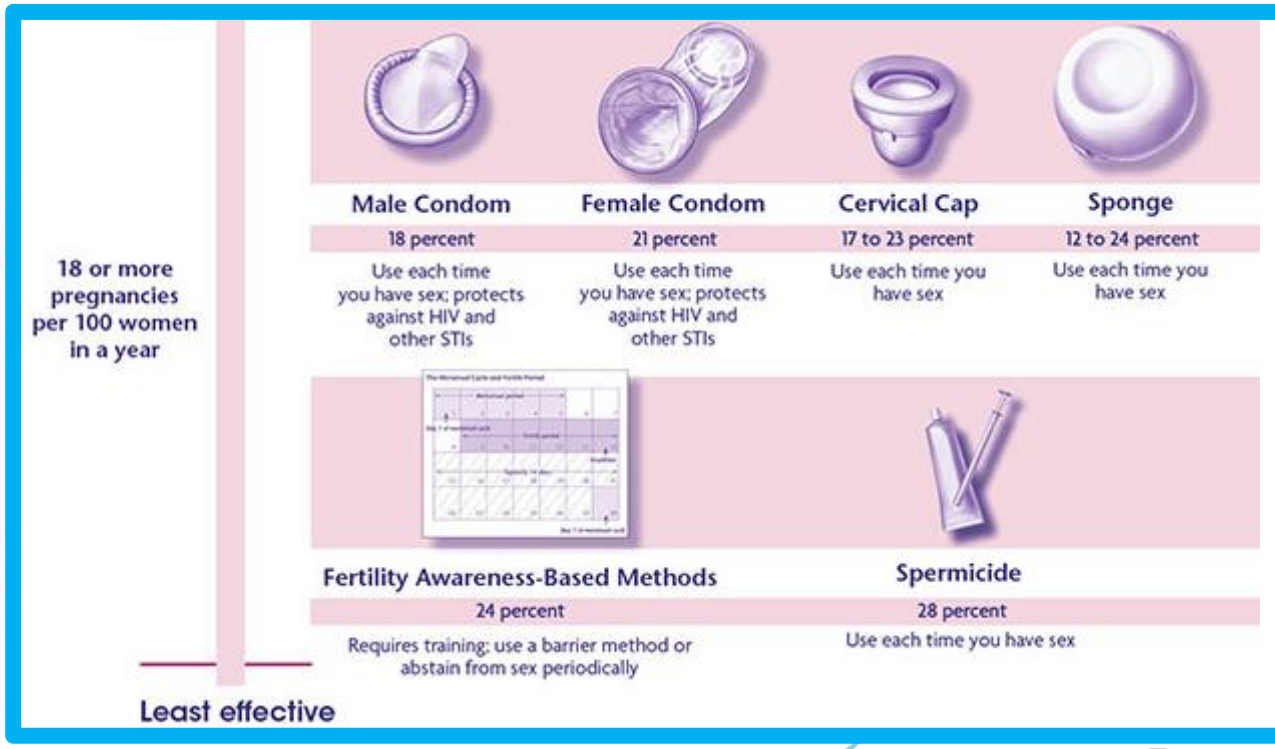

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Effectiveness of Birth Control Methods. ACOG.org. https://www.acog.org/womens-health/infographics/effectiveness-of-birth-control-methods. Published 2022. Accessed February 10, 2022.

	Failure	Duration	Adverse Effects
Intra-Uterine Device *(levonorgestrel or copper)* 	0.2 - 0.8%	3-10 years	**-Amenorrhea with levonorgestrel, but increased menstrual flow and cramping with the copper IUD** -Copper IUD can also be used for emergency contraception
Implant *(etonogestrel)* 	0.05%	3 years	-Weight gain and mood changes -Breast tenderness
Injection *(depot medroxyprogesterone acetate or norethindrone enanthate)* 	6%	3 months (+/- 2 weeks)	-**Osteoporosis – limit to 2 years** -**Weight gain** and mood changes **-Increased menstrual flow and cramping** -May reduce epileptic seizures by 30% -Reduces acute sickle cell crisis by 70%
Patch *(ethinyl estradiol & norelgestromin)* 	9%	1 week	**-Less effective in women > 198 lb (avoid)** -Increased exposure could increase risk of VTE?
Vaginal Ring *(ethinyl estradiol & etonorgestrel)* 	9%	1 month	-Vaginitis, vaginal secretion, weight gain, and sinusitis -Little impact on lipids as it bypasses hepatic metabolism

US Medical Eligibility Criteria (US MEC) for Contraceptive Use, 2016 | CDC. Cdc.gov. Published 2016. Accessed February 10, 2022. CDC. Selected Practice Recommendations. MMWR 2016; 65(4)

Combined Oral Contraceptive Differences

Length of Cycle	Estrogen Dosage	Dose Adjustments Within cycle	Unique Characteristics
• 21 days / 7 days placebo • 24 days / 4 days placebo • 84 days / 7 days placebo • Continuous active	• 50 mcg EE • 30-35 mcg EE • 10-25 mcg EE	• Monophasic • Biphasic, triphasic, and quadriphasic	• Small dose estrogen or iron in the last week

Cooper D, et al. Oral Contraceptive Pills. Ncbi.nlm.nih.gov. https://www.ncbi.nlm.nih.gov/books/NBK430882/. Published 2022. Accessed February 13, 2022.

Risks of Hormonal Therapy

Risk factors for each potential adverse event

Stroke/ Myocardial Infarction	• Smoking • Hypertension • Migraines with aura
DVT/ Pulmonary Embolism	• Smoking • History of VTE, stroke, diabetes with complications • ASCVD risk factors
Cancer	• Personal history of breast cancer

Cooper D, Mahdy H. Oral Contraceptive Pills. Ncbi.nlm.nih.gov. https://www.ncbi.nlm.nih.gov/books/NBK430882/. Published 2022. Accessed February 10, 2022.

Risk of VTE with Combined Contraception

	Results	Increased Risk	No Difference
Combined Oral Contraceptives *(estrogen and a progestin)*	2-3 fold increase in VTE	20 µg EE with levonorgestrel vs. non-use: RR 2.2 (95% CI, 1.3–3.6) 50 µg vs 20 µg EE with levonorgestrel: RR 2.3 (95% CI, 1.3–4.2)	30 µg vs. 20 µg EE with levonorgestrel: RR 1.1 (95% CI, 0.7–1.7)
Progesterone	Likely no increase in VTE	2 studies found that DMPA and progesterone only oral contraceptives increased odds of VTE in women (who smoked or had Factor V Lieden)	The majority of the studies showed that progesterone only oral contraceptives, implants, or IUDs did **not** increase the risk of VTE, myocardial infarctions, or stroke

Practice Committee of the American Society for Reproductive Medicine. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. *Fertil Steril*. 2017;107(1):43-51.

Tepper NK, et al. Progestin-only contraception and thromboembolism: A systematic review. *Contraception*. 2016;94(6):678-700. Bergendal A, et al. Association of venous thromboembolism with hormonal contraception and thrombophilis genotypes. Obstet Gynecol 2014; 124:600-9. Cardiovasuclar disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, caseontrol study. WHO Collaborative Study of Cardiovascular Disease and sSteroid Hormone Contraception. Contraception. 1998;57:315-24.

