Hormones and Mental Status in Women

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West London Menopause & PMS Centre
Gender Differences

U.S. National Comorbidity Survey reports lifetime prevalence rates of major depression at 21% in women, compared to 13% in men.

Gender difference is seen only after the onset of puberty and persists until the age of 55.
Mood & Depression

**Physiology**

CNS effects of Oestrogens

- **Genomic**: development of female CNS in fetal life e.g. neuronal structure & synaptic connectivity

- **Non-genomic**: regulation of brain plasticity and neurotransmission
Oestrogen and progesterone receptors are located in CNS

- hypothalamus, amygdala, pre-optic area, hippocampus & cerebellum

- mediate genomic effects e.g. limbic system functions sub-serving emotion & behaviour
Mood & Depression

*CNS neuro-receptor activity of oestrogen*

Direct effect on 5HT & noradrenaline receptors

Increases rate of degradation of MAO thus increasing levels of 5HT

Displaces tryptophan from albumin providing more 5HT substrate

Enhances transport of 5HT
Hormones and Mental Status in Women

Aetiology

Rapidly changing oestradiol and progesterone levels in vulnerable women can lead to the triad of hormone responsive depressive disorders.

Pisa 2006 – 6th IMS Workshop

Schmidt P – “Short arm of serotonin transporter gene affected in vulnerable women”
Mood & Depression

CNS neuro-receptor activity of progesterone

Psychological

• 3alpha 5alpha THP and allopregnanolone derived from progesterone stimulate GABAa receptor

• GABA is CNS depressant

• Levels lower in women with PMS especially in irritable depression

• Supplementary progesterone may increase GABA levels
Mood & Depression

*CNS neuro-receptor activity of androgens*

Psychological

• More androgen receptors within CNS in women than men!

• modulate for psychosexual parameters

• In menopause, testosterone production by ovaries and adrenals continues but...

• lower levels in surgically menopausal women associated with lower energy and libido
The triad of Oestrogen Responsive Depressive Disorders

- Postnatal depression
- Premenstrual depression
- Climacteric depression
Postnatal Depression
Postnatal Depression
Aetiology

Incidence of depression is low during the 2nd and 3rd trimesters of pregnancy  
*Kumar ’84*

Depression rates rise dramatically in the 3 months after delivery  
*Watson ‘84*

Severe and prolonged with lactation

Lower oestradiol levels in women depressed following delivery than with controls  
*O’Hara ‘90*
Postnatal Depression
Incidence

Affects 10-15% of women following childbirth

Persists for over one year in 40% of those affected \textit{Pitt '68}

Lack of an overall influence of psychosocial and background factors in determining postpartum disorder
Henderson & Studd ('91) showed that therapy with 200μg transdermal oestradiol significantly reduces depression score and accelerates recovery.

Gregoire and Studd ('96) double-blind placebo controlled study.

61 women 200μg transdermal oestradiol.

Edinburgh postnatal depression score.
Transdermal oestradiol in postnatal depression

Gregoire, Studd et al Lancet 1996
Proportions of subjects scoring above screening threshold for major depression

% subjects scoring 14+ on EPDS

Time (months) after starting treatment

Baseline, 1, 3, 5

Transdermal oestrogen, Placebo
Sub lingual 17β-estradiol in severe postpartum depression

Uncontrolled study of 23 women

1 mg tablets 3 to 8 times daily

MADRS scores weekly for 8 weeks

Baseline E2 79.8 pmol/L---450 at 8 weeks

Estrogen deficiency in severe post-natal depression  Ahakas et al 2002

1 week, recovery in 12/23 patients

2 weeks recovery in 19/23 patients

(but uncontrolled study in women with very low E2 levels)
Figure 1. How sublingual estradiol treatment alters postpartum depression

MADRS, Montgomery-Asberg Depression Rating Scale.

Adapted from Ahokas et al.2
Can we mimic postnatal depression hormonally??

16 women, 8 with a history of postnatal depression

Induced hypogonadism with leuprolide acetate

Simulated pregnancy by adding back supraphysiological doses of E and P for 8 weeks, and then withdrawing both steroids

Bloch M. Am J Psychiatry 2000
Can we mimic postnatal depression hormonally??

Results

• 5 of the 8 women (62.5%) with a history of postnatal depression and

• none of the women without a prior history,

• developed significant mood symptoms during the withdrawal period
Premenstrual Depression
Premenstrual Syndrome
History

Hippocrates - ‘….shivering, lassitude and heaviness of the head denotes the onset of menstruation….’

