



From Healthy to Hazardous

How reproductive system functions impact cancer risk

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Disclosures

- I have no financial disclosures
- Covering three broad categories of gynecologic cancers
- Generalizing to common cancer types without addressing nuances in histologies
- Presenting information on things that we know *something* about
- Wide variability in experiences that each of you have had

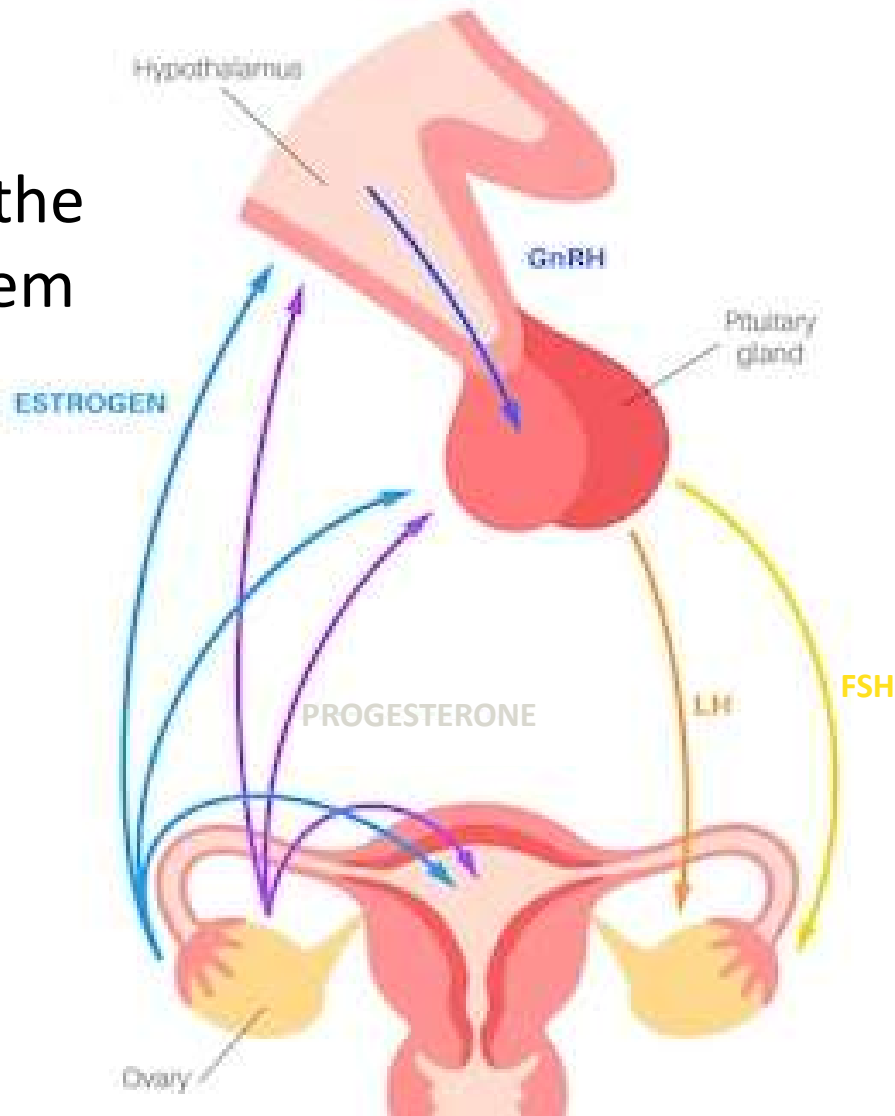


Objectives

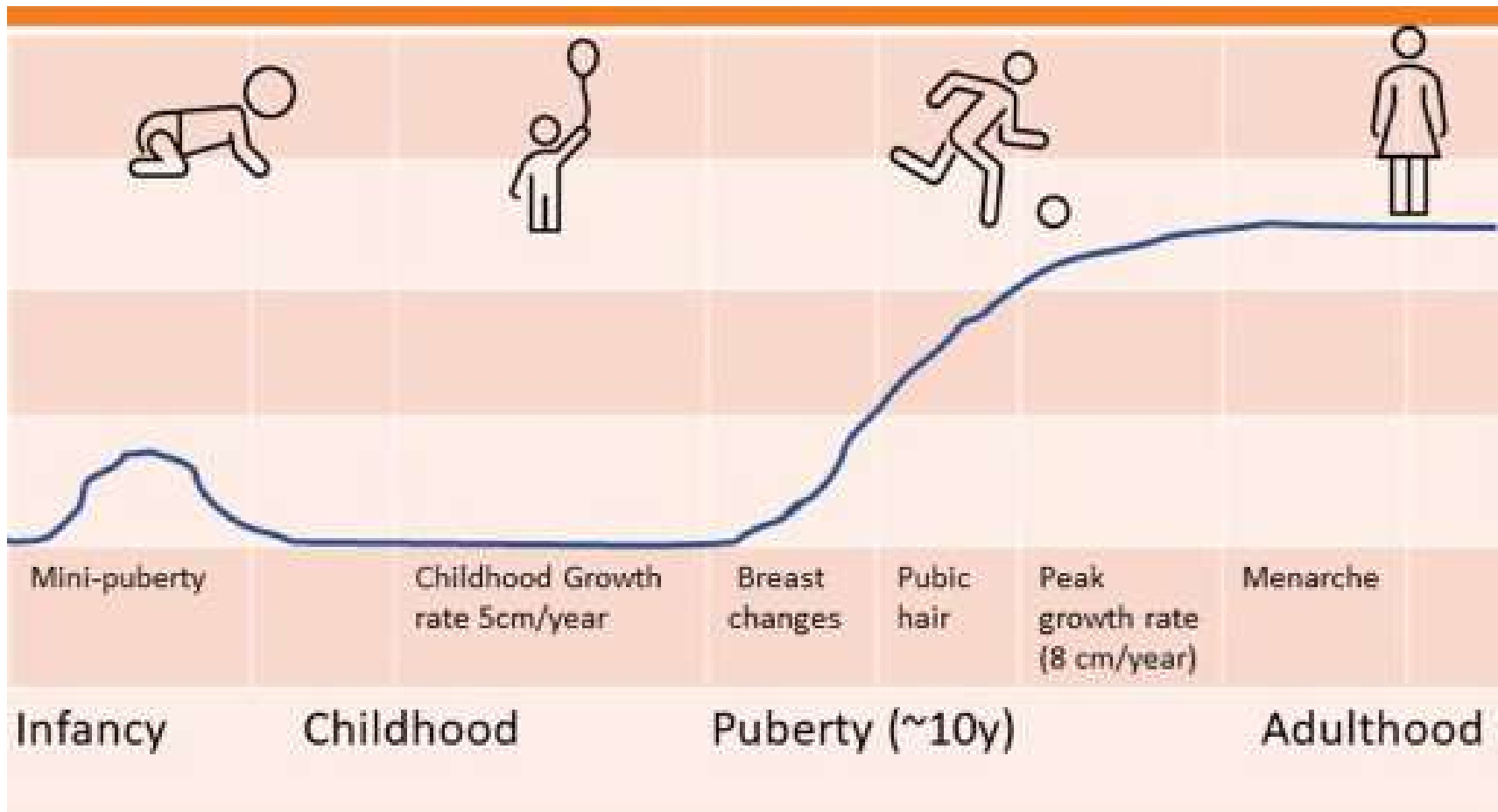
- Describe hormonal influences on cancer development
- Describe how ovarian/tubal processes influence cancer development
- Describe how natural sexual function puts us at risk for cervical cancer
- Look forward in using what we know to better care in the future

Hormonal Influences on Cancer Development

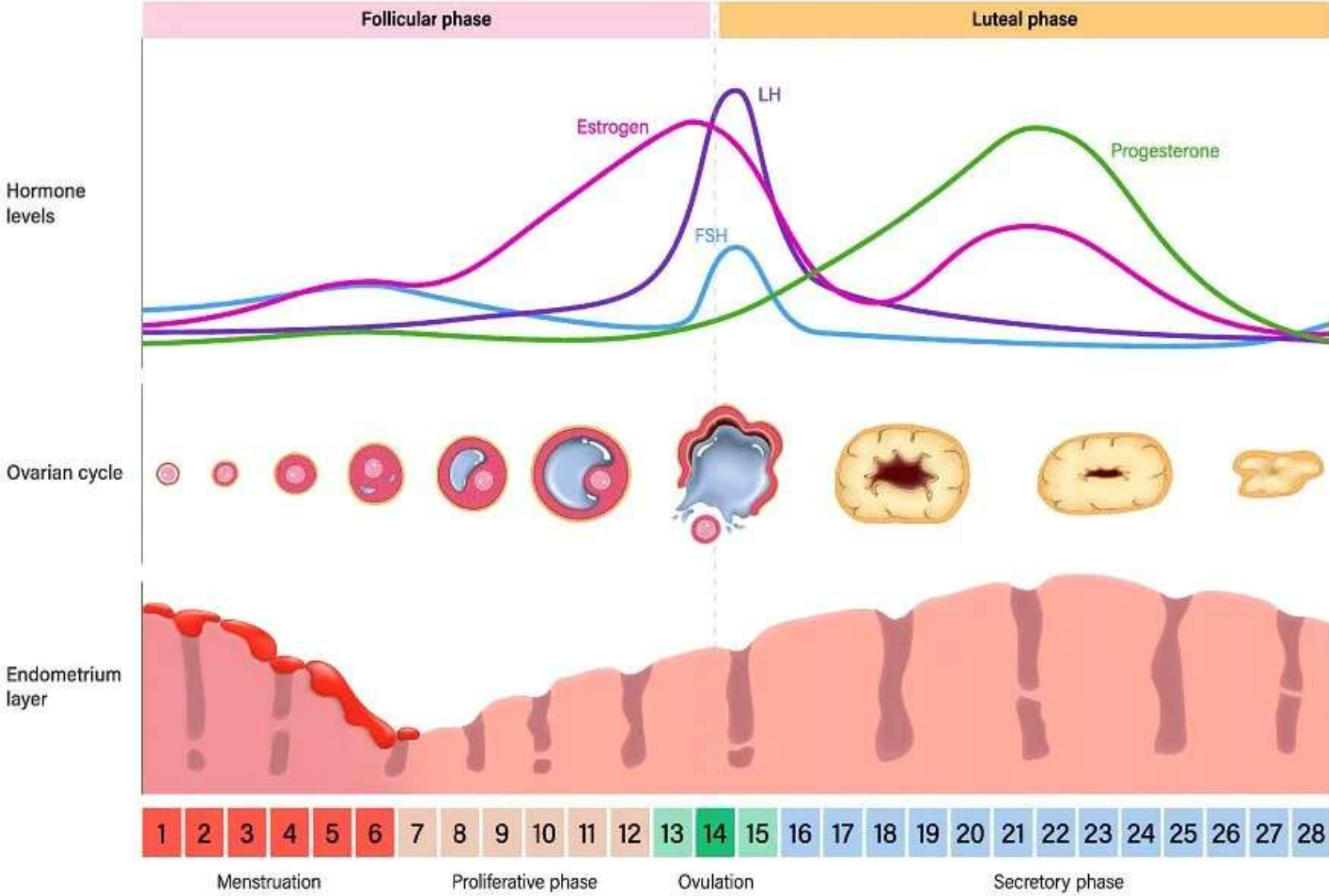
Hormonal Axis of the Reproductive System