Risk of VTE with Combined Contraception

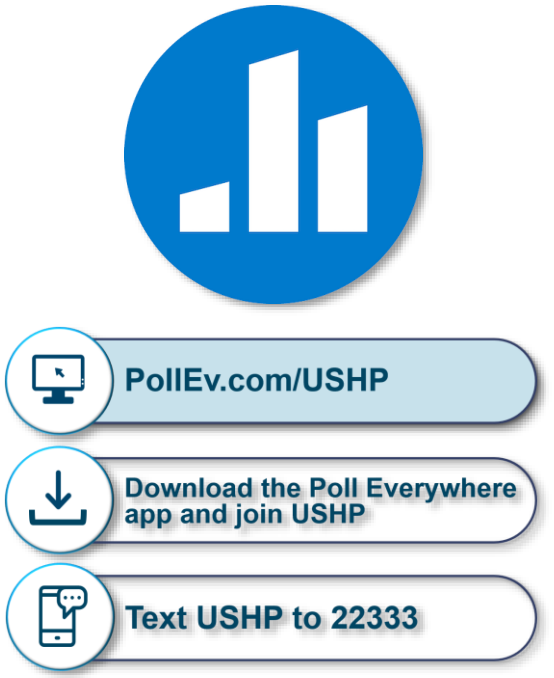
	Results	Increased Risk	No Difference
Patch	Inconclusive	2 studies found that patches increased the risk of VTE by 2.2-2.3 times compared to combined oral products containing levonorgestrel	1 found an elevated risk that was not statistically significant 4 found no increased risk
Ring	Inconclusive	1 study found the ring increased risk of VTE by 1.9 compared to levonorgesterel combined oral contraceptives	2 studies did not find an increased risk

S.S. Jick, H. Jick Cerebral venous sinus thrombosis in users of four hormonal contraceptives: levonorgestrel-containing oral contraceptives, norgestimate-containing oral contraceptives, desogestrel-containing oral contraceptives and the contraceptive patch. Contraception, 74 (2006), pp. 290-292. S.S. Jick, et al. Postmarketing study of ORTHO EVRA and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism.

Lidegaard O., et al. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. Br. Med J 2012; 344:e2990. Bergendal A., et al. Association of venous thromboembolism with hormonal contraception and thrombophilis genotypes. Obstet Gynecol 2014; 124:60-9. Dinger J, et al. Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. Obstet Gynecol 2013;122:800-8. D.D. Dore, et al. Extended case–control study results on thromboembolic outcomes among transdermal contraceptive users. Contraception, 81 (2010), pp. 408-413.

Test Your Knowledge: Technician Question

1. A “monophasic” oral contraceptive is one that:
   A. Contains only estrogen
   B. Only contains active medication with no placebo pills
   C. Has the same dose of either estrogen or progesterone each day
   D. Does not include added iron during the placebo week



Access to Contraception

Family Planning Access Act

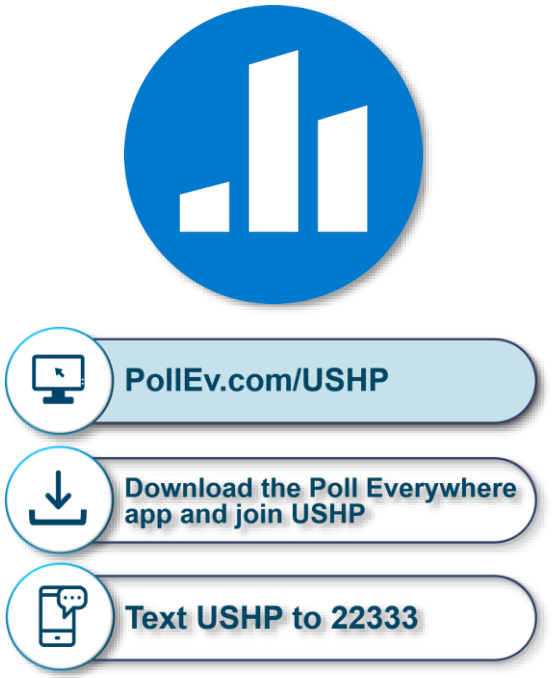
See Utah Health Code Chapter 64

Family Planning Access Act. https://le.utah.gov/xcode/Title26/Chapter64/C26-64_2018050820180508.pdf. Published 2018. Accessed February 10, 2022. Committee on Health Care for Underserved Women, 2015. *Access to Contraception*. [online] Acog.org. Available at: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2015/01/access-to-contraception> [Accessed 10 February 2022].

Test Your Knowledge: Technician Question

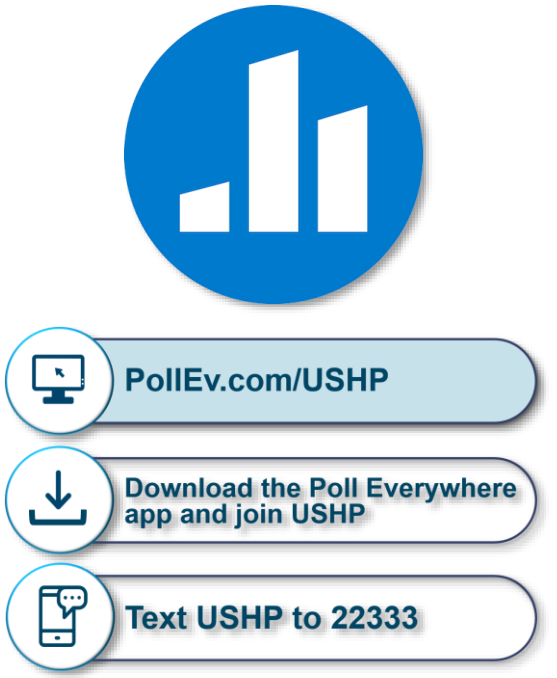
2. In Utah, why might a woman have difficulty obtaining contraception?

A. Cost
B. Difficulty affording contraception
C. Exaggerated concerns about the risks of contraception
D. All of the above



Test Your Knowledge: Pharmacist Question

1. MT is a 31 year old female with chronic kidney disease and type two diabetes who presents to the clinic inquiring about birth control options. She prefers not to take a daily medication and reports heavy, painful menstrual bleeds. Patient weighs 200 lbs and has osteopenia. What would be the best option for her?
   A. Copper IUD
   B. Injection
   C. Patch
   D. Intrauterine ring