Henry Maudsley (1873) - First to make connection between PMS & cyclical ovarian activity

Greene & Dalton (1953) - Introduced the term “premenstrual syndrome”

Studd (1988) - Ovarian cycle syndrome - Menstruation not an essential feature of PMS
Fashionable 19th. Century Disorders in Women

- Neurasthenia
- Insanity
- Menstrual madness
- Nymphomania
- Masturbation
- Moral insanity
- Hysteria

all often due to reading serious books or playing music
“…The monthly activity of the ovaries which marks the advent of puberty in women has a notable effect upon the mind and body; wherefore it may become an important cause of mental and physical derangement …”
Premenstrual Syndrome
Modern Definition

Distressing physical, psychological and behavioural symptoms, not caused by organic disease, which regularly recur during the same phase of the menstrual (ovarian) cycle and which significantly regress or disappear during the remainder of the cycle

Magos & Studd (1984)
PMDD Definition
(DSM IV - Diagnostic and Statistical Manual of Mental Diseases)

- Five or more of the following present premenstrually (one must be a core* symptom):
  - Markedly depressed mood *
  - Marked anxiety/tension*
  - Marked affective lability
  - Marked anger/irritability*
  - Decreased interest in usual activities*
  - Difficulty concentrating
  - Lethargy/fatigue
  - Appetite change/food cravings
  - Sleep disturbance
  - Feeling overwhelmed
  - Physical symptoms (e.g. breast tenderness, bloating)

- Symptoms in most menstrual cycles during the last year (retrospective confirmation) and in at least two cycles as prospective confirmation

- Occur the last week before menses and remit within a few days of onset of menses

- Marked interference with work, social activities, relationship
Premenstrual Syndrome
Symptoms – Prevalence

SWS 2007 Sadler Inskip Panay (Submitted)

- >25 000 Women Surveyed
- 30% stated that PMS severely affected their quality of life (cf PMDD 3-8%)
- Positive correlation of PMS with obesity / less exercise / less qualifications
- Less PMS with increasing hormonal contraceptive use
Premenstrual Syndrome
Symptoms

Over 160 PMS related symptoms Moos (1968)

- **Physical** e.g. breast tenderness, headache, bloating
- **Psychological** e.g. mood swings, irritability, depression
- **Behavioural** e.g. lowered cognitive performance, accidents, suicide attempts
PRADA OR PRINCIPLES
What fashion editors really wear

The weird and wacky ways some women lose weight

Does PMS really exist or are you just a grumpy cow?
Premenstrual Syndrome Diagnosis

▶ History

- **Primary PMS**: Complete resolution of symptoms at onset of menstruation  Dalton (1977)

- **Secondary PMS**: Improvement of symptoms following menstruation, even if only for a few days
Premenstrual Syndrome Diagnosis

- Validated Prospective symptom diaries
  - Confirm diagnosis more accurately than retrospective recall
  - Moos Menstrual Distress Questionnaire (MDQ/PDQ)
    » Moos 1968, Magos/Studd 1987 (Oestradiol trials)
  - Daily Record of Severity of Problems (DRSP)
    » Endicott & Harrison NY State Psych Inst 1990, Arch Women’s Mental Health 2006 (Yaz trials)
  - Premenstrual Symptoms Screening Tool (PSST)
    Steiner et al Arch Womens Ment Health 2003 (SSRI trials)
**Premenstrual Syndrome**

**Proposed Pathophysiology in PMS**

<table>
<thead>
<tr>
<th>Biological</th>
<th>Psychological</th>
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<tr>
<td>Glucocorticoids</td>
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<td>Androgens</td>
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<td>Prolactin</td>
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<td>Fluid retention</td>
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<td>Vitamin deficiency</td>
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<td>• A</td>
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<td>• B6</td>
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<td>Antidiuretic hormone</td>
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<td>Reactive hypoglycaemia</td>
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<td>Prostaglandins</td>
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<td>• excess</td>
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<td>• prolactin hypersensitivity</td>
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<td>Endogenous opiate peptides</td>
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<td>• mid luteal increase</td>
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<td>• premenstrual withdrawal</td>
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<td>Endogenous hormone allergy</td>
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<td>Menstrual toxin</td>
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<td>Magnesium deficiency</td>
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<td>Neurotransmitters</td>
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<td>• serotonin</td>
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<td>Melatonin</td>
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<td>Psychological</td>
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<td>Social &amp; evolutionary</td>
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<td>Genetic</td>
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</table>
Premenstrual Syndrome

