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GYNECOLOGY AND GYNECOLOGIC SURGERY

THOUGHTS OF THE DAY

- MENOPAUSE IS NOT "NATURAL"
- ESTROGEN IS NOT A "LUXURY HORMONE"
- POSTMENOPAUSAL HORMONE THERAPY IS NOT RAT POISION

MENOPAUSE IS NOT NATURAL

- HISTORICAL PERSPECTIVE
  - ~AVERAGE AGE OF DEATH FOR WOMEN
    - 1800: 38
    - 1900: 47
    - 2000: 85
  - ~MENOPAUSE = 20TH CENTURY PHENOMENON
- BIOLOGICAL PERSPECTIVE
  - ~HUMAN FEMALES ARE THE ONLY MAMMALS THAT OUTLIVE THEIR REPRODUCTIVE CAPACITY

ESTROGEN IS NOT A "LUXURY HORMONE"

- ALMOST ALL TISSUES IN THE HUMAN FEMALE HAVE ESTROGEN RECEPTORS
- TISSUES WITH ESTROGEN RECEPTORS PERFORM BETTER IN THE PRESENSE OF ESTROGEN

PHYSIOLOGIC EFFECTS OF ESTROGEN

- CARDIOVASCULAR PROTECTION
  - ↑ NITRIC OXIDE (EDRF)
    (ESTROGEN IS A VASODILATOR)
  - ↑ VASCULAR PROSTACYCLIN
    ↓ PLATELET AGGREGATION
  - MEDIATES ANTIOXIDENT ACTIVITY
    (ESTROGEN → ↓ ARTHROGENIC PROPERTIES OF OXIDIZED LDL)
  - ↑ CARDIAC STROKE VOLUME (INOTROPIC)
  - ↓ INSULIN RESISTANCE

PHYSIOLOGIC EFFECTS OF ESTROGEN

- NEUROPROTECTION
  - ↑ SEROTONIN LEVELS (↓ MAO)
  - ↑ NOREPHINEPHRINE LEVELS
  - ↑ HIPPOCAMPAL ACETYLCHOLINE
  - ↑ DENDRITIC SPINE DENSITY
  - ↑ POSTURAL STABILITY (↑ SENSORY INPUT PROCESSING)
  - ENHANCES CORTICAL FUNCTION AND PROTECTS AGAINST ANOXIC INSULTS
  - MAINTAINS VASOMOTOR STABILITY
  - ↑ REM SLEEP

THE ESTROGEN DEPRIVED BRAIN DOES NOT SLEEP WELL

PHYSIOLOGIC EFFECTS OF ESTROGEN

- BONE PROTECTION
  - ↑ CALCIUM ABSORPTION FROM GUT AND DEPOSITION INTO BONE
  - ↑ OSTEOBLAST FUNCTION
  - ↑ VITAMIN D RECEPTORS IN OSTEOBLASTS

LOSS OF ESTROGEN → 5-10% TRABECULAR BONE LOSS PER YEAR

PHYSIOLOGIC EFFECTS OF ESTROGEN

- LIPOPROTEIN EFFECTS
  - ↑ HEPATIC UPTAKE OF VLDL AND LDL
  - ↑ SYNTHESIS OF APO A-1 → ↑ HDL
  - ↑ BILE ACID SECRETION → ↑ CHOLESTEROL CLEARANCE

PHYSIOLOGIC EFFECTS OF ESTROGEN

- GENITOURINARY EFFECTS
  - MAINTAINS VAGINAL EPITHELIAL THICKNESS AND VASCULARIZATION
  - MAINTAINS NORMAL LACTOBACILLUS POPULATION AND ACIDIC VAGINAL pH
  - ↑ PELVIC FLOOR COLLAGEN CONTENT AND STRENGTH (HYDROXYPROLINE CROSSLINKS)
  - ↑ DETRUSOR COMPLIANCE
  - ↑ URETHRAL PRESSURE
  - ↑ UROEPITHELIAL RESISTANCE TO BACTERIA

PHYSIOLOGIC EFFECTS OF ESTROGEN

- MISCELLANEOUS EFFECTS
  - ❖SKIN THICKNESS, TURGOR AND COLLAGEN CONTENT
  - ❖GENERAL MUCOSAL THICKNESS AND HYDRATION
  - ❖LIBIDO AND ORGASMIC RESPONSE

BRIEF HISTORY OF HORMONE THERAPY

(FROM "FOUNTAIN OF YOUTH" TO "RAT POISON")

- MID 1940's PREMARIN INTRODUCED INTO CLINICAL PRACTICE/MPA ADDED IN 1980
- MID 1960's WILSON PUBLISHES "FEMININE FOREVER"
- 1990's CARDIOLOGISTS BEGAN ENCOURAGING USE OF HORMONE THERAPY IN ASYMPTOMATIC WOMEN FOR CARDIOPROTECTION
- MID 1990's NIH COMMISSIONS WHI
- JULY 2002 E – P ARM STOPPED AND SELECTED "RESULTS" LEAKED TO PRESS

2002 WHI "RESULTS"

- HORMONE THERAPY INCREASES BREAST CANCER RISK BY 26%
- HORMONE THERAPY INCREASES RISK OF HEART DISEASE
- HORMONE THERAPY INCREASES RISK OF DEMENTIA

PROBLEMS WITH WHI

- STUDY DESIGN
  - AVERAGE AGE OF PARTICIPANTS WAS 63
  - "INTENTION TO TREAT STUDY" >40% DROP OUT RATE EXCEEDED "DESIGN PROJECTIONS"
  - SCREEN FOR PREEXISTING CARDIOVASCULAR DX WAS HISTORY AND EKG
  - PARTICIPANTS WERE ASYMPTOMATIC
  - PREMARIN AND PROVERA WERE THE ONLY HORMONES USED
  - RELATIVE RISK vs ABSOLUTE RISK EMPHASIZED