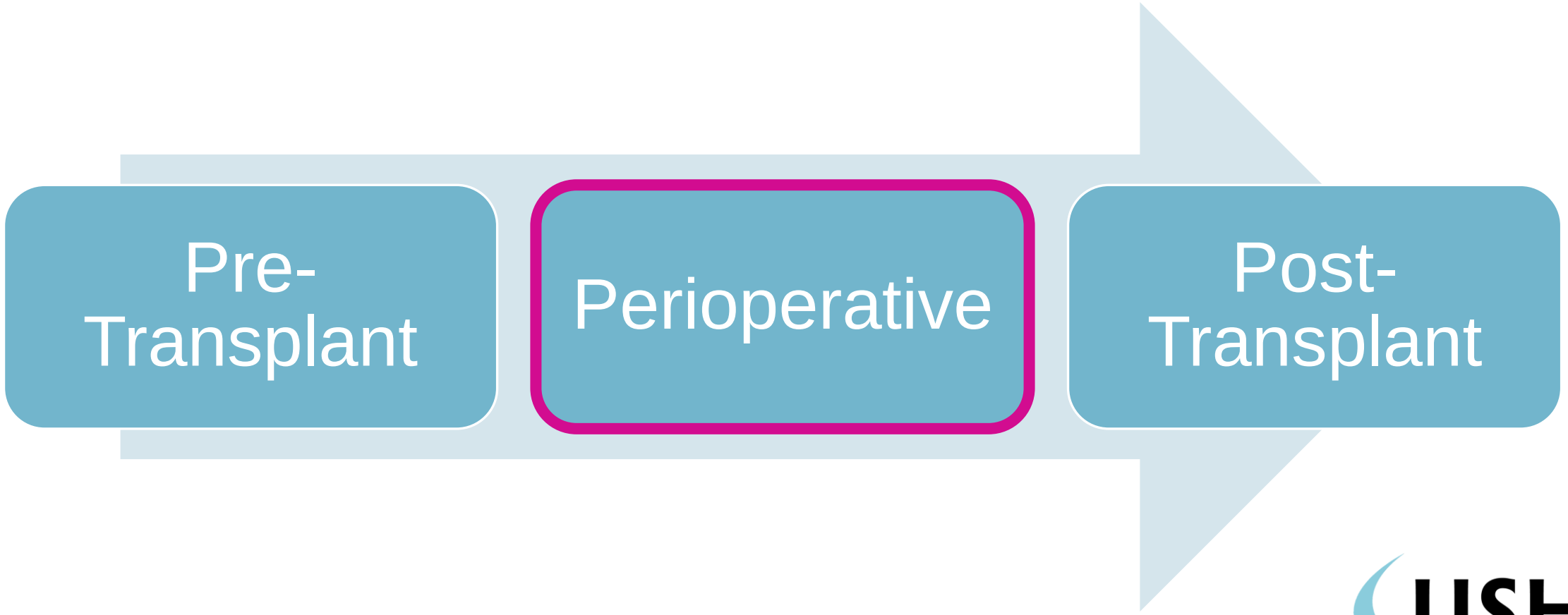
Pre-Transplant Counseling!

- Norwegian retrospective study of 118 female renal transplant recipients 22-49 years old
  - 37% did not receive advice on contraceptive methods in the early post-transplant phase
  - 45% had not received any advice on timing of pregnancy after transplant

Prior to transplant, all patients of child-bearing age should be counseled on importance of contraception

Eide IA, et al. Contraceptive Choices and Counseling in Norwegian Female Renal Transplant Recipients. *Transplant Proc*. 2019;51(2):470-474.

Contraception



Rates of VTE in Transplant

The overall annual incidence of VTE in the U.S. general population has been estimated to be 0.145%, with DVT rate of 0.048% and acute PE in 0.023%

Organ	DVT	Associated outcomes
Lung	1.78 - 45%	VTE predicted a lower post-transplant survival
Heart	9.3%	Increased death with PE that were secondary to VTE
Kidney	6 - 8.9%	Higher risk of death and death-censored graft loss compared to matched recipients who did not get a post-transplant VTE
Liver	3.5 - 8.6%	Intraoperative VTE are uncommon, but associated with elevated mortality (ranging from 45% to 68% for PE and 50% for early hepatic artery thrombosis and from 32% to 60% for portal vein thrombosis)

Gould MK, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in Chest. 2012 May;141(5):1369]. *Chest*. 2012;141(2 Suppl):e227S-e277S. Shen T., et al. Risk Factors and Prevalence of VTE in Lung Transplant Patients and It's Impact on Outcome. Chest 158: 4 - A2405. 2020. Elboudwarej O, et al. Risk of deep vein thrombosis and pulmonary embolism after heart transplantation: clinical outcomes comparing upper extremity deep vein thrombosis and lower extremity deep vein thrombosis. *Clin Transplant*. 2015;29(7):629-635. Lam NN, Garg AX, Knoll GA, et al. Venous Thromboembolism and the Risk of Death and Graft Loss in Kidney Transplant Recipients. *Am J Nephrol*. 2017;46(4):343-354. De Pietri L, et al. Perioperative thromboprophylaxis in liver transplant patients. *World J Gastroenterol*. 2018;24(27):2931-2948. Sakai T, et al. Pulmonary thromboembolism during adult liver transplantation: incidence, clinical presentation, outcome, risk factors, and diagnostic predictors. *Br J Anaesth*. 2012;108(3):469-477.

Perioperative Considerations

- IUD placement
  - No need for removal
  - Historic concerns for inefficacy
  - No de novo placement in patients with complicated graft function

- Risk of clot with estrogen products

Perioperative Considerations: Estrogen

- Due to the increased risk of clotting with estrogen products, some transplant centers require patients to be completely off estrogen products 2-4 weeks prior to transplant
- Other centers transplant patients while they are on these products, but may consider adding DVT prophylaxis

- However, there is no current data that describes the risk increase of using estrogen products in transplant patients
  - Clinical judgement is needed!

VTE Risk Considerations

- Type of transplant
- Prolonged surgical times and post-surgical immobilization times
- Estrogen exposure
- Other risk factors
  - Steroid use
  - COVID-19
  - Advancing age
  - African-Americans
  - History of VTE, stroke, diabetes, antiphospholipid syndrome, and migraines with aura
  - Other ASCVD risks

McLendon K, et al. Deep Venous Thrombosis Risk Factors. Ncbi.nlm.nih.gov. https://www.ncbi.nlm.nih.gov/books/NBK470215/. Published 2021. Accessed February 10, 2022.

VTE Risk Considerations

Depending on risk factors, consider avoidance of the patch, estrogen products, and/or any hormonal products 2-8 weeks before and 2-4 weeks after transplant surgery

Highest VTE Risk
- High doses 50 mcg EE

Consider adding DVT prophylaxis with aspirin, enoxaparin or another anticoagulation agent