Aetiology

► No convincing evidence for any of the postulated biological or psychological mechanisms

► May be multiple aetiologies (E2/serotonin, Progesterone-allopregnanolone/GABA)

► Ovarian function appears to play an essential role in the genesis of symptoms Studd (1979)
Premenstrual Syndrome
Aetiology

► Serotonin

• Lower platelet concentrations
• Lower luteal phase levels
• Enhanced sensitivity to progesterone
• Levels elevated by oestradiol
• SSRIs effective for PMDD

Premenstrual Syndrome
Aetiology

► GABA
  • Major inhibitory system in CNS
  • Low levels of GABA in mood disorders
  • Low levels in women with PMDD during late luteal phase

## Premenstrual Syndrome

### Proposed Treatments for PMS

<table>
<thead>
<tr>
<th>Pharmacological</th>
<th>Psychological &amp; Social Support</th>
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<tbody>
<tr>
<td>Diuretics</td>
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<td>Bromocriptine</td>
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<td>Magnesium</td>
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<td>Desensitization</td>
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<td>GnRH analogues</td>
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<td>Psychoactive drugs</td>
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<td>- SSRI inhibitors</td>
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<td>- tranquilizers</td>
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<td>- lithium</td>
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<td>Prostaglandin mediators</td>
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<td>- PG synthetase inhibitors, g linolenic acid</td>
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<tr>
<td>Vitamins</td>
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<tr>
<td>- B6, A, E</td>
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<tr>
<td>Sex hormones</td>
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<td>- progesterone</td>
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<td>- progestogens</td>
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<td>- combined pill</td>
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<td>- danazol</td>
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<td>- LHRH analogues</td>
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<td>- oestradiol implants and patches</td>
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<tr>
<td>- androgens</td>
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</table>

| Miscellaneous          |                                |
|                       |                                |
| Physical Activity      |                                |
| Diet                  |                                |
| Hypnosis              |                                |
| Meditation            |                                |
| Yoga                  |                                |
| Acupuncture           |                                |
| Bilateral oophorectomy|                                |
| Radiation menopause   |                                |
Management of Mild / Moderate PMS

- Healthier lifestyle
  - Stress management
  - Counselling/support

- Nutrition
  - Mild medications
  - Evening primrose
  - Diuretics

- Vitamins & minerals
  - B6, A & D
  - Magnesium
  - Zinc
Moderate / Severe PMS

- Psychological/physical
- Progesterone
- COC/ Oestradiol /Other
- Psychological
- SSRI's / SNRIs

Resistant PMS
- GnRHa + add-back

Resistant PMS
- TAH BSO HRT
Premenstrual Syndrome
Progesterone – Causative or Therapeutic?

- Magill et al Br J Gen Pract 1995
- Cyclogest pessaries, 400mg bd for 14/7 in 93 patients (141 randomised)
- Significant improvement in both physical & psychological PMS symptoms V placebo
- Not supported by O’Brien RCT meta-analysis data but…
  - 4 progesterone and 10 progestogen studies
Premenstrual Syndrome
Treatment - Ovulation Suppression Agents

- COC / POP / progestogens
- Levonorgestrel intrauterine system
- Depot progestogens / Implanon® / Cerazette®
- Danazol
- Oestradiol implants / patches
- GnRH analogues +/- add-back HRT
Premenstrual Syndrome
Treatment - Ovulation Suppression Agents

COCP

► Little benefit with COCP despite ovulation suppression.
  ▪ progestogenic PMS-like side effect & pill free week
► Rapkin (2003) Psychoneuroendocrinol
  ▪ anti-androgenic, anti-mineralocorticoid progestogen, drosperinone – Yasmin COCP showing promise
Premenstrual Syndrome
Treatment – Yaz®

- Yonkers K. (Yale) et al Obstet Gynecol 2005
- EE 20mcg / Drospirenone 3mg, 24 active/4 inactive
- RCT 2 month run in 3 treatment cycles in 450 women PMDD
- Response (50% reduction in daily symptoms): 48% active v 36% placebo p = 0.015
Premenstrual Syndrome 
Treatment – Yaz®

► Pearlstein T. (Rhode Island) et al Obstet Gynecol 2005
► RCT 2/12 run in, 6 treatment cycles with crossover at 3 months
► 511 women screened – only 25 completed study!!
► Symptom Scores (DRSP) -12.5 (active) v -6.5 (placebo) (P<0.001)
Premenstrual Syndrome
Treatment - Ovulation Suppression Agents

