Is it me or my Hormones?

Nick Panay

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West London Menopause & PMS Centre

Chairman of NAPS

Women’s Meeting

CHANA
Definitions

- **Menarche**
  - The first menstrual period

- **Menopause**
  - Defined retrospectively 1 year after last menstrual period
  - Average age 51

- **Amenorrhoea**
  - 6 months between periods

- **Early Menopause**
  - <45yrs

- **Premature Ovarian Failure**
  - <40yrs
Why do periods become irregular?

- **Brain**
  - e.g. Stress / weight related

- **Ovaries**
  - e.g. POF, PCOS

- **Genital Tract Disorders**
  - e.g. Fibroids, polyps

- **Endocrine Disorders**
  - e.g. Thyroid disorders, Hyperprolactinaemia

- **Drug therapy**
  - e.g. Anti-psychotics
Ovarian Failure
Ovarian Failure

- Follicle cohort shrinks throughout life
  - Newborn: 2 million
  - Puberty: 3 - 400,000
  - 40y+: Few thousand
  - Postmenopause: Few or no ova

- Number of ovarian follicles available to mature each cycle is depleted

- As one oocyte ovulates 1,000 are lost through programmed cell death
Oestrogen levels relative to age

Estrogen levels relative to age

Graph showing relative activity of estrogen over age (years) with stages of menopause: premenopause, menopause, postmenopause. The graph also indicates acute symptoms and long-term health consequences related to the hormone levels.
Making the diagnosis

50% of women whose periods stopped for more than six months saw three or more clinicians before any laboratory testing was performed

(Aluzubaidi NH et al. 2002)
26th Jan 2006 Yorkshire Post

Testing ovarian reserve

The Plan Ahead kit, which costs £179, assesses the number of eggs in a woman's ovaries compared with the levels expected for others of the same age.

- It can predict the ovarian reserve for the following two years

- The test developed by Professor Bill Ledger, of Sheffield University, measures three hormones in the blood – two ovarian hormones, Inhibin B and AMH, and the pituitary hormone called FSH.

- The kit is being launched by Sheffield-based Lifestyle Choices, a spin-out company from Sheffield University.
2 ways that ovarian failure can happen prematurely:

- Failure to attain the appropriate peak follicle number
- Accelerated loss of oocytes and follicles
Genetic

Roger Gosden, Cornell

“Twins at higher risk of POF”

418 pairs identical twins (5% chance POF)

? Genetic defect

ASRM October 2005
Iatrogenic

- Chen WY Manson JE 2006 JNCI
- “Premature Ovarian Failure in Cancer Survivors: New Insights, Looming Concerns”

- 598,000 hysterectomies 1994-1999 in women below 40 (1/3 with BSO) i.e. 100,000 pa!

- i.e. Every year in US 33,000 instantly menopaused and 66,000 left with increased risk of POF.
Fertility Options for women at risk of POF

Surgery

- Ovarian transposition

Ovarian Tissue Cryopreservation

- Transplantation – 3 reported pregnancies thus far
  - (Donnez 2004, Chaim Sheba Medical Centre Israel 2005, Oktay 2006)

- In Vitro maturation

IVF

- Own Embryo Cryopreservation
- Own Oocyte Cryopreservation (1st pregnancy 2001)
Fertility Options after POF

Realistic options but not for everyone!

- Oocyte Donation
- Embryo Donation
- Adoption

Potential Future Options:

- Cloning with somatic cell nuclear transfer to enucleated oocytes
- Stem Cell technology - UK 10 years; USA 2 years!
Fertility Options after POF

- Oocyte number and quality not the only factors in subfertility of POF

  - Elevated FSH levels reduce ovarian responsiveness by down regulation of the FSHr

  - If so, does suppression of FSH increases the chances of successful ovulation induction in women with proven POF?

Tartagni et al Fertil Steril 2007
Fertility Options after POF

50 women with proven POF

EE 20mcg (GP1) / placebo (GP2) 2 weeks prior to ovarian stimulation with gonadotrophins

Group 1 - 8/25 (32%) ovulated v Group 2 0/25 (0%) 4 pregnancies

Ovulation induction only possible if FSH < 15iu/l

Tartagni et al Fertil Steril 2007
Questions

- Which is preferable pill or HRT for POF?