Estrogen Over a Lifetime



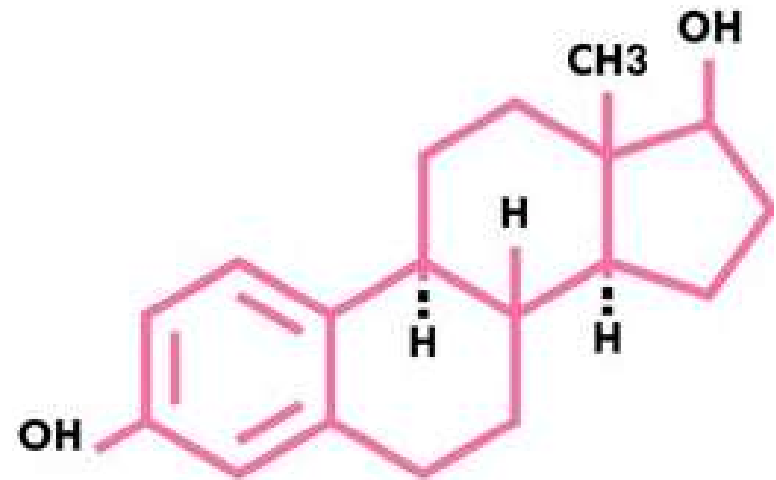
Menstrual cycle



Estrogen

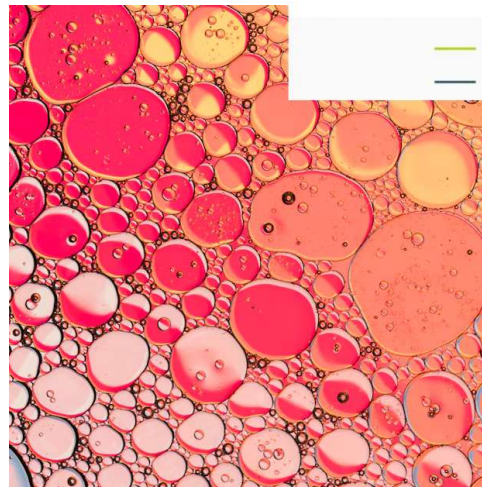
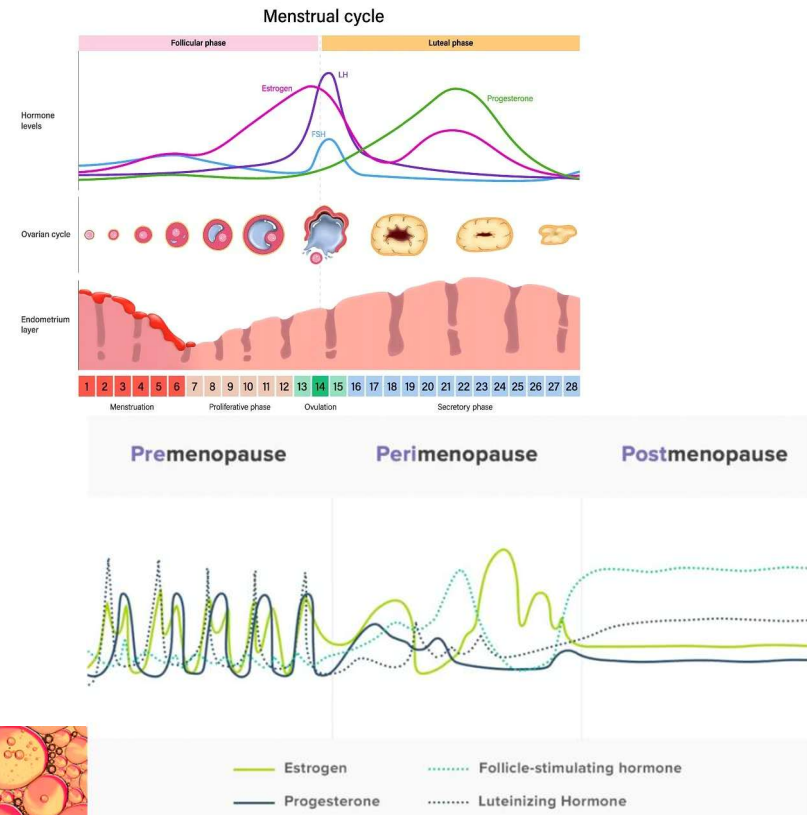
At its best

- Maturation of fallopian tubes, uterus, cervix, vagina
- Development of secondary sex characteristics at puberty
- Breast development at puberty
- Menstrual cycling
- Maintenance of pregnancy
- Sexual function