COCP

Take home messages

1) Use bicycling/tricycling or long cycle regimens

2) Extended cycle regimens on the way
Premenstrual Syndrome
Treatment - Progestogens

► AVOID! “Model for premenstrual syndrome”
  ▪ Magos & Studd BJOG (1986)
  ▪ Wyatt et al BMJ Meta analysis (2001)

► POP
  ▪ Replaces cyclical with continuous progestogenic SE’s
  ▪ Especially androgenic POP’s
Role of LNG IUS (Mirena®) in PMS

- Small benefit shown in some studies
- Progestogenic side effects
  - Physical
  - Psychological
- SE’s usually in 1st 3 months
Premenstrual Syndrome
Treatment - Ovulation Suppression Agents

- Depo Provera / Implanon® / Cerazette®
  - Some report improvement in PMS due to ovulation suppression.
  - Those with continuing cycle may have background in addition to cyclical PMS
  - PMS SE’s less common with Implanon® (acne reported)
Premenstrual Syndrome
Treatment - Oestradiol Patches

- 40 patients with PMS confirmed by PDQ and MDQ
- Randomised double blind placebo controlled with 3 month cross-over
  - Active treatment: 200mcg patches + Oral NET D19-26
  - Placebo treatment: Placebo patches + Oral NET D19-26
  - Gp1: Active treatment -> Placebo
  - Gp2: Placebo -> Active treatment

Mood Swings

Symptom cluster rating vs. Time (months)

- Placebo-Active
- Active-Placebo

Oestrogen Therapy

- 100µg patches tried subsequently
  - As effective
  - Fewer symptoms of breast discomfort and bloating
  - Less anxiety about high dose oestrogen therapy

Smith RNJ, Studd JWW et al; BJOG 1995
Is 100 μg – or 200 μg- Oestradiol Patch Anovulatory?

Important information for young women who need treatment for PMS and contraception.

But totally unproven - so don’t risk it!!
Randomised, Prospective, Placebo Controlled, Multicentre Study of Women with Severe PMS, Treated with 100 µg Transdermal Oestradiol (2006)

Panay N*, Rees M**, Domoney C*, Zakaria F*, Guilford S***, Studd JWW*

*Chelsea & Westminster Hospital
**John Radcliffe Hospital, Oxford
***Janssen Cilag, Saunderton, Bucks
Randomised, Prospective, Placebo Controlled, Multicentre Study of women with Severe PMS, treated with 100 µg Transdermal Oestradiol (2006)

Premenstrual Syndrome
Treatment - SSRI’s

- PMDD (premenstrual dysphoric disorder)
  - Premenstrual depression partly due to serotonin deficiency
  - SSRI’s increase serotonin levels
  - Fluoxetine was licensed in UK for Rx of PMDD – not renewed by company
Premenstrual Syndrome
Treatment - SSRI’s

- Steiner M. et al 1995 NEJM
  - Fluoxetine in treatment of premenstrual dysphoria
  - 405 women in 2 month placebo washout phase
  - 313 women randomised to fluoxetine 20mg, 60mg or placebo
  - Both doses significantly superior to placebo in reducing tension & irritability by VAS
Premenstrual Syndrome
Treatment - SSRI’s

► Luteal phase fluoxetine as effective with fewer side-effects

_Dimmock et al Lancet 2000_
Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review.

► **Take home tip:**
Mildest SSRI therapy

_Citalopram 10 – 20mg luteal phase (D15 – D28)_
Effect size of Yaz vs. SSRIs in PMDD

Standardized mean difference 95% CI on overall symptoms

SSRIs pooled data from 13 RCTs
844 patients

(Y Wyatt et al. Cochrane Library 2002)

Yaz parallel study
Yaz cross-over study

-2 -1 0 1
Favours treatment favours placebo

Large medium small (effect size)
Premenstrual Syndrome
Treatment - GnRH Analogues

► Very effective for PMS - also diagnostic
► Unsuitable for long term use alone
► HRT add back to prevent menopausal symptoms and bone loss

Leather, Studd Gyne Endocrinol 1999
Meta Analysis of RCTs
(GnRHa vs placebo)