PROBLEMS WITH WHI

- BREAST CANCER DATA
  - 26% INCREASE IN RR WAS IN E/P GROUP ONLY AND IN 5TH YEAR ONLY
  - RR = RISK OVER BASELINE
  - PLACEBO GROUP HAD UNEXPLAINED PAUCITY OF "ADVERSE EVENTS IN 5TH YEAR (17/30/23/22/12/20)
  - AJUDICATED DATA WAS NOT STATISTICALLY SIGNIFICANT

"THE 26% INCREASE OBSERVED IN THE ESTROGEN PLUS PROGESTERONE GROUP ALMOST REACHED NOMINAL STATISTICAL SIGNIFICANCE"

PROBLEMS WITH WHI

- BREAST CANCER DATA
  - NO DIFFERENCE IN IN-SITU CANCERS
  - ESTROGEN ONLY GROUP → 26% REDUCTION IN RR OF BREAST CANCER
  - NO INCREASED RISK IN INDIVIDUALS WITH FHx OF BREASK CANCER
  - NO INCREASED RISK OF DEATH FROM BREAST CANCER

PROBLEMS WITH WHI

- CARDIOVASCULAR DATA
  - REPORTED CARDIAC DATA WAS NOT ADJUDICATED
  - INCREASE IN EVENTS WAS IN FIRST 4 MONTHS OF USE ONLY
  - SCREENING FOR PREEXISTING DIAGNOSIS WAS NOT ADEQUATE
  - PREMARIN ≠ 17β ESTRADIOL
    - ↑ PRODUCTION OF CLOTTING FACTORS IN LIVER
  - PROVERA ≠PROGESTERONE
    - LONG HALF LIFE
    - BLOCKS VASODILATORY EFFECTS OF ESTROGEN

PROBLEMS WITH WHI

- WIMS/DEMENTIA DATA
  - SUBGROUP OF PARTICIPANTS OVER 75
  - PREMARIN ≠ 17β ESTRADIOL
    - THROMBOGENIC
    - CROSSES BLOOD BRAIN BARRIER POORLY
  - PROVERA ≠ PROGESTERONE
    - BLOCKS VASODILATORY EFFECT OF ESTROGEN
    - BLOCKS "SECOND MESSENGER" IN BRAIN
    - DOWN REGULATES ESTROGEN RECEPTORS

PROBLEMS WITH WHI • SUMMARY

- ALL CAUSE MORTALITY DECREASED IN HORMONE GROUPS vs PLACEBO
- FINDINGS ARE NOT CONSISTENT WITH BASIC SCIENCE DATA ["WHAT" BUT NO "WHY"]
- WITHIN STUDY PATIENTS BETWEEN 50-59 HAD 40% REDUCTION IN CARDIOVASCULAR EVENTS
- A RANDOMIZED PROSPECTIVE DOUBLE BLIND STUDY IS ONLY THE "GOLD STANDARD" FOR THE POPULATION STUDIED AND THE DRUGS EVALUATED
- WHI FINDINGS ARE NOT CLINICALLY APPLICABLE TO THE MAJORITY OF SYMPTOMATIC MENOPAUSAL WOMEN

HORMONAL MANAGEMENT OF MENOPAUSE

- CONSIDER HORMONE THERAPY IN ALL SYMPTOMATIC WOMEN WITHOUT CONTRAINDICATIONS
- USE FDA APPROVED BIOIDENTICAL ESTRADIOL AS FIRST LINE THERAPY
- THERE IS NO DATA TO SUPPORT THE SUPERIORITY OF PELLETS OVER ANY OF THE FDA APPROVED ESTRADIOL PRODUCTS
- TESTOSTERONE USE IN WOMEN IS RARLY APPROPRIATE AND SHOULD NEVER BE PRESCRIBED IN SUPRAPHYSIOLOGY DOSES

HORMONAL MANAGEMENT OF MENOPAUSE

- USE BIOIDENTICAL PROGESTERONE WITH ESTRADIOL IN WOMEN WITH UTERUSES
  - MIRENA IUD AND NORETHINDRONE ACETATE ARE ACCEPTABLE ALTERNATIVES (BAZEDOXIFENE)
- AVOID MPA FOR POST MENOPAUSAL HORMONE THERAPY
- SELECT ORAL vs NONORAL ESTRADIOL BASED ON INDIVIDUAL PATIENT CHARACTERISTICS

~WEIGHT ~FHx ~PMHx ~COST

HORMONAL MANAGEMENT OF MENOPAUSE

- DOSE FOR SYMPTOMATIC RELIEF NOT TO A PARTICULAR BLOOD LEVEL
- "COACH" PATIENT ABOUT THE BLACK BOX WARNINGS
- VAGINAL ESTROGEN MAY BE USED IN ANY AGE GROUP FOR THE RELIEF OF GENITOURINARY SYMPTOMS (GUSM)

VAGINAL ESTROGEN DOES NOT CHANGE SERUM LEVELS OF ESTRADIOL

HORMONAL MANAGEMENT OF MENOPAUSE

- BY 2025 THERE WILL BE OVER 825 MILLION FEMALES OVER THE AGE OF 65 WORLDWIDE
- WE ARE BECOMING A SOCIETY OF OLD WOMEN
- GOAL NEEDS TO BE TO HELP WOMEN LIVE WELL AS LONG AS THEY LIVE