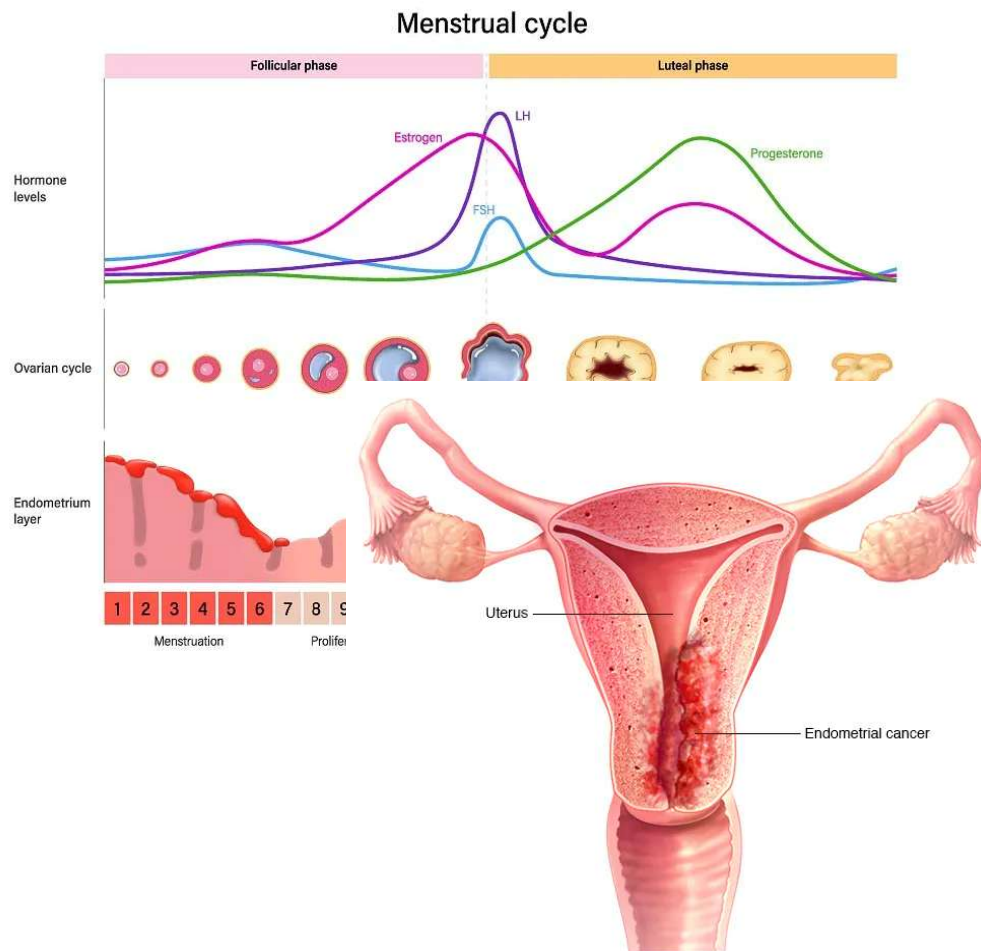


Causes of Estrogen Deregulation

- Anovulatory cycles
- Polycystic ovary syndrome
- Perimenopausal hormone dysregulation
- Hormone replacement therapy
- Obesity
- Early menarche
- Late menopause



Endometrial Cancer



- Excess/unopposed estrogen keeps uterine lining in a proliferative phase
- Unregulated and abnormal proliferation leads to development of hyperplasia and endometrial cancer