- Poor data but probably HRT based on
  - Bone mineralisation and
  - Cardiovascular prophylaxis
PCOS Mechanism
Interventions PCOS

Hormonal

- Dianette & Newer Pills e.g. Yasmin
  - Regular Periods
  - Less Body & Face Hair / Acne / Greasy Skin

- Clomid
  - If Pregnancy is Desired
  - Scanning is essential!

West London Menopause & PMS Centre

July 2007
Interventions PCOS

- **Metformin v COCP in PCOS**
  - Systematic review and meta analysis - 4 RCTs identified (104 subjects)

- **COCP superior to metformin in**
  - improving menstrual pattern
    - All COCP v 10/16 (62.5%)
  - Reducing serum total testosterone

- **Metformin superior to COCP in**
  - Reducing fasting insulin
  - Not increasing TG levels

Costello et al Hum Reprod 2007

West London Menopause & PMS Centre
Women’s Moods!
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.

Recent work at Harvard (Dr P Schmidt) has found gene (serotonin transport) defective in women vulnerable to hormonal fluctuations.
Premenstrual syndrome
Aetiology

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

Postnatal depression

Premenstrual depression

Climacteric depression
Premenstrual syndrome
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

Frank (1931) - Described the hormonal basis of premenstrual tension

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

Studd (1988) - Ovarian cycle syndrome - Menstruation not an essential feature of PMS
Fashionable 19\textsuperscript{th} century disorders in women

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

all often due to reading serious books or playing music
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)
Premenstrual syndrome

Prevalence

Reid (1985) - Summary of evidence for prevalence of PMS in general population

- 10 -15% women asymptomatic
- 50% mild PMS symptoms
- 30% moderate PMS
- 5 -10% severe PMS (up to 1 000 000 women in UK alone!)
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

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
Management of mild / moderate PMS

Healthier lifestyle
Nutrition

Stress management
Counselling/support

Mild medications
Evening primrose
Diuretics

Vitamins & minerals
B6, A & D
Magnesium
Zinc
She found if administered correctly, evening primrose oil had a remarkably calming effect.
Moderate / severe PMS

Psychological/physical

??Progestosterone

Psychological/physical

COCP / Oestradiol

Psychological

SSRI's / SNRIs

Resistant PMS

GnRHa + add-back

Resistant PMS

TAH BSO HRT
Premenstrual syndrome

Treatment

- The Pill
  - Didn’t Work because…
    - PMS-like side effects & pill free week
  - Newer pills do work!
    - Yasmin / Yaz / Seasonale / Anya
    - Bicycling / Tricycling
Premenstrual Syndrome
Treatment - Oestradiol Patches

40 patients with PMS

Randomised double blind placebo controlled with 3 month cross-over

- **Active treatment:** Oestrogen Patches + synthetic progesterone
- **Placebo treatment:** Placebo patches + Synthetic progesterone

- Gp1: Active treatment -> Placebo
- Gp2: Placebo -> Active treatment

Mood Swings

[Graph showing symptom cluster rating over time (months) with two lines: Placebo-Active and Active-Placebo. The graph data is sourced from Watson & Studd (1989) Lancet.]
Role of LNG IUS (Mirena®) in PMS

- **Progestogenic side effects**
  - Physical
  - Psychological

- SE’s usually in 1st 3 months

- Better with patches
Premenstrual syndrome

Treatment - SSRI’s

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

Treatment - SSRI’s

- Take home tip:
  - Mildest SSRI therapy
    - Citalopram 10 – 20mg / day
    - Second half of cycle as effective!
Premenstrual syndrome
GnRH analogue injections / nasal spray

- Mimick Menopause

- Take 2 – 3 months to work

- Very effective for PMS - also diagnostic

- HRT add back to prevent menopausal symptoms and bone loss
Resistant PMS

- TAH BSO (BSO otherwise Ovarian Cycle Syndrome (OCS [Studd 1988] develops)

- Negligent not to give adequate ERT

- Also Testosterone for energy and libido
  - (Cronje & Studd 2002)
Pregnancy and Post Pregnancy
Postnatal Depression

- Affects 10-15% of women following childbirth
- Persists for over one year in 40% of those affected
- Lack of an overall influence of psychosocial and background factors in determining postpartum disorder
Transdermal oestradiol in postnatal depression