Early Post-Operative Management

IUDs

- No need for removal
- Consider de novo placements

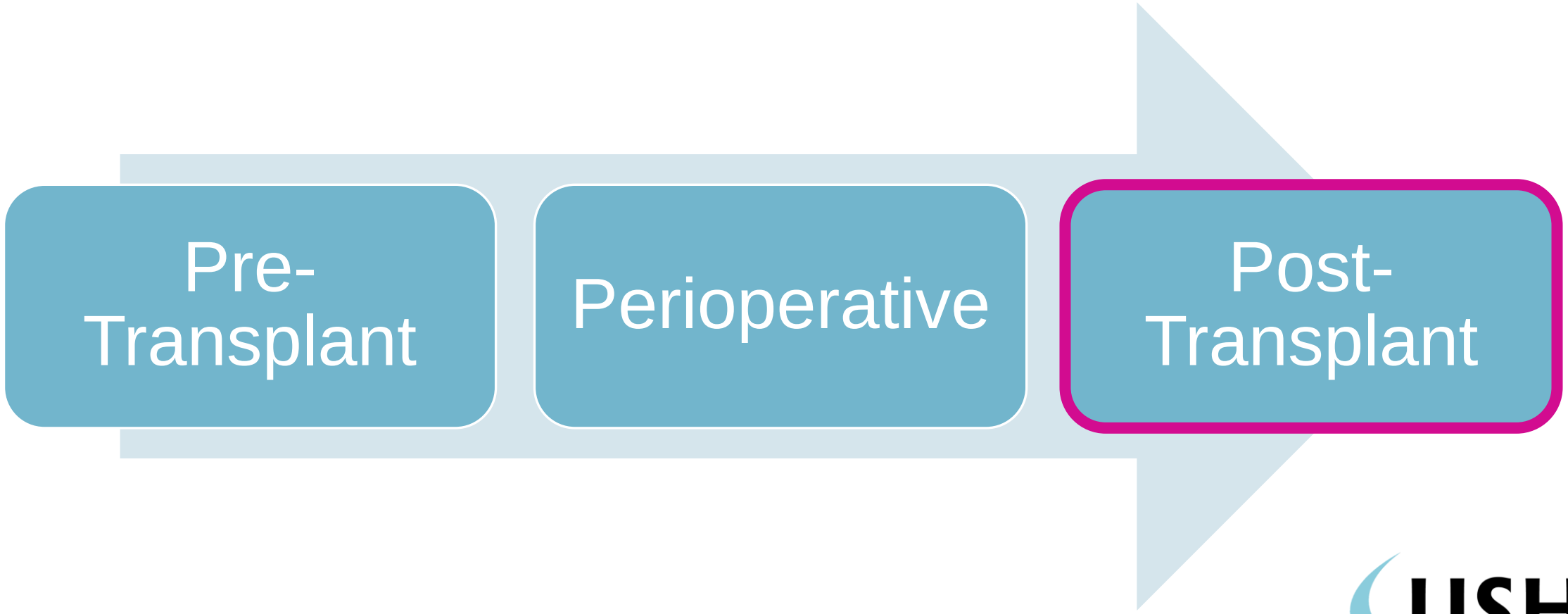
Progesterone only

- Can continue prior to surgery
- Hold oral products during admission, but likely safe to continue any therapy on discharge

Combined hormonal contraceptive methods

- If able, hold 4-8 weeks prior to surgery
- If able, hold 2-4 weeks after surgery

Contraception



Post-Transplant Considerations

- Amenorrhea pre-transplant
- Pregnancy Avoidance:
  - Pregnancy should be avoided for **at least** 1 year after transplant
  - High risk pregnancies due to potential complications of preeclampsia, preterm delivery, and low birth weight
  - Mycophenolate
- Cardiovascular Risks




Kidneys: Facts, Function & Diseases. livescience.com. https://www.livescience.com/52047-kidneys.html. Published 2022. Accessed February 13, 2022. 2018 Viral Hepatitis Surveillance Report | CDC. Cdc.gov. https://www.cdc.gov/hepatitis/statistics/2018surveillance/index.htm. Published 2022. Accessed February 13, 2022. Gaea Marelle Miranda M. Structure and Function of the Heart. News-Medical.net. https://www.news-medical.net/health/Structure-and-Function-of-the-Heart.aspx. Published 2022. Accessed February 13, 2022. Facts, Function and Diseases. livescience.com. https://www.livescience.com/52250-lung.html. Published 2022. Accessed February 13, 2022.

Post-Transplant Contraceptive Guidance

AST 2005 recommendations

- No recommendation for a specific agent
  - Balance risk and benefits of each method
- IUDs not recommended given potential decrease in efficacy and potential risk for infection

CDC 2016 recommendations

- Stable graft function – all contraception is safe
- No hormonal contraception if:
  - Complicated graft function (acute or chronic graft failure or rejection)
  - Uncontrolled hypertension, history of stroke, thrombosis, or hypercoagulable state
- IUD placement
  - No de novo placement in patients with complicated graft function

McKay DB, Josephson MA, Armenti VT, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant*. 2005;5(7):1592-1599.

McKay DB, Josephson MA, Armenti VT, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant*. 2005;5(7):1592-1599.
Gordon, C., & Harken, T. (2019). US Medical Eligibility Criteria (US MEC) for Contraceptive Use, 2016 | CDC. Cdc.gov. https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html. Published 2016. Accessed February 13, 2022.Controversies in family planning: intrauterine device placement in solid organ transplant patients. *Contraception*, *100*(3), 250–252.

Mycophenolate REMS Program

- Mycophenolate is teratogenic
  - Unless female patients choose to abstain from sexual intercourse with a man, patients must use acceptable contraception while taking mycophenolate and **for 6 weeks after stopping**
  - Link to the MPA REMS program: https://www.mycophenolaterems.com
- **May also decrease the effectiveness of hormonal therapy**
  - Mean level of levonorgestrel decreases by about 15% and great inter-patient variability in ethinyl estradiol levels

Welcome to Mycophenolate REMS. Mycophenolaterems.com. https://www.mycophenolaterems.com/#Main/Prescribers. Published 2022. Accessed February 13, 2022

Mycophenolate REMS Program

MYCOPHENOLATE REMS

Option 1 | Use Method Alone

- Pick one item from (A)
  - ► Most effective: Less than 1 pregnancy per 100 women in one year

A


Intrauterine Device (IUD)


Tubal Sterilization


Vasectomy

Option 2 | Use Hormone & Barrier

- Pick one item from (B) **and** one item from (C1) or (C2) shown below
  - ► 4-7 pregnancies per 100 women in one year

B


Progesterone Only Injection


Birth Control Pill


Birth Control (Progesterone) Patch


Vaginal Ring


Progesterone Only Implant

Option 3 | Use Two Barriers

- Pick one item from (C1) **and** one from (C2)
  - ► Least effective: 13 or more pregnancies per 100 women in one year

C

1


Female Condom


Male Condom

2


Female Diaphragm with Spermicide


Female Birth Control Sponge


Cervical Cap with Spermicide

USHP

Post-Transplant Contraceptive Experience

Three recent literature reviews:

- 2010 - 7 studies showed that the combined oral contraceptives and patch effectively prevented pregnancy without significant variation in biochemical markers from the general population
- 2019 - Transplant recipients with either IUD did not have unintended pregnancies or complications compared to those without organ transplants
- 2018 – In heart transplant recipients almost all forms of contraception are acceptable
  - However, in a complicated transplantation, combined hormonal contraceptives are contraindicated and de novo IUD insertion is not recommended

Krajewski CM, Geetha D, Gomez-Lobo V. Contraceptive options for women with a history of solid-organ transplantation. *Transplantation*. 2013;95(10):1183-1186. Gordon C, Harken T. Controversies in family planning: intrauterine device placement in solid organ transplant patients. *Contraception*. 2019;100(3):250-252.

