Women, Hormones, Mood and Sex

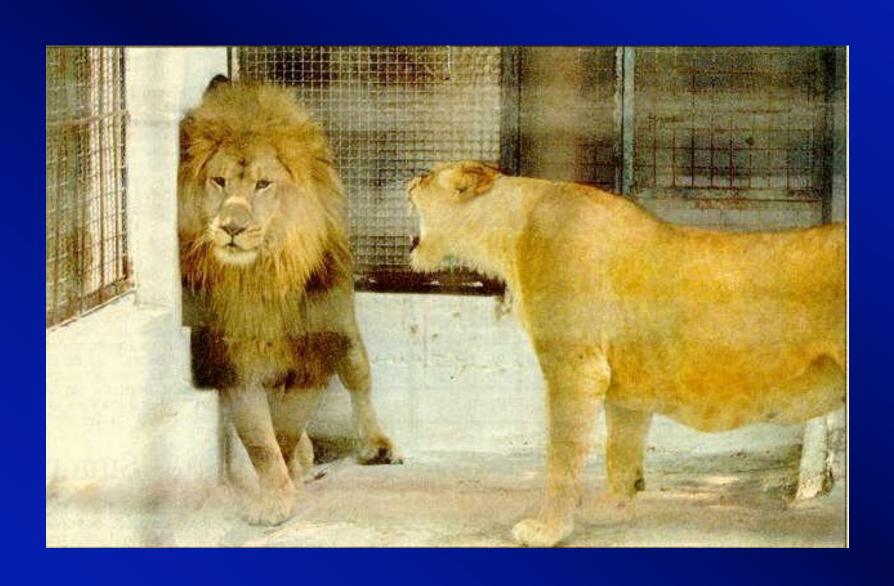
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How the king of beasts handles PMS:



Outline

- The Female Brain
- Puberty, the Menstrual Cycle and PMDD
- Pregnancy, Mood and Postpartum
- Perimenopause, Mood and Sex
- Menopause, Mood and Sex

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- The Female Brain
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Male: XY

- Until 8 wks old, every fetal brain looks female. Female is nature's default gender setting
- At 8 weeks of fetal age: Y chromosome (SRY gene) produces the fetal testicle, which produces a testosterone surge
- Testosterone kills off cells in the communication centers and grows more cells in the sex and aggression centers
- This permanently changes structure and function into the male brain program

Female: XX (the archetypal brain)

- If the testosterone surge doesn't happen, the female brain continues to grow
- The female brain sprouts more connections in the communication areas and areas that process emotion
- Women are more talkative than men

 Under fMRI scan, we can see differences in female vs male brains.....

WOMEN:

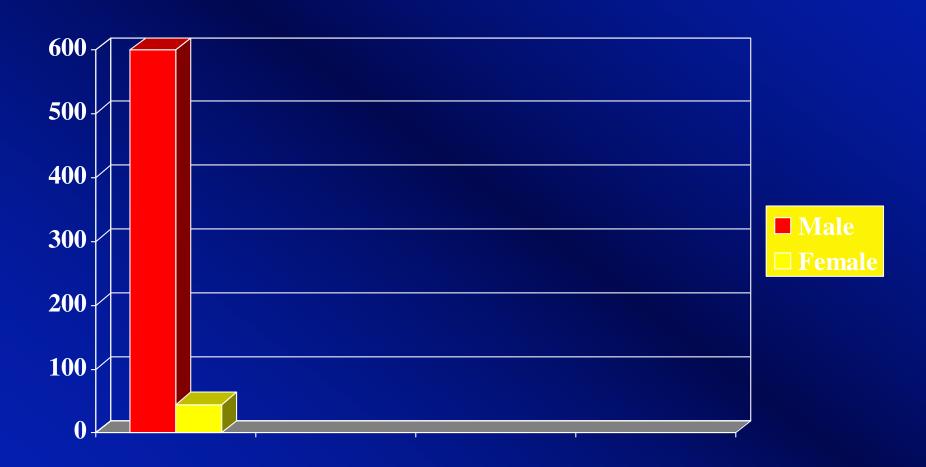
- Language and hearing brain centers: women have 11% more neurons than men
- The <u>hippocampus</u> (hub of emotion and memory formation) is larger in women
- Circuitry for <u>language and observing emotion</u> in others is larger in women
- Women (on ave) are better at <u>expressing emotion</u> and <u>remembering details</u> of emotional events

MEN:

- Men have 2 ½ times the brain space devoted to sexual drive
- Larger brain centers for action and aggression

- Sexual thoughts float through a man's brain every 52 sec on average
- Through a woman's mind.....?
- About 1x/ day. 3-4x on her hottest day

Male/Female Testosterone Levels



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Female Puberty

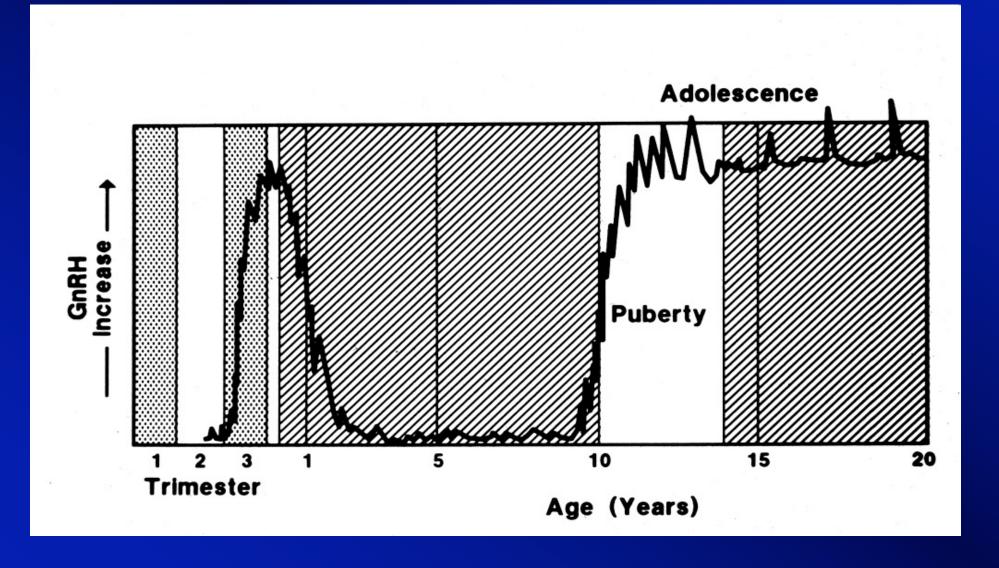
- Starts age 8-9 years old
- Gradual awakening of the ovaries
- Ovaries secrete more and more estrogen every year finally triggering puberty
- Estrogen takes control of the hypothalamus and initiates the menstrual cycle, age 12.4