Hormonal Methods of Managing Hormones



- Intrauterine device use
- Oral contraceptive use



Spreading Awareness of Risk Factors and Risk Mitigation Strategies

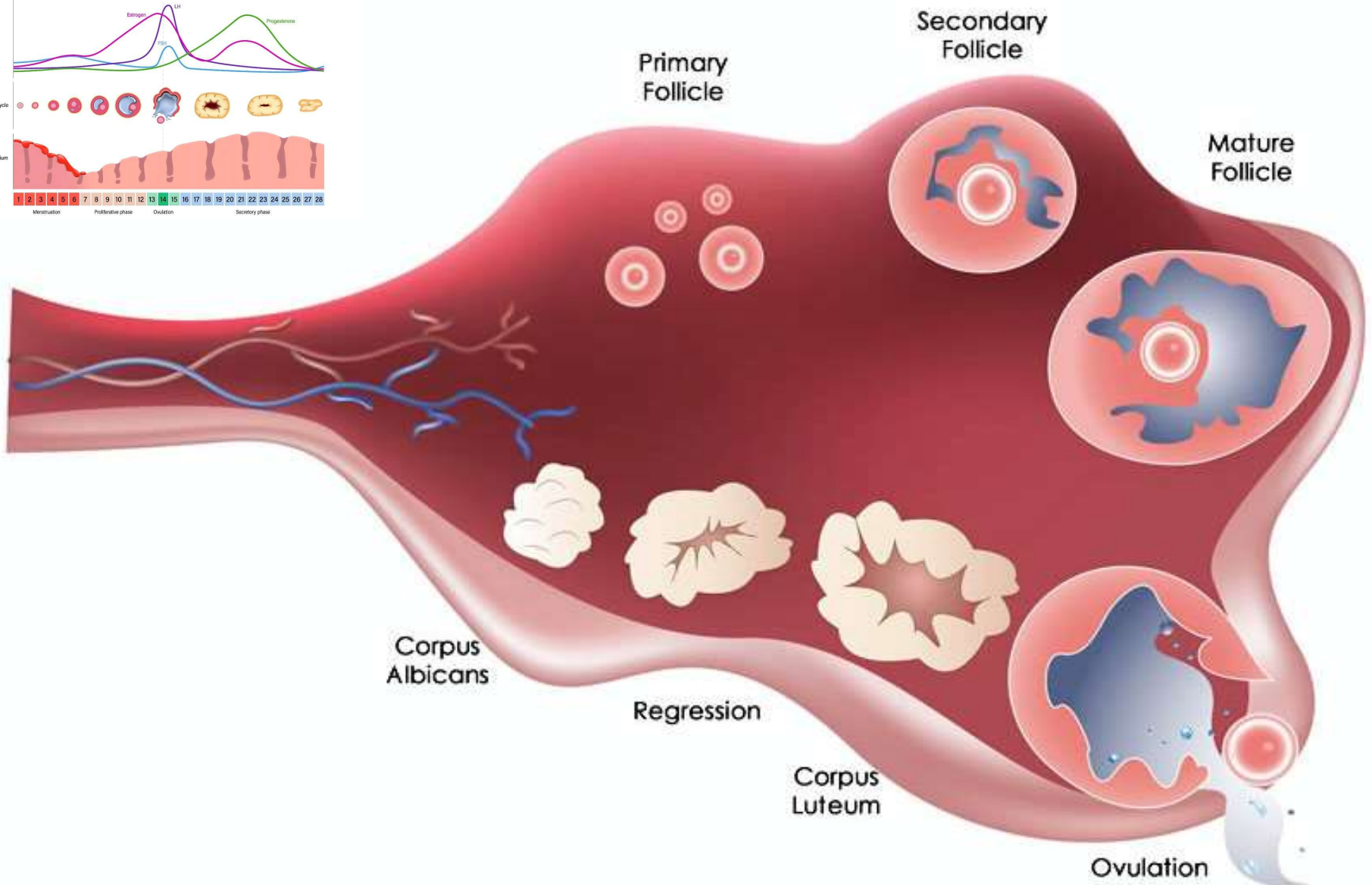
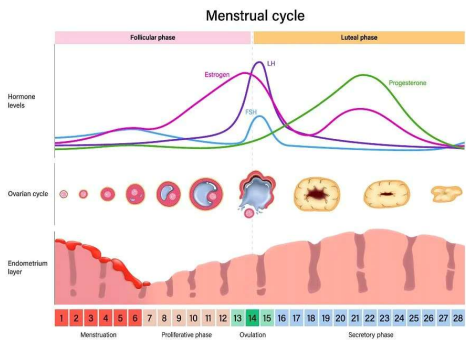
- Abnormal bleeding
- Abnormal bleeding refractory to typical interventions
- Prolonged periods of time in between menstrual cycles/no cycles at all
- Any vaginal bleeding after menopause
- Asking physician about protective hormonal options



Summary

- Risk of endometrial cancer is impacted by hormones that are essential to our normal reproductive functions
- Hormone deregulation can lead to a proliferative environment in the endometrium that allows abnormal cell growth
- Forward focus on methods of managing endometrial hormone exposure and symptom awareness for early detection

