IN SUMMARY
ENDOMETRIOSIS

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- Attachment of endometrial cells to the peritoneal surface
- Invasion of these cells into the mesothelium
- Recruitment of inflammatory cells
- Angiogenesis around the nascent implant
- Endometrial cellular proliferation

- Monkeys are only animal (cyclic)
- No cases reported prior to puberty
- Often seen in teenage years
- Short cycle and longer flows have twice the risk of endometriosis
- Early menarche
- Delayed childbearing
- Menstrual outflow obstruction

- Implantation (Sampson's theory)
- Viable endometrial tissue is refluxed through the fallopian tubes during menstruation
- Implants on peritoneal surface or pelvic organs

Retrograde menstruation
- Occurs through the fallopian tubes
- Refluxed endometrial cells are ***viable***
- Refluxed endometrial cells are able to ***adhere*** to peritoneum

Coelomic Metaplasia
- Ovary & Mullerian ducts derive from coelomic mesothelium
- Germinal epithelium attempts to recapitulate endometrium
- Only explains ovarian endometriosis
- Peritoneal mesothelium is **totipotential**
- Develops from metaplasia of cells that line the pelvic peritoneum
- Infectious, hormonal, or other inductive stimuli may result in metaplasia

Dissemination
- Disseminated tissue can cause metaplasia
- Injection into ear vein of rabbit causes endometriosis of lungs
- Laparotomy scar
- Episiotomies
- Cesarean sections
- Transplantation confirmed in animal experiments

Embryonic rest theory

- Cell rests of Mullerian origin
- Lymphatic and hematogenous dissemination of endometrial cells
- Evidence suggests that endometrial cells can metastasize
- Pleura, umbilicus, retroperitoneal space, lower extremity, vagina, and cervix - are anatomically possible
- Endometrial tissue in uterine veins in women with adenomyosis
- Induced pulmonary endometriosis by injecting endometrial tissue intravenously in rabbits
- Lymph node endometriosis was found to be present in 6.7% autopsies

Found In

- Bone
- Muscle
- Brain
- Nerve
- Lung parenchyma
- Vertebral space
- Extremities

Genetics

- Much more common in patients with a FH
- Maternal inheritance pattern
- 7% in first degree relatives
- More severe in women with a + first degree relative
- 6/8 monozygotic twins had endometriosis
- 3.8% of non-monozygous sisters
- Polygenic/multifactorial
- No HLA system seems involved
- Perhaps different diseases

Adherence

- Endometrial fragments obtained in either phase of the cycle – adhere to the epithelial side of the amnion but only at locations where the amniotic epithelium was damaged or absent
- Cultured peritoneal explants adhered to peritoneal explants only at locations where the mesothelium was absent or damaged and the basement membrane was exposed
- Intact mesothelium constitutes a defense barrier
- Occasionally there is attachment to intact mesothelium

Integrins

- Intracellular adhesion molecule-1
- Vascular cell adhesion molecule-1
- Integrin-blocking antibodies do not interfere with endometrial stromal or epithelial cell adherence to mesothelium

Hyaluronic Acid

- Peritoneal mesothelium produces *hyaluronic acid*
- Hyaluronic acid is expressed along the cell membrane and contributes to the pericellular matrix
- Major component of the extracellular matrix ground substance
- *CD44* is the principal receptor for hyaluronic acid
- Involved in binding of gastric cancer and ovarian cancer cells to mesothelium
- Endometrial stromal end epithelial cells express CD44
- Hyaluronidase pretreatment of mesothelial cells decreases the binding of endometrial stromal and epithelial cells to mesothelium

- Invasion follows initial adhesion
- Matrix metalloproteinase (MMP) enzymes - implicated
- MMPs (and inhibitors) play a significant role in normal endometrial remodeling that accompanies menses
- MMP family contains several structurally related Zn^{++} dependent endopeptidases
- Responsible for the degradation of various extracellular matrix components
    - collagen
    - gelatins
    - proteoglycans
    - laminin
    - fibronectin
    - elastin