Female Puberty

Female

- The hypothalamic neurons gradually 'wake up' to their tonically 'ON' pulsatile state
- This stimulates the pituitary to make hormones
- The pituitary hormones LH (Luteinizing Hormone) and FSH (Follicle-Stimulating Hormone) stimulate the ovary to start ripening eggs and make estrogen (menstrual cycle)
- And growth of secondary female characteristics (pubic hair, genital growth and breast growth)

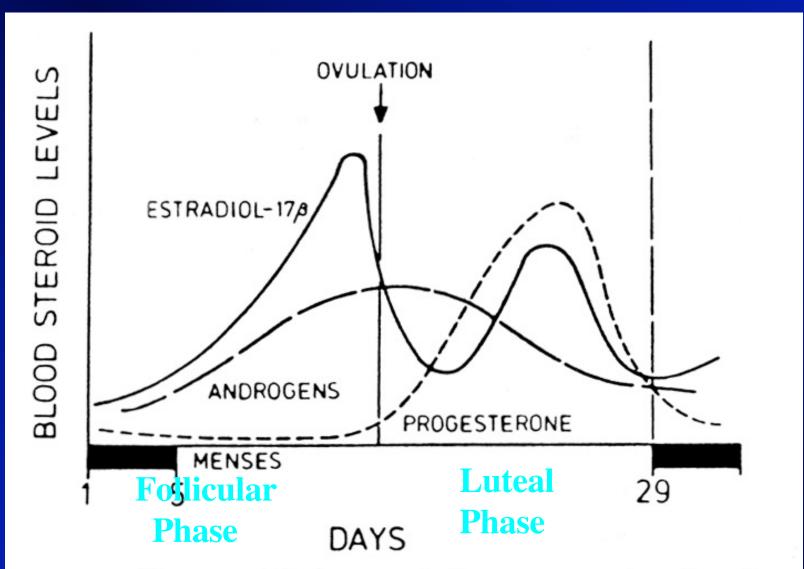
Hormone Pulses from the Hypothalamus: Fetal Life to Puberty



Ovaries Take Over the Brain

- Fluctuating levels of estrogen from the ovaries now control the hypothalamus and pituitary
- Estrogen activates the brain (more alert effect) and progesterone deactivates the brain (more calming effect) during the normal menstrual cycle

Menstrual Cycle



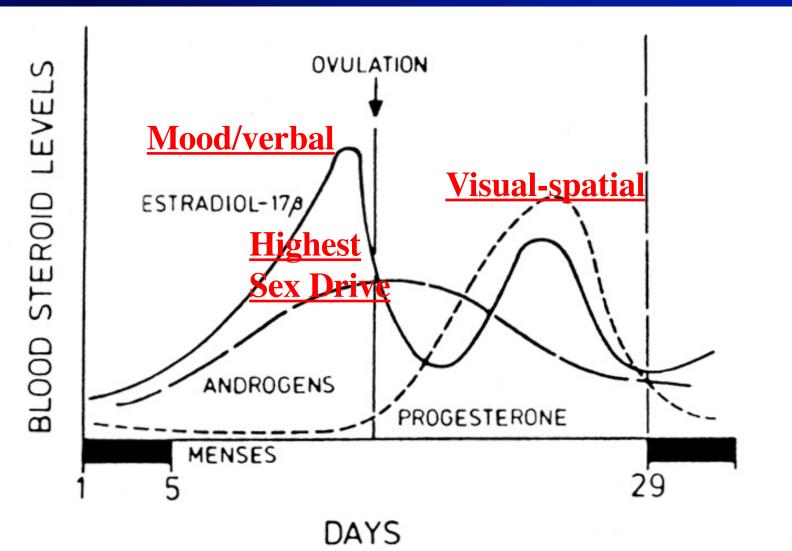
Sex steroid changes in human menstrual cycle.

Brain Variability Controlled by Ovarian Hormones

Depending on where a woman is in her cycle, there is variability in the following:

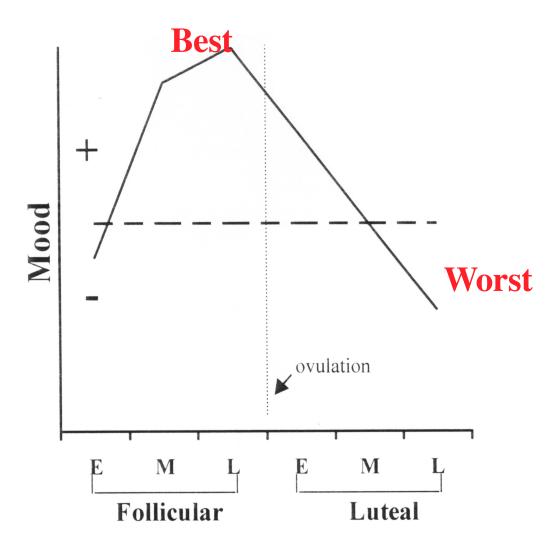
- Mood: 20% variability in normal women
- Verbal performance: 25% variability in normal women
- Sexual interest: 30% variability in normal women
- Visual-spatial performance: 20% variability in normal women

Menstrual Cycle



Sex steroid changes in human menstrual cycle.

Mood Changes Across the Menstrual Cycle



week

2

3

-Morales, 1986

Mood

- 80% of women acknowledge some increased emotional sensitivity before their period starts
- 8-10% have severe 'hell-on-earth' mood changes the 2 weeks before their period

What is going on here?

- The female brain experiences hormonally determined emotional fluctuations
- Not a big deal for 80%
- A VERY big deal for 8-10%

PMDD vs Normal PMS

Normal PMS (Premenstrual Syndrome):

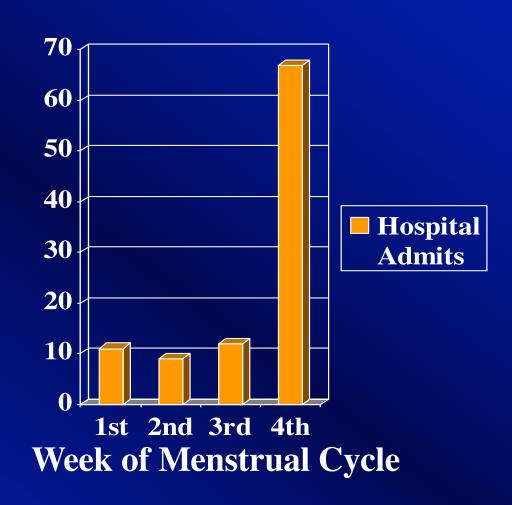
- 80% of women
- Mild to moderate emotional fluctuations

PMDD (Premenstrual Dysphoric Disorder):

- 8-10% of women
- Severe moods swings, depressed mood, irritability, anxiety and physical symptoms (occurring exclusively during the luteal phase (weeks 3-4) and remitting within 3 days of the onset of menses

Menstrual Cycle Week and All Psychiatric Admissions

If random, admissions of women to psychiatric hospitals for all psychiatric diagnoses would be 25% on each week of the menstrual cycle



How does estrogen and progesterone effect the brain?