*Gregoire, Studd et al Lancet 1996*
Menopause
Screening and Monitoring

- General: Screening & Monitoring
  - Cervical smears 3 yearly (5 yearly > 50) - 65y
  - Mammography 3 yearly (indefinite if on HRT) - 65y
  - Blood pressure, Blood fats (annual check)
  - ?Osteoporosis checks
Lifestyle

- Regular Exercise
  - CVS & Bone Health

- Well balanced diet
  - Complex carbohydrates
  - Oily fish

- Moderating Smoking / Alcohol / Caffeine

- Phytoestrogen rich diet
  - Soy, legumes, pulses etc
Vasomotor treatment algorithm: conservative, clinical approach

Mildly symptomatic

Lifestyle and complementary

**Lifestyle modifications**
- Core body temperature
- Exercise
- Non-smoking
- Relaxation

**Complementary therapies**
- Red clover isoflavones
- Soy isoflavones
- Black cohosh

Review after 3 months then annually, or as required by patient
Vasomotor treatment algorithm: a conservative, clinical approach

**First line**

**Lifestyle and complementary**
- Lifestyle modifications
- Complementary therapies such as red clover isoflavones, soy isoflavones, black cohosh

**Review after 8–12 weeks**

If treatment is not satisfactory within 12 weeks, discuss second line options

- Averse or contra-indicated to HT
- Patient understands risks and benefits of HT

**Second line**

- Non-HT prescription medications and/or Lifestyle and complementary
- HT
  - Low dose est +/- prog

Review after 3 months then annually, or as required by patient
Vasomotor treatment algorithm: a conservative, clinical approach

Severely symptomatic

Averse or contra-indicated to HT

Patient understands risks and benefits of HT

Non-HT prescription medications

Trial non-HT prescription therapies for symptoms

- Antidepressants
- Gabapentin
- Antihypertensives

and/or

Lifestyle and complementary

- Lifestyle modifications
- Complementary therapies such as red clover isoflavones, soy isoflavones, black cohosh

HT

- Low dose estrogen +/- progesterone

Review after 3 months then annually, or as required by patient
HRT: Don't Forget Testosterone!

- Women have more testosterone receptors in the forebrain than men!

- Levels drop by 50% after a surgical menopause and 20% after a 'natural' menopause

- This can lead to problems such as lack of energy, headaches & libido

- Only implanted pellets licensed in women @ present
Now, the love patch

A ‘Viagra’ to restore ladies’ joie de vivre

WOMEN could be wearing stick-on patches to boost their sex drive within months, say researchers.

The patches release the male sex hormone testosterone to help women overcome a loss of desire.

Some experts claim it will be the female version of Viagra, which was introduced to help men overcome impotence.

Experts say the patch could help women achieve a higher sex drive.

From Jenny Hope, Medical Correspondent in Philadelphia.

Research by a team of scientists at the University of Pennsylvania showed that women who took the patch had a significant increase in their sex drive.

The patch works by releasing a small amount of testosterone into the bloodstream, which helps to increase the amount of sexual activity experienced by women.

Men suffering from male sexual dysfunction can also benefit from the patch.

The patch is currently being tested in clinical trials and is expected to be available on the market within the next few years.

How coming off the Pill can boost women’s sex drive

COMING OFF the Pill can boost women’s sex drive, according to researchers.

Taking the hormonal contraceptive causes a loss in sexual desire in one in five women, scientists claimed yesterday.

Four weeks after abandoning the Pill, women who had complained of a lack of desire round their appetite for sex returned.

They had increases in libido, arousal and orgasm, according to a report at the American Society for Reproductive Medicine conference in Philadelphia.

Not taking the Pill led to rising levels of the sex hormones testosterone and a fall in a hormone that can suppress desire.

Experts also believe that the loss of sexual appetite experienced by some women on the Pill may be triggered by the elimination of ovulation — nature’s way of telling women to have sex.

Researcher Dr Susan Sarajedini of the University of California, Los Angeles, said: “Discontinuing hormonal contraception should be considered a first-line treatment for women complaining of sexual dysfunction.”

Around 15 per cent of women taking the Pill, injectables or using a hormonal patch have symptoms of sexual dysfunction such as sexual distress, low libido and vaginal dryness, she said.

In a pilot study, 20 women aged around 34 stopped taking the Pill after six months. Their sex life improved significantly, with increases in sexual appetite and orgasm, and a cut in sexual distress.

Dr Marian Damerwood, president of ASRM, said: “This study presents evidence for an effect many women are familiar with.