TGF-β

- Produced by endometrial tissue in response to progesterone
- TGF-β suppresses expression of MMP-7
- Antibody to TGF-β abolishes this suppression
- Blocking the action of TGF-β opposes progesterone-mediated suppression of MMP-3 and MMP-7
- Blocks the ability of progesterone to prevent experimental endometriosis
- TGF-β alone does not lead to sustained suppression of MMPs
- Possibly because of resumption of MMP production in the absence of progesterone
- Consistent with the fact that peritoneal fluid levels of TGF-β are elevated in endometriosis

IL-1α

- Potent stimulator of MMP-3 in proliferative phase endometrium
- Progesterone exposure in vivo reduces the IL-1α stimulation of MMP-3 in secretory phase tissue
- IL-1α stimulation of MMP-3 is restored in a dose-dependent manner with progesterone withdrawal
- Cultured endometriotic cells obtained from a rat endo model express higher levels of MMP-3 mRNA than eutopic rat endometrial stromal cells when treated with progesterone
- Elevated and persistent MMP-3 expression by endometriotic stromal cells cultured in the presence of progesterone correlates with elevated levels of IL-1α mRNA detected in the endometriotic stromal cells
- Production of IL-1α by the endometriotic lesions - overcomes the progesterone-induced suppression of MMP-3
- IL-1α - related mechanism promotes MMP-3 production by endometriotic cells even in the presence of progesterone

Contributes to pain and infertility

- Cytokines
- Prostaglandins
- Dyspareunia
- Chronic pelvic pain
- Inflammation --> Infertility
- adhesion formation
- scarring
- disrupt fallopian tube patency
- impair folliculogenesis
- fertilization
- embryo implantation

Hormonal Dependence

- Endometriosis is an estrogen-dependent disorder
- Aberrant estrogen synthesis and metabolism –
- Aromatase catalyzes the synthesis of estrone and estradiol from androstenedione and testosterone, respectively
- Expressed by many human cell types
- Ovarian granulosa cells
- Placental syncytiotrophoblasts
- Adipose cells
- Skin fibroblasts
- Estrogen produced by aromatase activity in the cytoplasm of leiomyoma smooth muscle cells or endometriotic stromal cells
- Disease-free endometrium and myometrium lack aromatase expression

Aromatase

- Cultured stromal cells derived from endometriotic implants and incubated with a CAMP analog display extraordinarily high levels of aromatase
- Growth factors, cytokines - possible inducers of aromatase
- Prostaglandin E2 was identified as the most potent inducer
- Estrogen - up-regulates prostaglandin E2 formation
- Stimulates cyclo-oxygenase type 2 enzyme in endometrial stromal cells
- Positive feedback loop for continuous local estrogen and prostaglandin E2 production
- Possible genetic defect in aromatase expression in endo
- Androstenedione of adrenal and ovarian origins – premenopausal women
- Adrenal androstenedione in postmenopausal women
- Estrone - weakly estrogenic
- Must be converted to estradiol
- 17α-hydroxysteroid dehydrogenase (17α-HSD) type 1 is expressed in endometriosis
- In contrast 17α-HSD type 2 inactivates estradiol by catalyzing its conversion to estrone in eutopic endometrial glandular cells during the luteal phase
- Progesterone induces the activity of 17α-HSD
- Inactivation of estradiol to estrone one of the anti-estrogenic properties of progesterone
- 17α-HSD type 2 is absent from endometriotic glandular cells

FUDAMENTAL QUESTIONS

1. What are the three theories of the development of endometriosis?
2. Where is endometriosis most commonly found?
3. What clinical impact does endometriosis have on the woman?
4. What treatment modalities are available for endometriosis?
5. Other than steroid hormones, what causes endometriosis to grow and proliferate?
6. Discuss in some detail, the steroidal environment that alters endometriotic development?
7. Describe the histology of endometriosis?