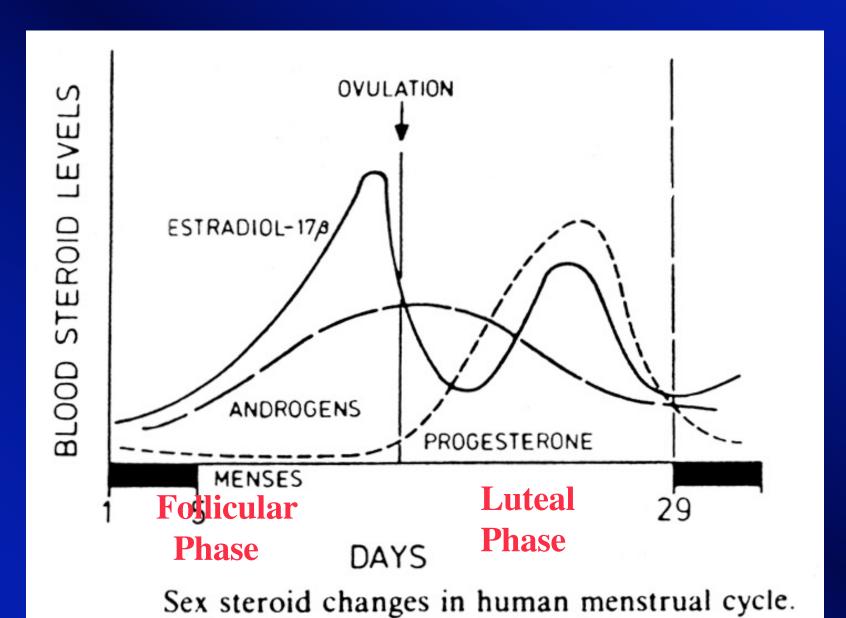
 Estrogen acts to increase neuronal excitability thus producing a brain stimulant-like effect.

 The progesterone metabolite, allopregnanolone (ALLO), produces a sedating/calming Valium-like effect.

Hypotheses of Key Factor(s) in Dysphoric Mood in Cycling Women

- Estrogen deficiency
- Progesterone effects
- Repeated fluctuations in hormones during menstrual cycles

Menstrual Cycle



PMDD

Progesterone --> Allopregnanolone (ALLO) soothing, like Valium

- ALLO= a neuroactive metabolite of progesterone and works on GABA (gamma-aminobutyric acid) receptors in the brain
- Hence, ALLO is a powerful anxiolytic, anticonvulsant, and anesthetic agent which decreases anxiety and depression.
- Barbituates, benzodiazepines and EtOH also work at this receptor.

PMDD

Progesterone --> Allopregnanolone (ALLO) soothing, like Valium

- -Prozac, Paxil and Zoloft were found not only to increase Serotonin, but also to increase ALLO production by activating 2 enzymes (lowering their Km, activation of energy) that convert progesterone to ALLO
- -Imipramine (Tofranil) had no effect on ALLO production.

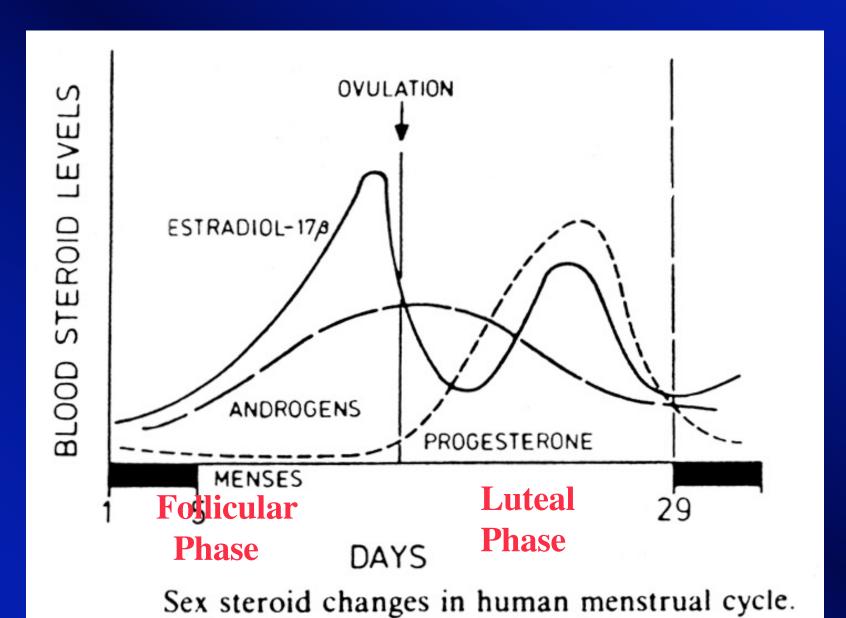
Journal:

-Lisa Griffin, MD, PhD and Synthia Mellon, PhD.

Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes.

Proc Natl Acad Sci U S A. 1999 Nov 9;96(23):13512-7.

Menstrual Cycle



PMDD

Possible Treatments

Hormones:

- Start an OCP, or change to one with a progesterone good for mood
- Take OCP continuously
 - Women are sensitive to hormones in different ways some to the hormone fluctuation, some to the amount, and some to the progestin type

SSRI's:

 Either 7-10 days before menses to help boost ALLO, or daily if also depressed

Which birth control pill is good for mood?

Lower progestin potency:

Ortho Evra patch

Ovcon 35

Ortho-TriCyclen

Othro-Cyclen

Brevicon

Modicon

Necon 1/35

Alesse

Levlite

Tri-Levlen

Triphasil

Trivora

Which birth control pill is good for mood?

- Women are sensitive to hormones in different ways – some to the progestin, some to the amount and some to the hormonal fluctuation.
- Seasonale, or any monophasic oral contraceptive pill (OCP) taken continuously (having only 1 period every 3 months) can also help stabilize mood.
- Of note, YAZ® is the only OCP given an indication for PMDD. However, it has a high progestin potency and may not be ideal for every woman.
- YAZ shortens the placebo week from the regular 7 days to 4 days – to minimize the time of hormonal fluctuation.
- Women who are sensitive to hormonal fluctuation should avoid triphasic OCP's.

Which birth control pill is good for mood?