Klein CL, Josephson MA. Post-Transplant Pregnancy and Contraception. *Clin J Am Soc Nephrol*. 2022;17(1):114-120. doi:10.2215/CJN.14100820 Paulen ME, Folger SG, Curtis KM, Jamieson DJ. Contraceptive use among solid organ transplant patients: a systematic review. *Contraception*. 2010;82(1):102-112.

Contraceptive Summary

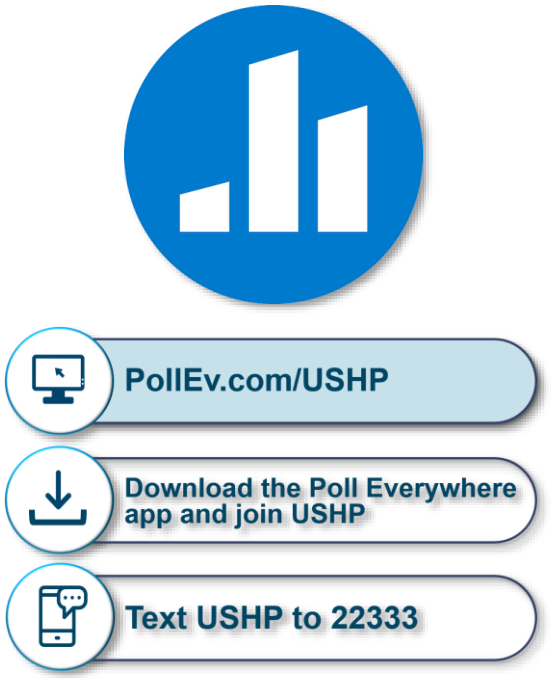
Individualize therapy!

- Post-transplant may have to consider holding estrogen therapy or giving DVT prophylaxis
- Consider:
  - Time from Transplant
  - Graft Stability
  - CV Risk

Test Your Knowledge: Pharmacist Question

2. MT returns to clinic 5 years later (age 36) 2 months after undergoing a renal transplant due to ESRD secondary to diabetes. She is currently on tacrolimus, mycophenolate, and prednisone for immunosuppression. She returns to clinic and is inquiring about what birth control she should start. Which of the following options would be optimal for her?