Ovulation



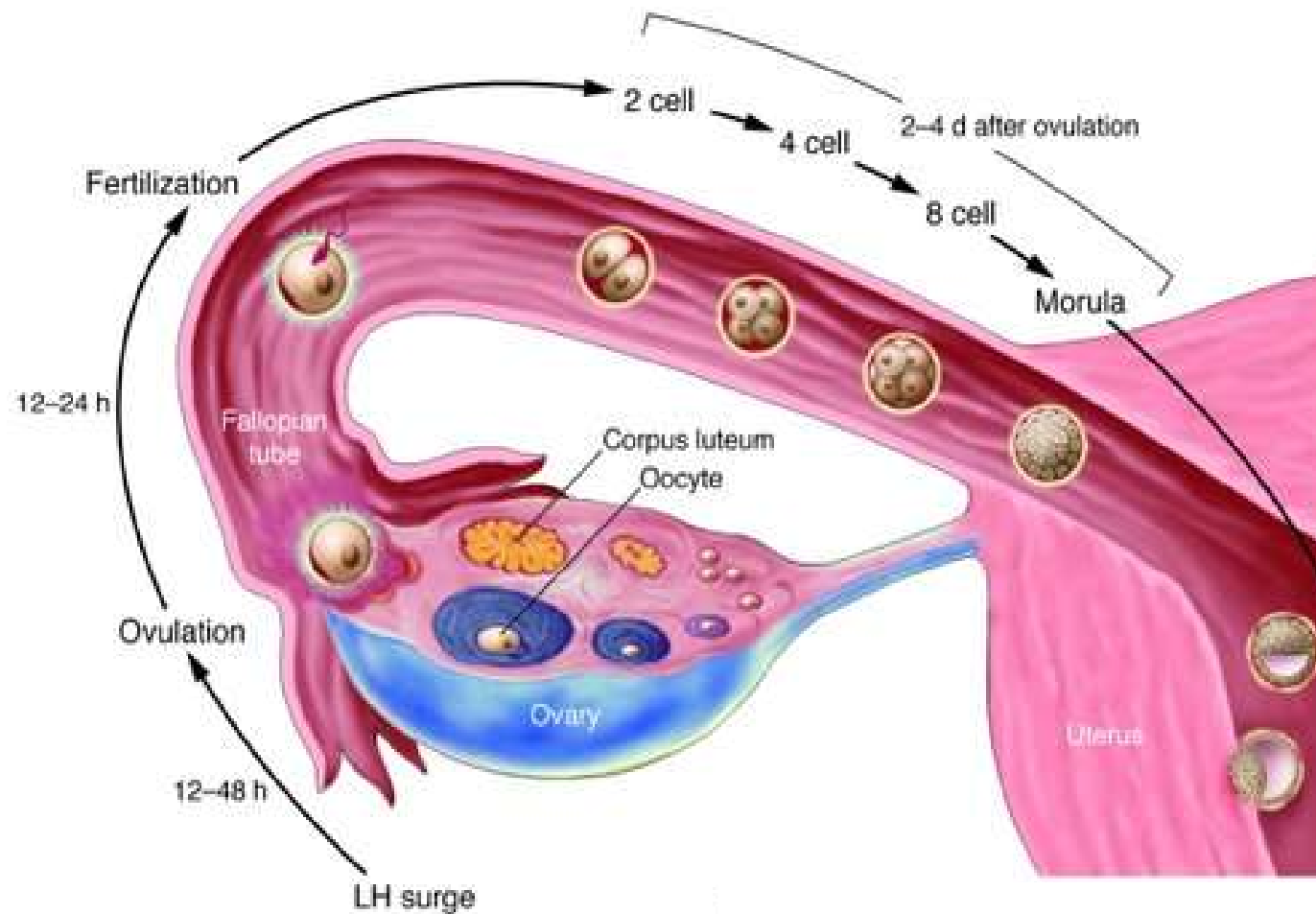


Normal fallopian tube



- Lined by ciliated cells
- Where fertilization occurs
- Carries fertilized egg toward the uterus

Fertilization or non fertilization



...& the cycle continues throughout our reproductive years



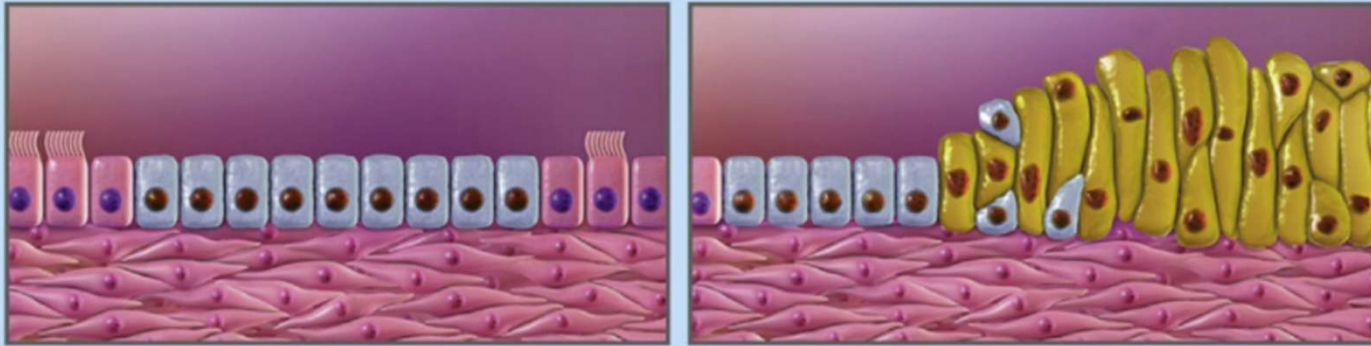
Changes in the Fallopian Tubes

- Loss of ciliated epithelium over time and as estrogen decreases
- Increased proportion of secretory cells
- Exposed to inflammatory environment throughout ovulatory period of life

Dormant p53 Signature

Dormant STIC

Wang 2021

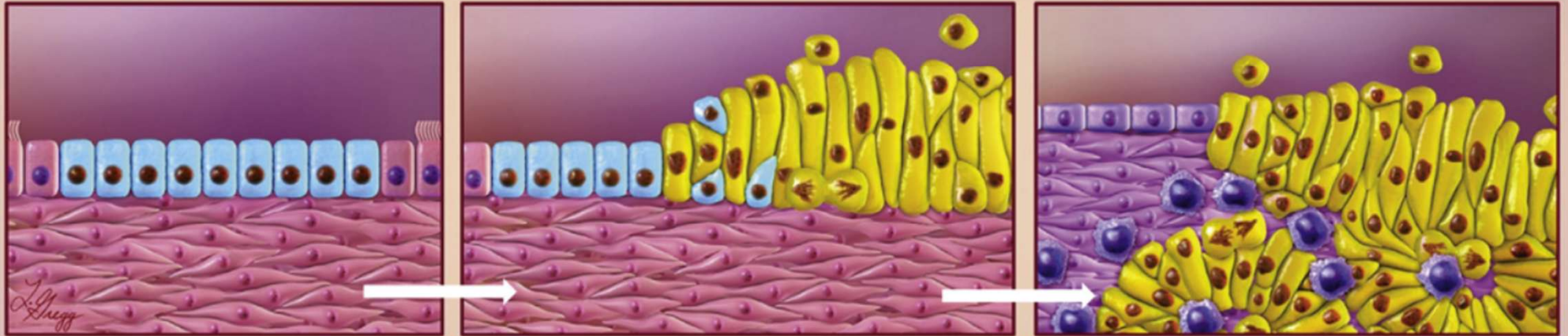


Tumor growth

Initiation: p53 Signature

Expansion: STIC

Invasion: HGSC



- Development of genetic mutations in the tissue that allow cancer development (ex: P53 signature)
- These mutations hastened/propagated in setting of hereditary cancer syndromes