 Bottom line: Treatment needs to be individualized for each patient and trial and error may be necessary. It takes about 2 cycles to see if a certain OCP will work for a woman or not. Evidence based studies comparing one OCP to another are lacking.

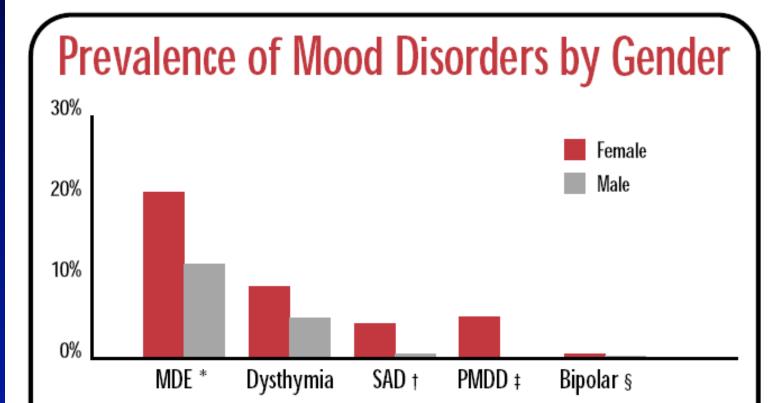
Disorders with Premenstrual Exacerbation (PME)

- Affective disorders
- Anxiety disorders
- Psychotic disorders
- Eating disorders
- Personality disorders

- Substance abuse
- Migraine
- Allergies
- Asthma
- Seizures

Male/Female Differences in Mood Disorders

- 2:1 ratio worldwide female greater than male
- 165 cultures, ratio varies from 1.7:1 up to 2.2:1
- Remarkably stable throughout cultures
- Ratio in childhood is 1:1
- Ratio starts to move toward 2:1 during puberty
- Near menopause, ratio returns towards 1:1

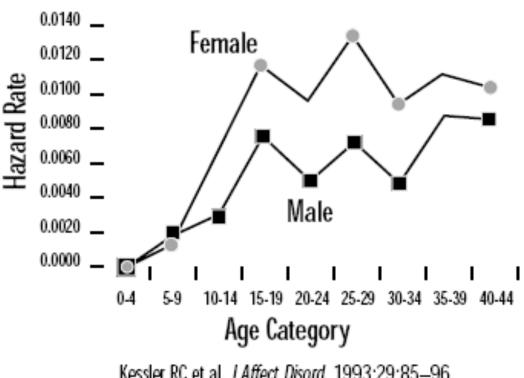


* Kessler RC, et al. Arch Gen Psychiatry. 1994;51:8-19. † Parry BL. In: Psychopharmacology: The Fourth Generation of Progress. 1995:1029-1042. ‡ Rivera-Tovar AD, Frank E. Am J Psychiatry. 1990;147:1634-1636. § Weissman M, et al. J Affect Disord. 1993;29:77-84.

Risk for Depression by Age & Sex



MDE Hazard Rates by Age and Sex



Kessler RC et al. J Affect Disord. 1993;29:85–96.

Clinical Research Considerations When Including Women as Subjects

- 18-30% Variability during the menstrual cycle of common end points
 - like mood, verbal performance, sex interest, etc
- 75% of antidepressant prescriptions are written for women
- Drug company clinical trials do NOT currently control for day of the menstrual cycle! (bad for them and bad for us)

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- The smell of a newborn baby stimulates the woman to produce <u>oxytocin</u> – a love potion creating baby lust.
 - Oxytocin is also released when talking to friends, or creating a connection
 - "A feel good" hormone released in bonding and during orgasm
- Throughout pregnancy, a woman is marinated in neurohormones manufactured by the fetus and placenta.

- Progesterone: Spikes from 10-100x normal!
 - This has a calming, Valium-like effect
 - Get sleepy, eat more
- Thirst and hunger centers on full blast
- Women become sensitive to smells, especially of foods, to avoid eating something that could harm the fragile fetus.
 - But, it could make her nauseated most of the time.

- <u>Estrogen</u> and <u>progesterone</u> help protect against stress hormones (like cortisol) during pregnancy.
- By late pregnancy, the stress hormones in a woman's brain are as high as they'd be with strenuous exercise!
 - However, their impact isn't stress, but to make a pregnant woman more vigilant about her safety, nutrition, surroundings – and less concerned with other tasks: like conference calls and organizing her schedule.
 - That's why pregnant woman (especially in the last month of pregnancy) c/o feeling disorganized, distracted, forgetful.

- At the same time, the size and structure of a woman's brain are changing, too!
- Between 6 months to the end of pregnancy, fMRI scans show that her brain is shrinking!
- This state gradually returns to normal 6 months after giving birth.
 - This may be parts getting larger as others get smaller.
 - Some studies show that the cortex (the thinking part) enlarges during pregnancy.
 - We still don't know what this means.
 - Major restructuring and metabolic changes going on.
 - It's not that the woman is losing brain cells. Scientists think the woman is about to start restructuring so the shrinkage is a result of changes in cellular metabolism required for restructuring brain circuits.
 - In the final few weeks before birth, the brain begins to increase again, as it constructs large networks of maternal circuits.

- Out of every 10 women who are pregnant, one or two have symptoms of major depression.
- Women who have been depressed before are at higher risk.
- Depression is a serious medical condition. It poses risks for the woman and her baby. But a range of treatments are available:
 - counseling, psychotherapy, support groups, therapy with light, and medications
 - Individual therapy is highly recommended

- Often a pregnant woman wonders whether antidepressant drugs, such as Zoloft and Prozac, will harm her baby or herself.
- There are no simple answers. Each woman and her health care providers must work together to make the best decision for her and her baby.
- The drugs used to treat depression have both risks and benefits.

- Depression carries serious risks for the pregnant woman and her baby. These risks include:
 - Poor weight gain
 - Use of drugs or alcohol to self-medicate
 - Suicidal Thoughts and/or Suicide
 - Poor nutrition
- The above symptoms can lead to premature birth, low birth weight and developmental problems.
- In addition, depressed mothers are often less able to care for themselves or their children, or to bond with their children.

What are the symptoms of depression?

- A woman who is depressed feels sad or "blue" and has 4 other symptoms that last for two weeks or longer:
 - Trouble sleeping
 - Sleeping too much
 - Lack of interest
 - Feelings of guilt
 - Loss of energy
 - Difficulty concentrating
 - Changes in appetite
 - Restlessness, agitation or slowed movement
 - Thoughts or ideas about suicide
- Things other than depression can cause some of these symptoms. For instance, changes in appetite and trouble sleeping are common in pregnancy. Some medical conditions, such as anemia and hypothyroidism, can cause a pregnant woman to lack energy.