A. Combination hormonal oral product
B. Patch
C. Implant
D. IUD
E. Two barrier methods

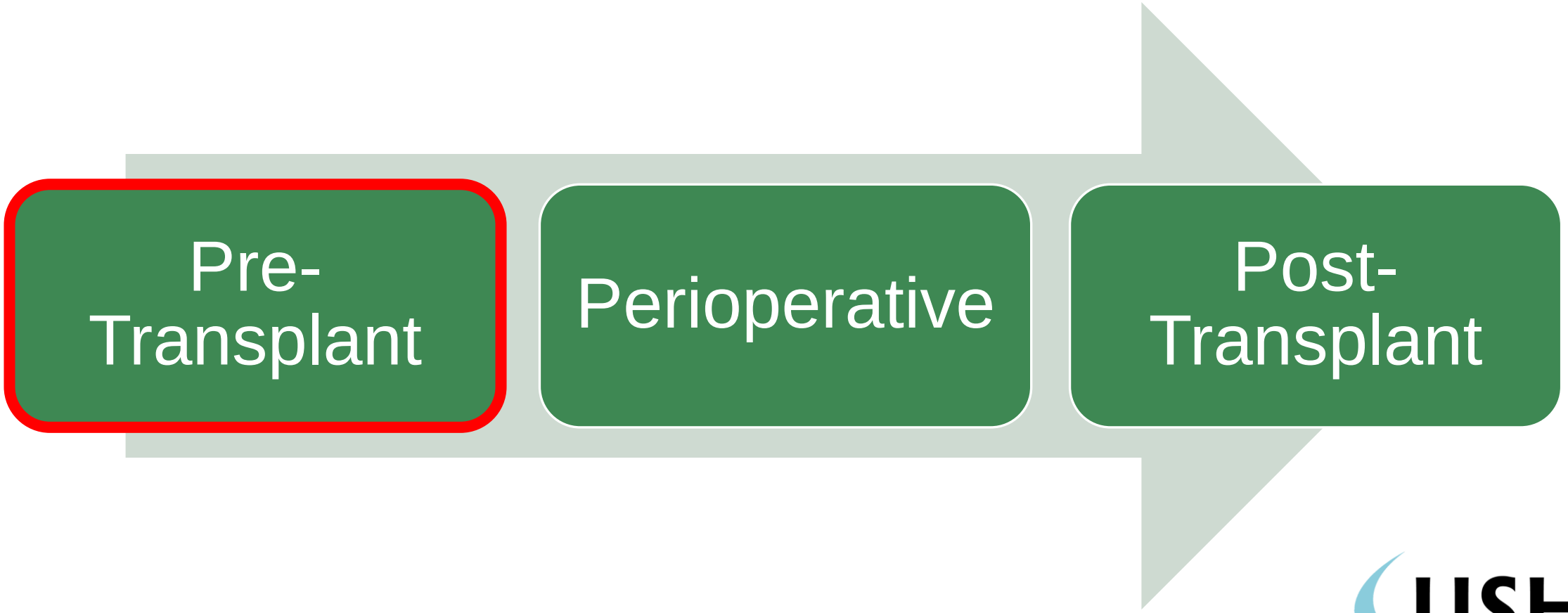


Contraception → Menopause

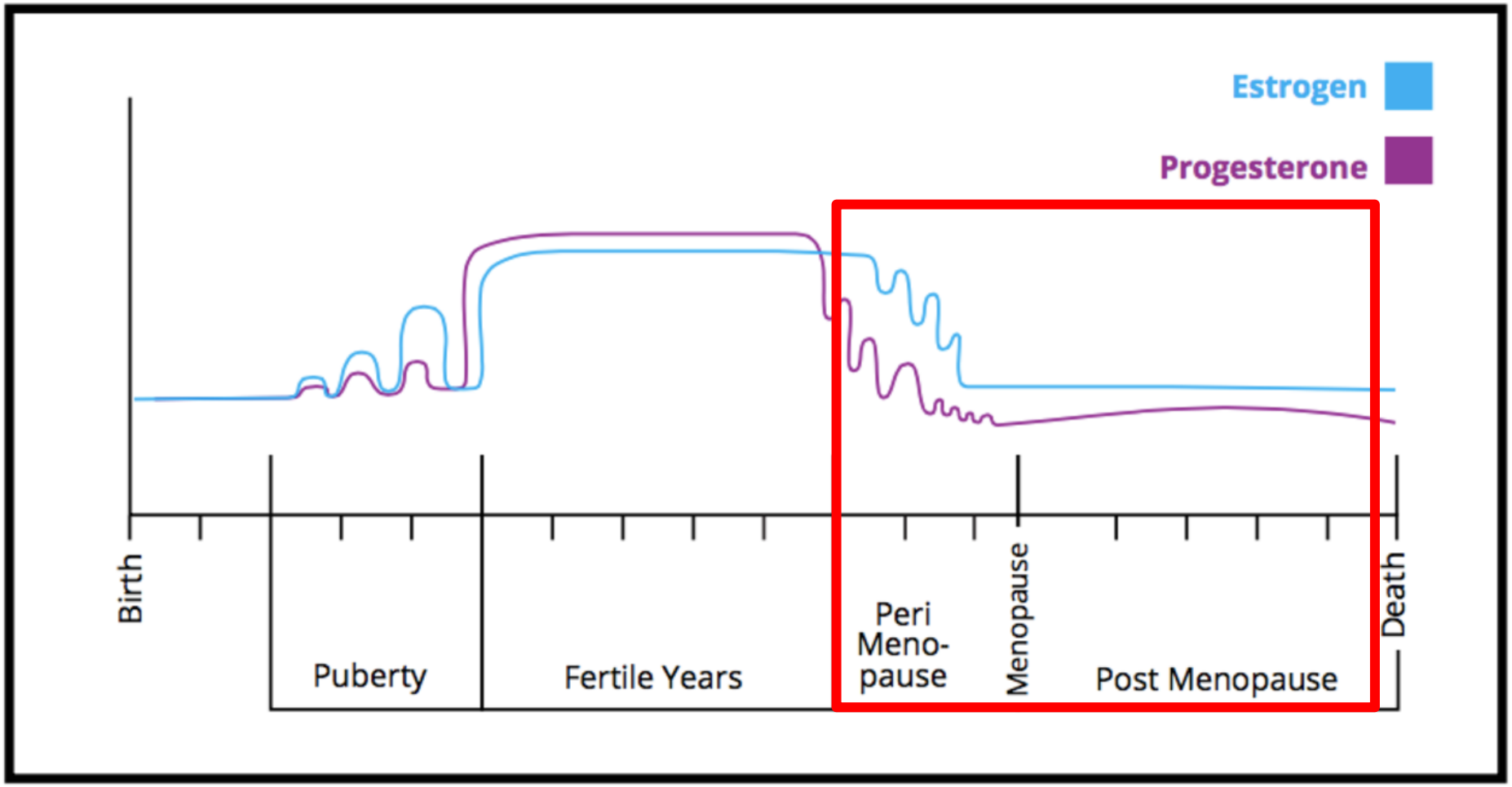



Kidneys: Facts, Function & Diseases. livescience.com. https://www.livescience.com/52047-kidneys.html. Published 2022. Accessed February 13, 2022. 2018 Viral Hepatitis Surveillance Report | CDC. Cdc.gov. https://www.cdc.gov/hepatitis/statistics/2018surveillance/index.htm. Published 2022. Accessed February 13, 2022. Gaea Marelle Miranda M. Structure and Function of the Heart. News-Medical.net. https://www.news-medical.net/health/Structure-and-Function-of-the-Heart.aspx. Published 2022. Accessed February 13, 2022. Facts, Function and Diseases. livescience.com. https://www.livescience.com/52250-lung.html. Published 2022. Accessed February 13, 2022.

Menopause



Hormone Levels Over a Lifetime (for a female with ovaries)



Female Hormone Lifecycle. Menopausenaturalsolutions.com. https://www.menopausenaturalsolutions.com/blog/female-hormone-lifecycle. Published 2022. Accessed February 13, 2022.
Data are based loosely on on puberty (Elmlinger et al., 2005), menopause (Kratz et al., 2004), and in pregnancy (Abbassi-Ghanavati et al., 2009).

Perimenopause

- Symptoms:
  - Changes in menstrual patterns
  - Vasomotor symptoms
  - Psychological and mental disturbances
  - Sexual dysfunction
  - Somatic symptoms
  - Other

Paciuc J. Hormone Therapy in Menopause. *Adv Exp Med Biol*. 2020;1242:89-120.

Post-Menopausal Products

Oral Estrogen	Transdermal Estrogen	Vaginal Estrogen	Progestin Products
• Tablets	• Patch • Gel • Spray	• Cream • Ring	• Oral products

- Estrogen alone should <u>not</u> be used for patients with an intact uterus
  - Increased risk of **endometrial hyperplasia** and **glandular endometrium carcinoma** within 6 months of monotherapy with estrogen

Paciuc J. Hormone Therapy in Menopause. *Adv Exp Med Biol*. 2020;1242:89-120.

Estrogen & Risk for VTE

In studies of healthy post-menopausal women on estrogen:

- Bayesian meta-analysis of 12 studies showed a pooled risk of 2.14 (95% CI 1.64-2.81)

Age (years)	Annual Incidence of VTE with Estrogen Use per the American College of Obstetrician & Gynecologists
40-49	0.05%
50-69	0.06-0.12%
70-80	0.3-0.4%
80 +	0.7%

Silverstein MD,et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585-593.

Miller J, et al. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force [published correction appears in Ann Intern Med. 2003 Feb 18;138(4):360.]. *Ann Intern Med*. 2002;136(9):680-690. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41(1):3-14.

Hormonal Therapies

- Transdermal estrogens have the same effect as oral estrogens
  - Same effect on bone density and treating menopausal symptoms
  - BUT results in lower risk of VTE and myocardium infarcts
  - AND less pronounced influence on serum lipid concentrations in comparison to oral agents

- A multicenter case–control study (women ages 45–70)
  - Compared with patients who didn't use estrogen, the odds ratio for VTE in users of
    - Oral estrogen was 4.2 (95% CI, 1.5–11.6)
    - Transdermal estrogen was 0.9 (95% CI, 0.4–2.1)

Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation*. 2007;115(7):840-845.

Non-Hormonal Therapies

Non-Hormonal Medications:

- Antidepressants
- Gabapentin
- Vitamin E

Alternative Medicine:

- Isoflavone extracts
- Black Cohosh
- St. John's Wort

Non-Pharmaceutical Therapies:

- Exercise and healthy diet
- Relaxation techniques
- Layered clothing
- Sleep and stress management
- Reduce caffeine, alcohol, and spicy food intake