Risk Mitigation

Challenges

- These changes are imperceptible to us
- Can't predict in whom and when physiologic changes transform to cancer
- No reliable method of detecting these early, predisposing changes

Looking forward

- Opportunistic salpingectomy
- Oral contraceptives
- Symptom awareness
- Cascade testing of family members when hereditary mutation is diagnosed

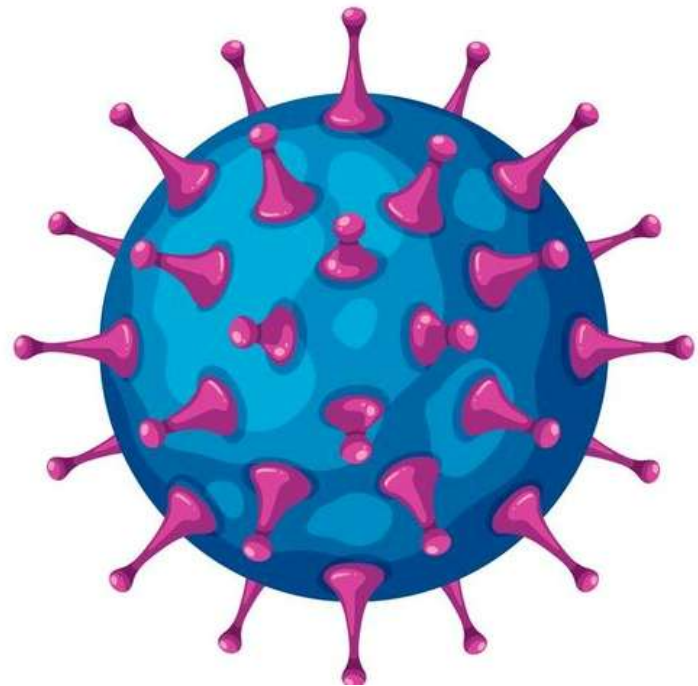


Summary

- Years of repetitive cycles and aging lead to physiologic tissue changes in the ovary and fallopian tube
- These changes lead to mutations in tissue that can evolve into pre invasive and cancerous lesions
- Forward focus on awareness, management of hereditary cancer conditions, ongoing research into detection and early intervention

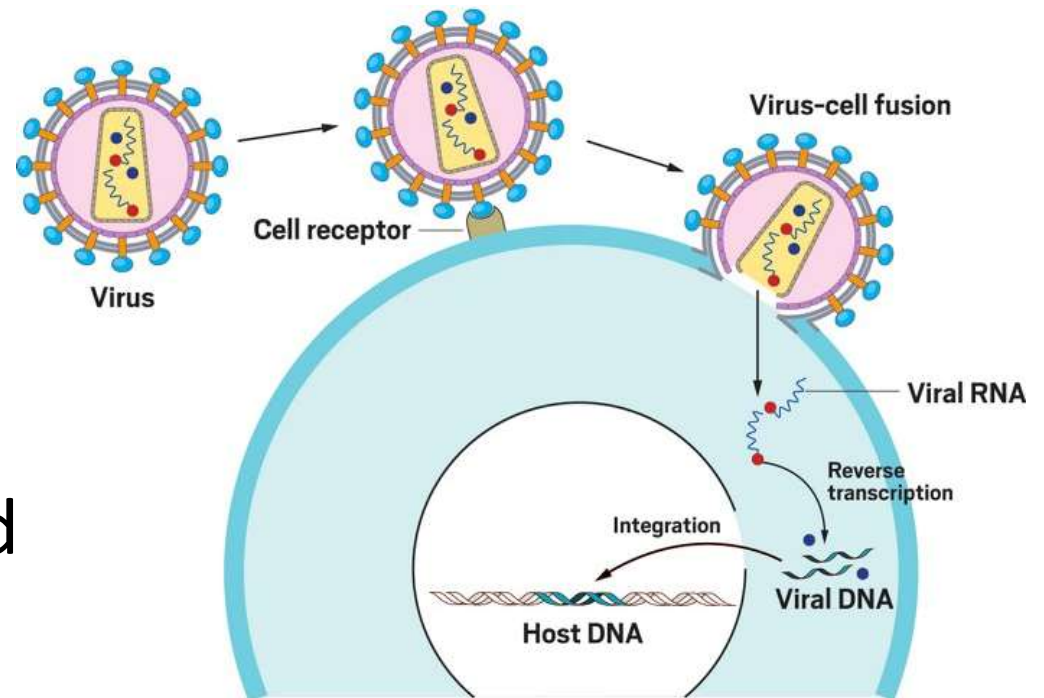
A “Natural” Infection?