Muse et al. 18 (IM[D-Trp-ProNEt-GnRH 50 µg daily)
Freeman et al. 19 (depot leuprolide 3.75 mg monthly)
Brown et al. 20 (depot leuprolide 3.75 mg monthly)
Leather et al. 22 (depot goserelin 3.6 mg monthly)
Overall anovulatory GnRHa doses

Non-anovulatory dosing regimens
Sundstrom et al. 21 (100 µg nasal buserelin daily)*

Overall GnRH doses (anovulatory and non-anovulatory)

Wyatt et al. 2004
Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy for Premenstrual Syndrome Cronje Studd 2002
Perimenopausal Depression
Early placebo controlled studies of estrogen therapy which looked at mood in menopausal women

Utian
Premarin (1972)

Campbell and Whitehead
Premarin (1983)

Montgomery Studd et al
E2/ E2 + T implants (1987)
EFFECT OF OESTROGEN AND
TESTOSTERONE IMPLANTS ON
PSYCHOLOGICAL DISORDERS IN THE
CLIMACTERIC

J. C. Montgomery
M. Brincat
A. Tapp

L. Appleby
E. Versi
P. B. C. Fenwick
J. W. W. Studd

Dulwich Hospital Menopause Clinic, Dulwich Hospital,
London SE22 8PT; and Institute of Psychiatry, London
Effect of oestrogen and testosterone implants on the psychological disorders in the climacteric

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>E50</th>
<th>E50/T100</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>25</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Mean age /yrs</td>
<td>46</td>
<td>50</td>
<td>48</td>
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<tr>
<td>Perimenopausal</td>
<td>14</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>11</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Montgomery & Studd Lancet 1987
Psychiatric scores in peri-menopausal patients

Mean SRD scores

- Placebo
- E50
- E50/T100

Time/months

p<0.05
Psychiatric scores in post-menopausal patients

Mean SRD scores

Time/months

placebo
E50/T100
E50
Effect of oestrogen and testosterone implants on the psychological disorders in the climacteric

Both oestrogen and oestrogen / testosterone better than placebo at two months in the peri-menopausal woman with depression

But no improvement in the depression of post-menopausal women with this treatment

Montgomery & Studd Lancet 1987
Mean (+SD) SRD30 scores in the 2 treatment groups at baseline and at follow-up
(mean duration of follow-up = 23 months)

<table>
<thead>
<tr>
<th>SRD30 scores</th>
<th>E50 (n = 32)</th>
<th>E/T (n = 28)</th>
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<tbody>
<tr>
<td>pre</td>
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<td>on RX</td>
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</table>

* p < 0.01
Transdermal estrogens in peri-menopausal depression

50 depressed peri-menopausal women

26 Major depressive disorder
11 dysthymic
13 Minor depressive disease

100 μg estradiol patches in 12 week placebo controlled study

• Soares et al 2001 Arch Gen Psych. 58 529-34
Transdermal estrogens in peri-menopausal depression

Remission of depression in 17/25 (68%) of E2 patients

Remission of depression in 5/25 (20%) of placebo patients

Regardless of DSM-IV diagnosis

• Soares et al 2001 Arch Gen Psych.58 529-34
Depression and early peri-menopause

332 ♀ with a history of major depression

644 ♀ without a history of major depression

♀ with a history of depression had ↑ FSH and ↓ E2 at enrolment to the study

Major depression may be associated with early decline in ovarian function

Harlow et al 2003 Arch.Gen Psych 60.29-36
Depression and early peri-menopause

Women with a history of depression have twice the rate of early menopause

Women with a history of severe depression have 3 times the rate of early menopause

Women with a history of anti-depressant medication have 3 times the rate of early menopause

Harlow et al 2003 Arch.Gen Psych 60.29-36
Premenstrual Syndrome: Pathophysiology, Definition of the Disease and Treatment Options

Summary

- Training of Health Professionals of paramount importance to aid recognition of condition
- Management ideally should be by multidisciplinary teams
- Moderate/severe PMS usually needs medical intervention - sooner rather than later to avoid unnecessary suffering
Premenstrual Syndrome
Future Aims

► Training of GPSI’s in women’s health
  • ?funding from PCT’s / PBC

► “Evidence based treatment options for PMS”
  • Panay N RCOG Green Top Guidelines 2007
  • www.rcog.org.uk
National Association for Premenstrual Syndrome – NAPS
A Registered Charity

Website www.pms.org.uk
(>10000 hits per day)
Help-line
Monthly e Newsletter (Once a Month)
Annual scientific meetings
Policy planning for PMS
Liaison with media
PMS Database
Thank you for your attention!