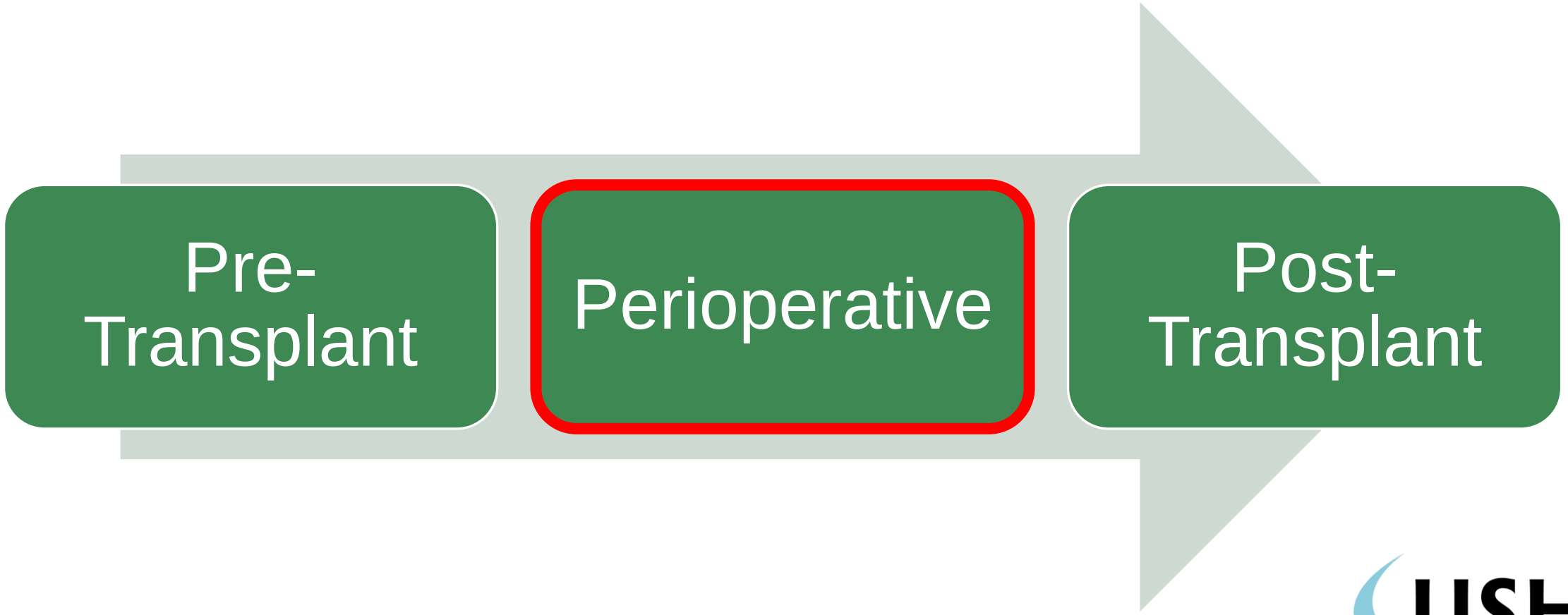
Hickey M, Saunders CM, Stuckey BG. Non-hormonal treatments for menopausal symptoms. *Maturitas*. 2007;57(1):85-89. doi:10.1016/j.maturitas.2007.02.016

Pre-Transplant Management

Consult with PCP or OBGYN prior to transplant to develop a plan

- Patient buy-in!
- Slow taper
- Consider non-hormonal therapies and lifestyle modifications
- Avoid alternative medicine prior to transplant

Menopause



Early Post-Operative Management

Risk of VTE with estrogen

Major differences from contraception:

- Total lifetime exposure to estrogen
- Patch confers less risk of thromboembolism
- Patient's experience

Early Post-Operative Management

Consider holding estrogen products prior to surgery

- If able, wean off therapy 4-6 weeks prior to surgery
- If able, hold for 2-4 weeks after surgery

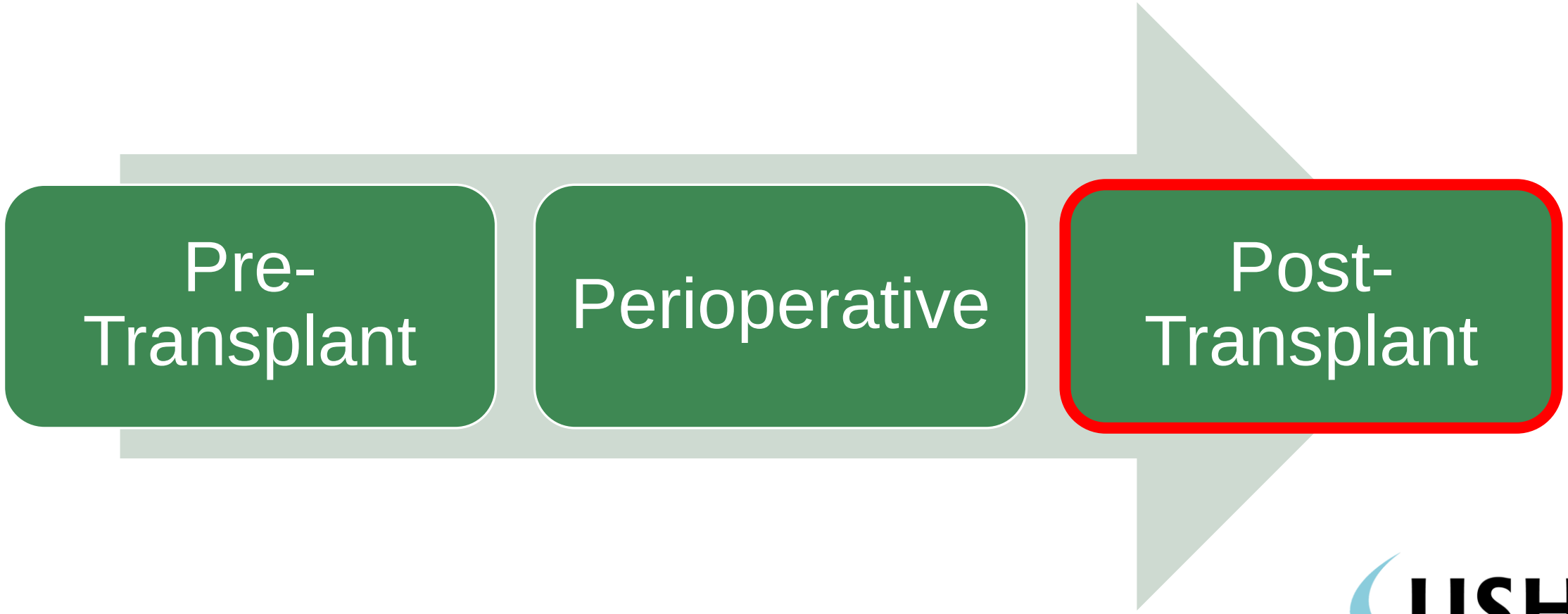
*Hold progesterone

Highest VTE Risk:

- High total years of estrogen
- High dose
- Oral route

Consider adding DVT prophylaxis with aspirin, enoxaparin, or another anticoagulation agent

Menopause



Menopause in SOT

- If continued on therapy, periodically assess ongoing need
- Consider total years of estrogen!
  - VTE risk
  - Breast cancer risk
- Osteoporosis




Kidneys: Facts, Function & Diseases. livescience.com. https://www.livescience.com/52047-kidneys.html. Published 2022. Accessed February 13, 2022. 2018 Viral Hepatitis Surveillance Report | CDC. Cdc.gov. https://www.cdc.gov/hepatitis/statistics/2018surveillance/index.htm. Published 2022. Accessed February 13, 2022. Gaea Marelle Miranda M. Structure and Function of the Heart. News-Medical.net. https://www.news-medical.net/health/Structure-and-Function-of-the-Heart.aspx. Published 2022. Accessed February 13, 2022. Facts, Function and Diseases. livescience.com. https://www.livescience.com/52250-lung.html. Published 2022. Accessed February 13, 2022.