- During pregnancy, two patients—the mother and the fetus—are exposed to the drug.
- Medications that are safe for a woman are sometimes risky for a fetus.
- Because of this, researchers have not studied many drugs during pregnancy.
- Several drugs have been used for many years without any obvious signs of serious risk to the baby. But some researchers have reported that some antidepressants may have increased risks.
- Research has clearly shown that women who are not pregnant and are depressed are very likely to become ill again if they stop taking their medications.
- A recent study in 2006 suggests that the risk of depression relapse is high in pregnant women who discontinue their antidepressant during pregnancy.

- What I tell women: the risks....
 - During pregnancy
 - During delivery
 - After delivery

During Pregnancy

- One study in 2006 found that pregnant women with major depression are very likely to become ill again during their pregnancy if they stop taking their medication.
- Many studies have found no link between antidepressants and serious malformations in newborns. But in 2005, the FDA issued a warning about <u>Paxil</u> based on several studies: taking the drug during the first three months of pregnancy may increase the risk of birth defects, particularly heart defects.
- In one study in 2006, three of 60 infants exposed to SSRIs for the complete pregnancy had major congenital anomalies, including ventricular septal defect, hydronephronsis, and cleft palate. (5% vs the usual 2-4%)

During Pregnancy (cont)

Two large studies in the June 28, 2007 issue of The New England Journal of Medicine found that despite some significant associations, any increase in birth defects associated with exposure to SSRIs is "likely to be small in terms of absolute risk." There was a small increased risk for right ventricular outflow tract lesions with Paxil and a small increased risk for septal defects with Zoloft.

During Delivery

Neonatal Abstinence Syndrome (NAS):

- Some babies born to mothers who are taking SSRI antidepressants show signs of "withdrawal:" breathing or feeding problems, jerky movements, seizures, irritability, abnormal crying and tremor.
- Symptoms usually subside from 48 hours to a few days.

Persistent Pulmonary Hypertension of the Newborn (PPHN):

- In February 2006, Christina Chambers and her team came out with this study.
- Babies exposed to SSRIs in late pregnancy (after 20 weeks) may be more likely to have PPHN.
- Only 6 to 12 women per 1,000 who use SSRIs late in pregnancy will have babies with pulmonary hypertension.
- One explanation is that Serotonin has vasonconstrictive properties and can increase pulmonary vascular resistance

During Delivery (cont)

- One study in the August 2007 issue of The American Journal of Psychiatry followed 90 pregnant women, and found that compared with lower SSRI doses, higher SSRI doses were significantly associated with earlier birth.
- Yet a second study in the August 2007 issue of *Psychosomatic Medicine* found that women with higher anxiety were significantly more likely to have spontaneous preterm birth than less anxious women.

After Delivery

- Some researchers have studied children whose mothers took antidepressants. They have found no link to serious problems with language, behavior or intelligence.
- There has been no data reported on long term effects of antidepressants on the baby's well being. So far, there is no evidence of long term effects.

Choosing an Antidepressant

- We don't know all the answers. No drug is entirely safe. A woman and her health care team must look at her case and carefully weigh:
 - The risks and benefits of various drugs
 - The risks and benefits of other types of treatment
 - The risk of untreated depression for the woman and her baby
- If a woman has been or is currently stable on a certain SSRI, that medication is sometimes continued, unless it is Paxil, which is generally contraindicated.
- Choosing an antidepressant needs to be done on a case by case basis. Of note, the literature changes frequently in this area.

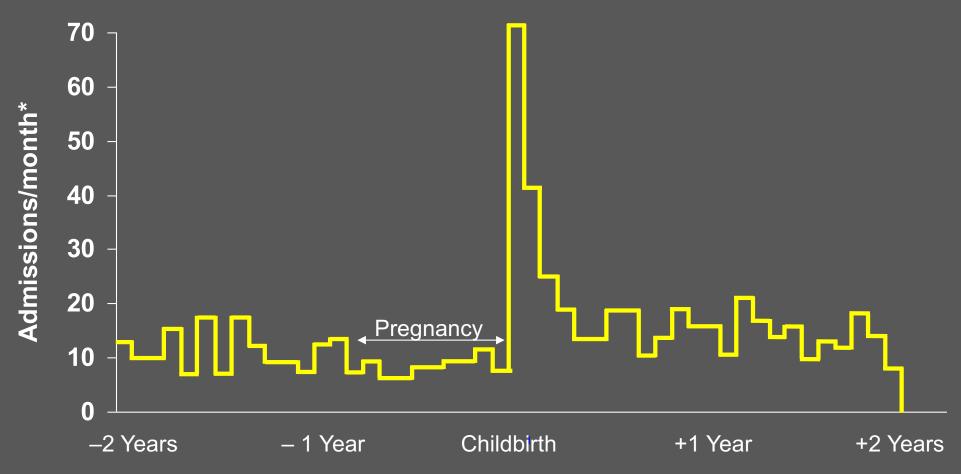
Important Points

- Make sure that the pt is followed closely by a therapist and/or psychiatrist and an Ob/Gyn
- Recommend prenatal vitamins and folic acid
- Check thyroid, blood count and other lab work to rule out medical reasons for low mood or energy
- It is a good idea to deliver the baby in a hospital versus at home by a midwife, as they can adequately monitor and assess any possible delivery complications
- Stress reduction techniques and individual therapy (at least weekly) are both encouraged
- It is always a good idea to be on the lowest number of medications possible, and on the lowest dose necessary
- With any medication during pregnancy, start low and go slow

Within the first 12 months after giving birth: 10% of women will have had 'Postpartum Depression'

- Huge 'crash' in hormones after pregnancy
- Postpartum: the brain and ovaries experience the re-establishment of menstrual cycle hormone-pulses just as during the onset of puberty

Psychiatric Admissions in 2 Years Before and After Delivery



^{*}Rate of psychiatric admissions in the 2 years before and after delivery in a population of 470,000 people with 54,087 births in a 12-year period Kendell RE, et al. *Br J Psychiatry.* 1987;150:662.