- Human papillomavirus causes >90% of cervical cancers
- Not a virus that’s essential to our reproductive function
- But sex is a part of our reproductive physiology
- >80% of sexually active adults acquire HPV in their lifetime



Persistent HPV Infection

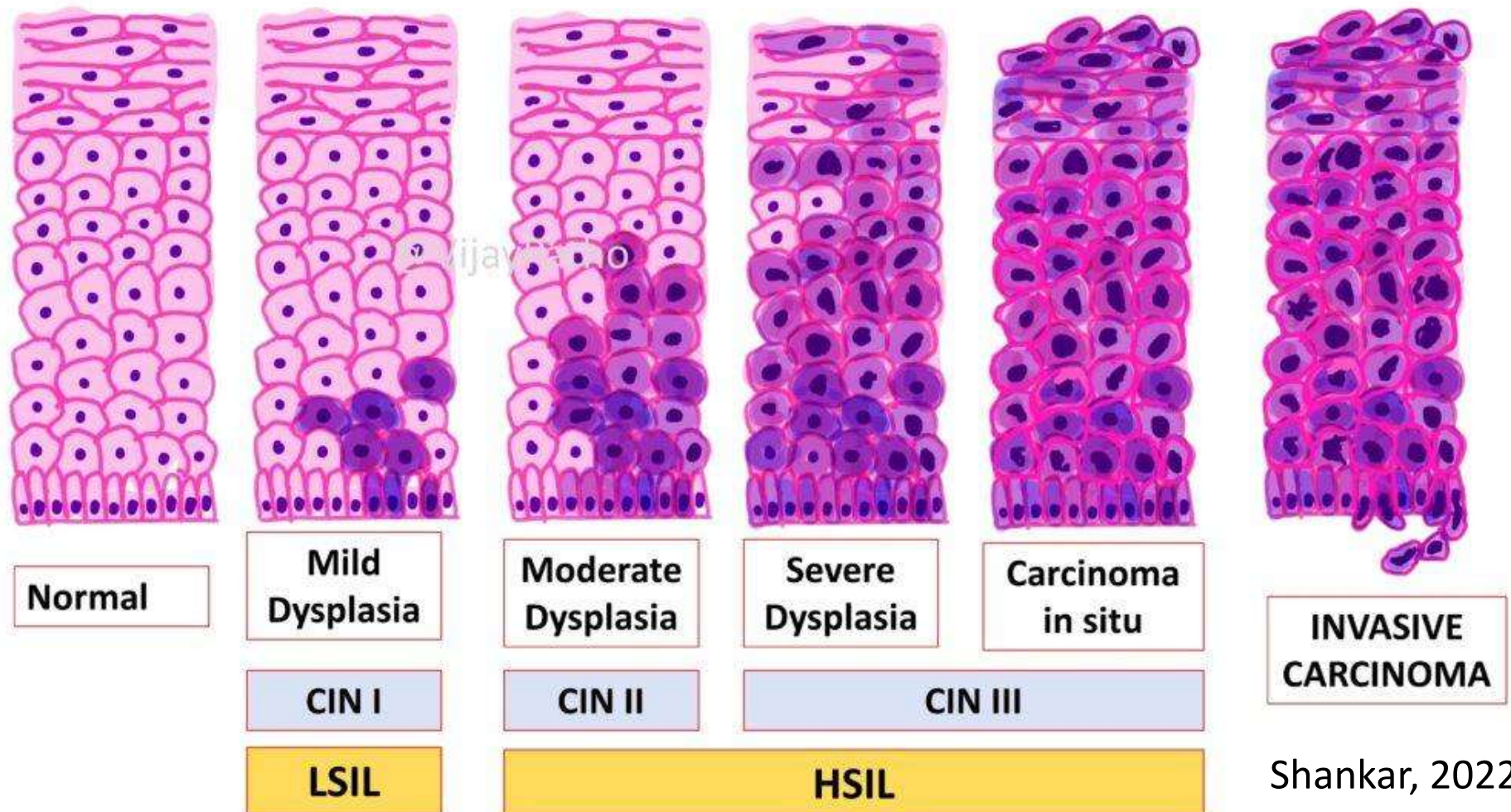
- Majority of HPV infections resolve spontaneously in 1-2 years
- Persistent infection precedes precancerous cervical changes
- HPV virus integrates into genome of host cells
- Allows propagation of virally infected cells and ongoing infection



Plackett 2022

Progression to Cervical Cancer

- Mutations in host genome allow growth of unregulated and abnormal cells





Risk Factors for Persistent Infection

- Smoking and alcohol use
- Immune suppressing conditions
- Other host immune factors
- Co-infection affecting immune response
- Many other factors not yet known

Progress in Prevention

Primary prevention
HPV vaccination



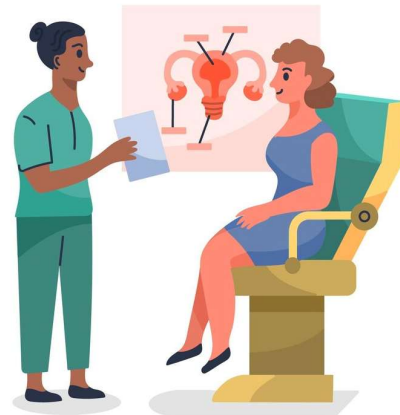
Vaccination to prevent infection with high risk strains of HPV



Secondary prevention
Screening



Goal of detecting changes early to intervene before progression to carcinoma





Summary

- Sexual function is an essential reproductive process
- More than 80% of people will acquire an HPV infection in their lifetime
- Some HPV infections will persist and cause mutations that lead to abnormal cell growth
- Focus on prevention and early detection with vaccines and screening



Other Factors

- Pregnancies
- Breastfeeding
- Genetics
- Other gynecologic/hormonally mediated medical conditions



Conclusion

- Our reproductive anatomy and physiology is complex
- Increasing complexity of a system increases room for errors
- Reviewed some of the potential areas of deregulation, mutation, abnormal cell growth that enable cancer development
- Every answered question asks 10 more questions

Acknowledgements