Risk of Cancer

- A systematic review of >79,000 renal transplant patients found:
  - Higher risk of all cancers (standard incidence ratio of 2.89; P<0.001)
  - Skin cancer (12.14; P<0.001)
  - Breast cancer (1.11; P<0.001)
  - No link between transplant and risk of uterine cancer (P=0.171)
- The Women's Health Initiative showed increased risk of breast and endometrial cancer being exposed to estrogen for a long period of time or to high levels
  - Starting menstruation early
  - Going through menopause late
  - Being older at first pregnancy
  - Never having given birth

Wang Y, et al. Cancer risks in recipients of renal transplants: a meta-analysis of cohort studies. *Oncotarget*. 2017;9(20):15375-15385. Published 2017 Dec 16.

Aedo S, et al. Women's Health Initiative estrogen plus progestin clinical trial: a study that does not allow establishing relevant clinical risks. *Menopause*. 2015;22(12):1317-1322. Donneyong MM, et al. The Women's Health Initiative Estrogen-alone Trial had differential disease and medical expenditure consequences across age groups. *Menopause*. 2020;27(6):632-639.

Osteoporosis

- Solid organ transplant recipients have an increased risk of bone disease
- Bone mass loss after transplant
  - Largest decline in the first 6-12 months
  - Worse for liver transplant patients with autoimmune hepatitis and primary biliary cirrhosis
- New fractures after one year of glucocorticoid therapy can be as high as 17%
  - No "safe dose" of glucocorticoid therapy
    - Fractures can occur within 3 months of initiation of steroid therapy and with daily doses as low as 2.5 mg of prednisone in terms of skeletal safety
  - Even inhaled steroids can lead to bone loss, if used for prolonged periods of time

Bia M. Evaluation and management of bone disease and fractures post transplant. *Transplant Rev (Orlando)*. 2008;22(1):52-61. Civitelli R, Ziambaras K. Epidemiology of glucocorticoid-induced osteoporosis. *J Endocrinol Invest*. 2008;31(7 Suppl):2-6.

Aedo S, et al. Women's Health Initiative estrogen plus progestin clinical trial: a study that does not allow establishing relevant clinical risks. *Menopause*. 2015;22(12):1317-1322. Donneyong MM, et al. The Women's Health Initiative Estrogen-alone Trial had differential disease and medical expenditure consequences across age groups. *Menopause*. 2020;27(6):632-639.

Effect of low dose steroids

Fractures are seen at bone mineral density levels that usually carry lower risk in women with post-menopausal osteoporosis

- Effects may be independent of bone mass

The Women's Health Initiative showed that healthy women taking estrogen had temporary protection from osteoporosis

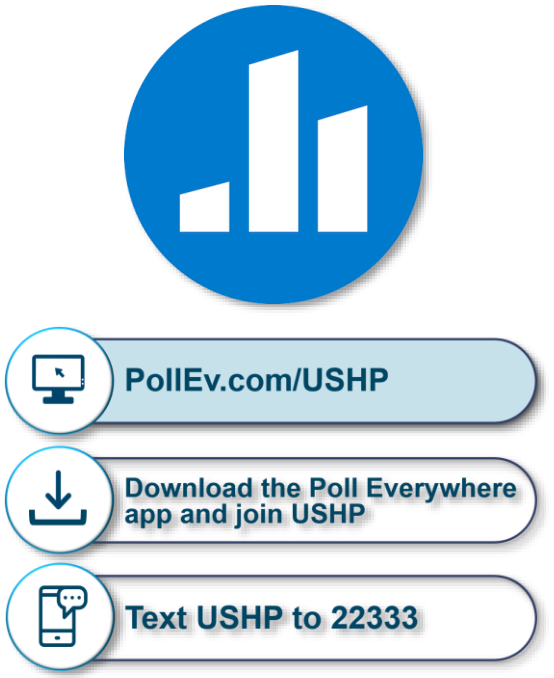
Bia M. Evaluation and management of bone disease and fractures post transplant. *Transplant Rev (Orlando)*. 2008;22(1):52-61. Civitelli R,et al. Epidemiology of glucocorticoid-induced osteoporosis. *J Endocrinol Invest*. 2008;31(7 Suppl):2-6.

Aedo S, et al. Women's Health Initiative estrogen plus progestin clinical trial: a study that does not allow establishing relevant clinical risks. *Menopause*. 2015;22(12):1317-1322. Donneyong MM, Chang TJ, Roth JA, et al. The Women's Health Initiative Estrogen-alone Trial had differential disease and medical expenditure consequences across age groups. *Menopause*. 2020;27(6):632-639.

Test Your Knowledge: Technician Question

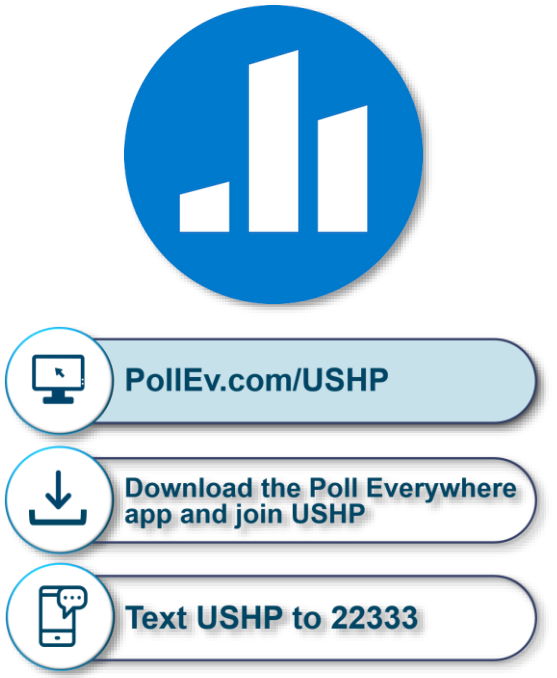
3. Match the product with its use

1.	Combination Estrogen/Progesterone Oral Tablets	A.	Vaginal Atrophy (Menopause)
2.	Copper IUD (Intrauterine device)	B.	Contraception OR Menopause
3.	Premarin Vaginal Cream	C.	Contraception



Test Your Knowledge: Pharmacist Question

3. Our renal transplant recipient MT patient recently turned 55. She is complaining of vaginal dryness and painful intercourse. Which of the following is the most appropriate option for treatment?
   A. Increase her daily exercise
   B. St. John's Wort once daily
   C. Start conjugated estrogens intravaginal cream
   D. Start conjugated estrogens oral product once daily



Summary

	Contraception	Menopause
Pre-transplant	May regain fertility after transplant Counsel patients on contraceptive options prior to transplant	Develop a peri-operative plan if patient is on estrogen therapy
Peri-operative	If using estrogen products peri-operatively, consider • Holding estrogen products • Starting DVT prophylaxis	If using estrogen products peri-operatively, consider • Holding estrogen products • Changing oral products to a transdermal patch • Starting DVT prophylaxis
Post-transplant	Transplant is not a contraindication to therapy - individualize! Consider: • Adherence • DVT risk with estrogen • Graft function stability • Use of mycophenolate	Transplant is not a contraindication to therapy - individualize! Consider: • DVT risk with estrogen products • Decreased risk with transdermal patch • Breast cancer risk • Potential benefit on bone health • Avoid herbal supplements

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