Postpartum Depression

Postpartum Depression:

- Technically, onset is within 4 weeks after childbirth, but can be seen up to 1 yr later
- 10-15% of women will experience postpartum depression within the 1st 12 mo after giving birth

'Baby blues':

- Affect up to 80% of women during the 10 days postpartum (usually lasts 2 weeks)
- These are transient, do not impair function, and don't meet MDD criteria

Postpartum Mood Conditions

Disorder	Incidence (%)	Onset/tx	Presentation	Sequellae
Postpartum blues	80%	1-2 wks, support-reassurance	80% resolve by week 2; 20% evolve into PPD; Mood lability, irritability, tearfulness	None
Postpartum depression	10 to 15%	sx begin within 1 month; antidepressants	Major depression often with obsessions re: baby's health	Increases risk of future postpartum and non-postpartum mood disorders
Postpartum psychosis	0.2%	95% begin within days-antipsychotics, mood stabilizers, benzodiazepines, consider ECT	Symptons like BPAD/ mixed/rapid cycling risk of infanticide	Increases risk of future postpartum and non-postpartum mood disorders

Bright. Am Fam Physician. 1994;50:595. Suri R and Burt VK: Jrnl Prac Psych Behav Hlth 3:67-77, 1997. Cogill et al BMJ: 1986;292:1165-7, Sharp et al J Child Psychiatry 1995:36:1315-36, Stein et al Brit J Psychiatry 1991;158:46-52

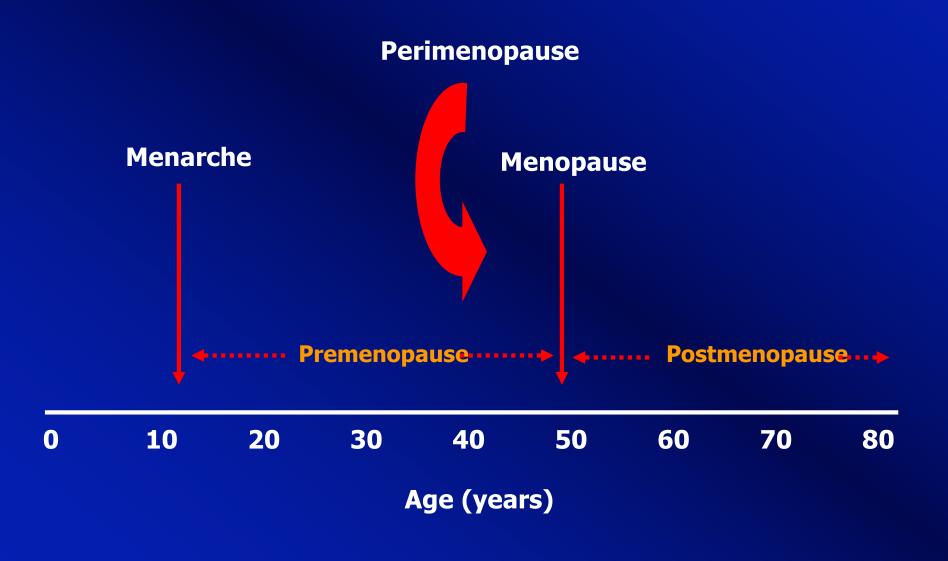
Return of Sexual Interest after Delivery

- If breastfeeding, after 6-12 months
 - Testosterone levels and menstrual cycle remain suppressed longer
- Without breastfeeding: 3-4 months

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Reproductive Life Cycle



Perimenopause: 2-9 years

- 40-60% complain to M.D. about
 - Irritability and insomnia
 - Mood swings and crying easily*
 - Fatigue and weight gain
 - Sexual complaints
- 52% get a first time diagnosis of depression or anxiety, even without a prior history of depression!!

Depression and the Menopausal Transition

- Symptoms may appear up to 7 yrs prior to last menses
- Mild mood symptoms are common
- A hx of Major Depression increases the risk of Major Depression during menopause
- Estrogen replacement therapy often relieves minor symptoms, but not MDD

Signs and Symptoms of Ovarian Decline in Peri and Postmenopausal Women

- Menstrual cycle changes
- Insomnia
- Vasomotor symptoms
 - hot flushes, night sweats
- New or increased depression
- Generalized anxiety
- Increasing FSH with hormonal variability
- Vaginal dryness
- Cognitive symptoms: brain fog
- New onset migraines
- Low libido

Perimenopausal Transition

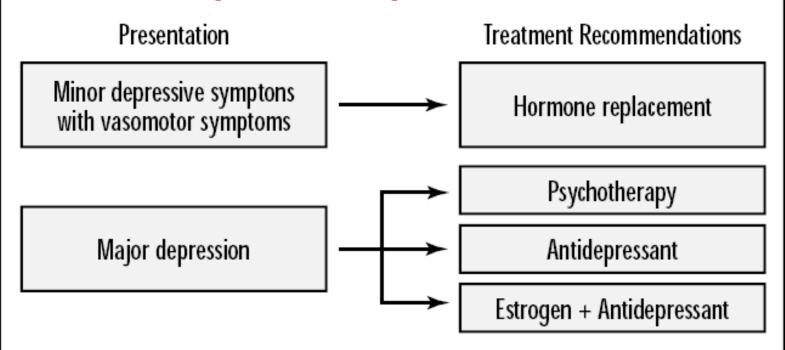
Community-based studies show an increased prevalence of depressive symptoms in the perimenopausal transition

- Massachusetts Women's Health Study Avis & McKinlay, 1991
- Manitoba Project Kaufert et al., 1992
- Harvard Study of Moods and Cycles Harlow et al., 1999

Risk Factors for Perimenopausal Depressive Symptoms

- Hot flushes
 - Depressive symptoms 4.6 times more likely
 - Association specific to perimenopause
- Prior depression
 - Depressive symptoms 4–9 times more likely

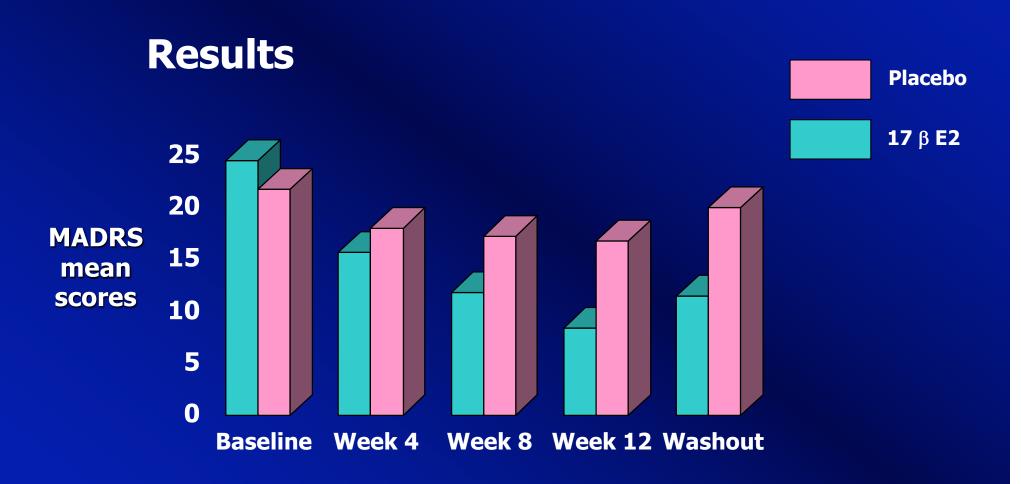
Perimenopausal Depression: Treatment



* If no contraindicatations exist. Brady. Available at:

http://www.medscape.com/Medscape?CNO/2000/APA/Story.cfm?story_id+1188. Accessed: 5/31/00. Hunter. Brit Med J. 1996;313:1217. Burt et al Harv Rev Psychiatr 6:121-132, 1998.

Efficacy of 17 β-estradiol (n=25) vs placebo (n=25) for the treatment of perimenopausal depressive symptoms



Sexual Desire in Women

Norms:

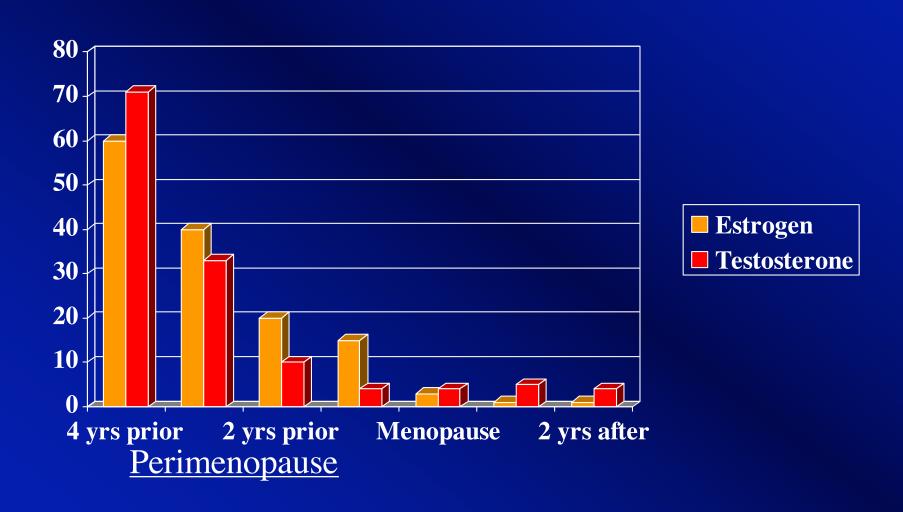
"I think about sex <u>less than</u> 1x per month or NEVER"

age 20-30: 32% Premenopause

age 40-60: 56% Perimenopause

age 60-80: 77% Postmenopause

Transition to Menopause



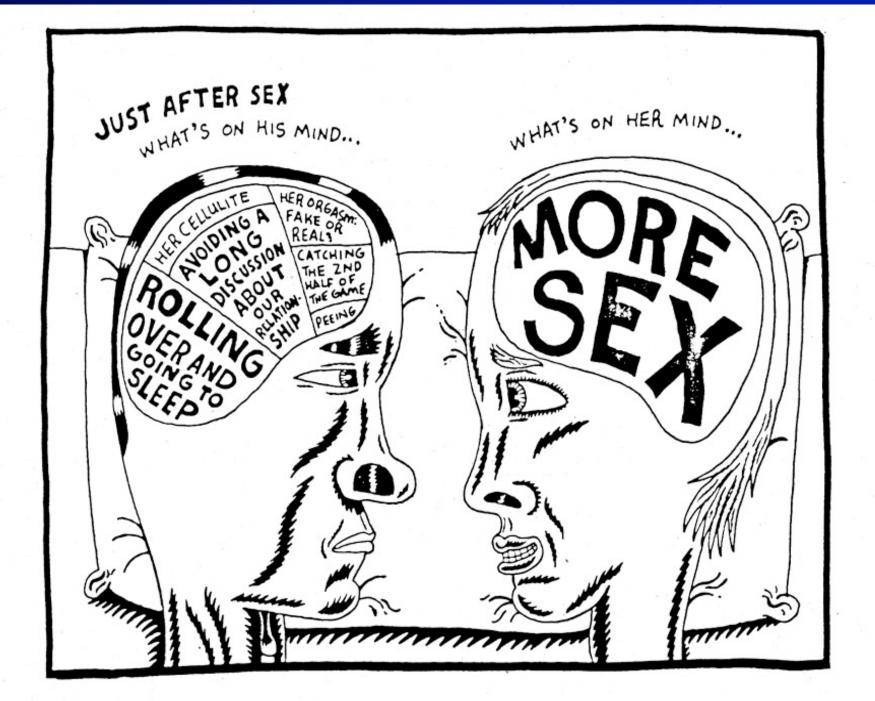
Lack of Sexual Desire

Prevalence - married, well-adjusted couples

Women 35%

• Men 16%





Sexual Desire in Men

Norms:

"I think about sex more than twice per day":

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• Age 20-30 85%
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• Age 60-80 38%

[•] Age 40-60 68%

Female Sexual Interest

- Which hormone is primarily responsible?
 - TESTOSTERONE
- When is the testosterone level highest during the menstrual cycle?
 - DAY 10 14, just before ovulation (Mother Nature's sexual boost)
- What decreases a woman's testosterone?
 - Birth control pills, nursing, oral estrogen, perimenopause and menopause decrease it
 - Exercise increases body's production of testosterone

Lack of Desire

Causes of new onset Lack of Desire:

- Low free testosterone
 - Ovarian and adrenal production decreases in perimenopause, menopause and aging
 - Increased binding protein: estrogen, birth control pills, overactive thyroid
- Medical
 - Vaginal atrophy, hyper- or hypothyroidism
- Medication side-effects
 - Antidepressants: all except Serzone, Remeron and Wellbutrin
 - Antihypertensives: especially B-blockers
 - Estrogen and birth control pills
- Psychosocial
 - Stress, fatigue, relationship conflict
- Psychological Problem
 - Depression, anxiety, substance abuse

Determinants of Free Testosterone

Production

- Ovarian 25%
- Adrenal 75%

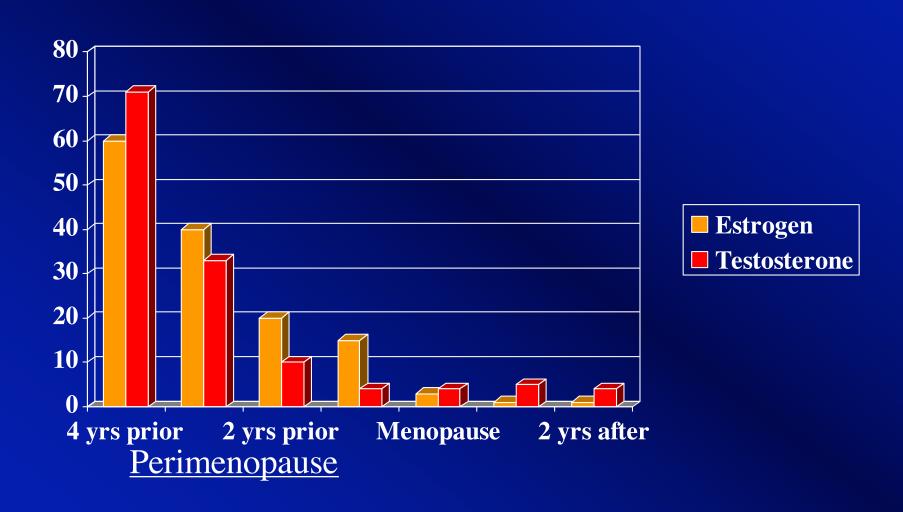
Binding hormone

- SHBG=sex hormone binding globulin
- Increased SHBG lower free testosterone
- Oral estrogen and thyroid increase SHBG
 - Oral estrogen passes through the liver (vs the patch or endogenous estrogen) and binds up SHBG, increasing production of SHBG
 - SHBG also binds free T3 and T4
 - So when you start a woman on oral estrogen you should re-check her TSH after 3 months

Sex and Estrogen

- Estrogen is a mood elevator. It works in the brain to maintain interest in sex, but it also works at the level of the genitals, helping to increase sensation and just making sex more pleasurable
- Without it, not only can desire take a dive but vaginal tissue begins to dry and shrink
- As a result, intercourse can become uncomfortable, or even painful
- Moreover, avoiding sex because of pain only leads to more pain
- The old "use or lose it" theory really does apply

Transition to Menopause



Female Sexual Response

- Sexual Desire
 - Sexual fantasy
 - Testosterone dependent
 - Masturbation
 - Testosterone dependent
 - Tactile stimulation
 - Testosterone dependent (nipples/clitoris)

Symptoms of Androgen Deficiency in Women

- Decreased libido
- Decreased interest in being intimate
- Decreased motivation
- Flat mood
- Decreased well being

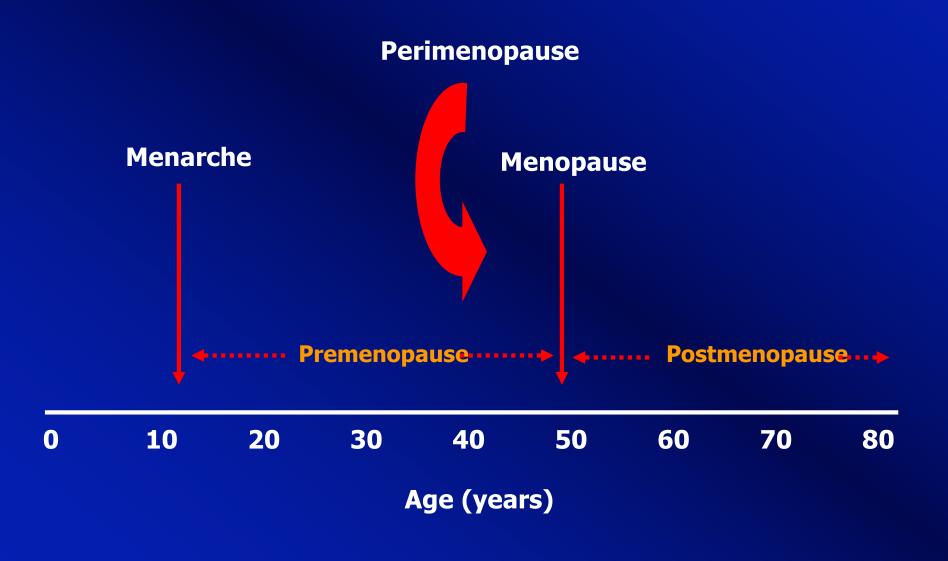
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Menopause

- Many people think of menopause as encompassing a several-year time span.
- In actuality, menopause lasts for <u>one single</u> <u>day</u> – the day 12 months after a woman has had her last period.
- After this, we use the term "postmenopausal."
 - Perimenopause, which is also termed "the menopausal transition," refers to the several-year period leading up to menopause and usually begins in the mid 40s.
 - Most of the troubling physical and psychological symptoms occur during perimenopause.

Reproductive Life Cycle



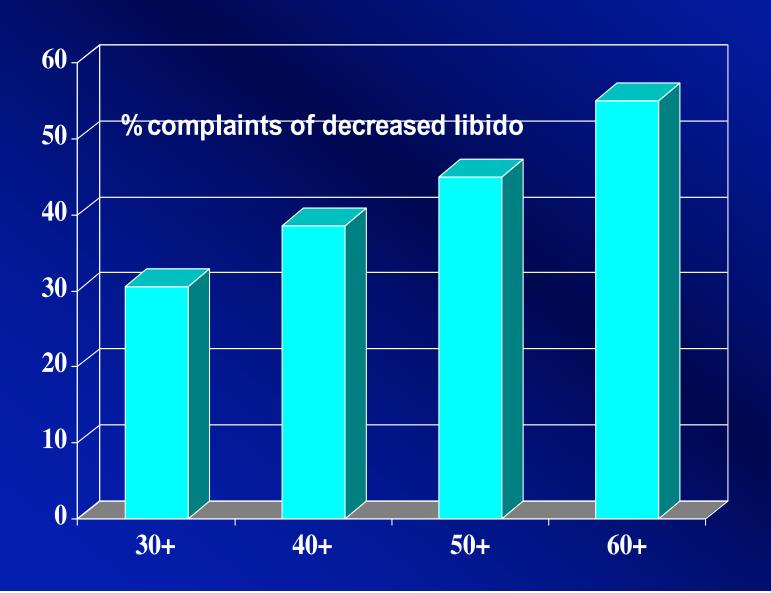
Menopause

- Average age: 51.2
- Surgical menopause: 15-20% in USA today
- Complete cessation of menses for 12 months
- Symptoms have usually been present for at least several years prior
- 20% have few or no symptoms

Clinical Features of Menopause

- Vasomotor symptoms
 - HOT FLASHES, night sweats
- Sleep disruption
- Psychological complaints
 - Forgetfulness
 - Mood changes
- Reduced skin collagen and skin thickness
- Urogenital changes
 - Vaginal dryness, atrophy
 - Frequent urogenital tract infections
- Sexual dysfunction

% of Women Complaining of Decline in Libido by Age



Solutions to Sexual Interest Decline

- Exercise more
- Stop oral estrogen (HRT, Birth control pills)
- Can try estrogen patch
- MORE FOREPLAY, better sex
- New partner (works for 6 months)
- Add TESTOSTERONE

Summary

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- Puberty, the Menstrual Cycle and PMDD
- Pregnancy, Mood and Postpartum
- Perimenopause, Mood and Sex
- Menopause, Mood and Sex

The End

Thank You!

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