When a healthy pre-menopausal woman experiences decreased sexual function, hormonal contraception could be considered as a possible cause and may be discontinued to determine whether it is indeed a factor.”

But Dr Anne Scardamalia, author of Contraception: A User’s Guide, said it was difficult to prove that a loss of libido is directly attributable to the Pill.

“Ther are many factors that affect sexual desire, including stress, lifestyle and bereavement,” she said.

STAPLES

EXCLUSIVE

THE UK’S LOWEST PRICED RAPOPOD

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The Daily Mail, Thursday, October 21, 2004

West London Menopause & PMS Centre
Testosterone Transdermal Patch (TTP) Phase III Clinical Trials

- Two Similar Phase III Clinical Trials INTIMATE SM 1 (n= 562) and INTIMATE SM 2 (n=533)

24-week, randomized (placebo or TTP 300 mcg/day), double-blind, multi-centre phase III trial

- Surgically menopausal women receiving estrogen

- Thin, clear, oval matrix-type transdermal patch
- Twice-a-week application to abdomen

Buster J. et al., Obstet Gynecol 2005;105;944-52
Significant effects at 4 weeks of treatment

Total Satisfying Activity

Sexual Desire

Distress

§Analysis combined Intimate SM1 & SM2

Placebo*

Transdermal testosterone patch*

*All women received concomitant estrogen therapy

* p< 0.05

Kingsberg S et al. Poster presentation at the Annual Meeting of the American Obstetrics and Gynecology Society, May 2005
## Overall Adverse Events (AE) profile

<table>
<thead>
<tr>
<th>Adverse Event (%)</th>
<th>Placebo (N = 279)</th>
<th>TTP (N = 283)</th>
<th>Placebo (N = 266)</th>
<th>TTP (N = 266)</th>
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<tbody>
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<td>Patients with AEs</td>
<td>79.6</td>
<td>77.7</td>
<td>74.1</td>
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<td>Serious AEs</td>
<td>2.5</td>
<td>2.5</td>
<td>2.3</td>
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<td>Withdrawal due to AEs</td>
<td>6.8</td>
<td>8.5</td>
<td>8.3</td>
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<td>Most Common AEs</td>
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<tr>
<td>Application Site Reaction</td>
<td>39.1</td>
<td>31.1</td>
<td>28.9</td>
<td>29.7</td>
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<tr>
<td>Upper Respiratory Infection</td>
<td>9.3</td>
<td>9.9</td>
<td>19.9</td>
<td>21.4</td>
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<tr>
<td>Unwanted Hair Growth</td>
<td>6.5</td>
<td>5.7</td>
<td>5.3</td>
<td>9.0</td>
</tr>
</tbody>
</table>

### References
- Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
- P&GP Data on file - ES02-2005
Media and HRT
HRT DANGER FOR WOMEN

'Huge increase' in killer disease risk

MILLIONS of women on hormone replacement therapy are in danger of getting heart disease or breast cancer, a study showed yesterday.

The US research programme revealed such huge increases in risk that it was stopped three years early.

It claimed HRTolfen taken by millions

By JACQUIE THOMAUGHTON, Sun desk
Now experts say hormone therapy can CUT heart attack danger

U-TURN ON THE RISKS OF HRT

MILLIONS of women may have been scared into abandoning HRT unnecessarily. It was revealed yesterday.

A US report which hailed the treatment to heart disease and osteoporosis has been proven to be medically flawed.

A detailed new look at the recent studies revealed that hormone replacement therapy may actually prevent many problems linked to menopause.

Deaths experts told the medical journal of the omenopause. Medical experts now argue that the findings are flawed.

It has been suggested that any extra risks may come from women who are already vulnerable to heart disease and osteoporosis.

The study in the Journal of the Menopause found a 23% increase in risk of death from heart disease for all women taking hormone replacement therapy.

Should hostage Britons be allowed to turn captivity into cash?

Should hostage Britons be allowed to turn captivity into cash?

SEE PAGES 6-7

Turn to Pages 4
New menopause library is UK first

The first ever UK menopause library started at the Trust last month and is available to anybody wishing to find out about all aspects of menopause, from the newest HRT information to complementary and alternative therapies.

It was set up by Ruth Bunham, Volunteer Trust Library and Information Officer for charity the Daisy Network, who operates the library from Gynaecology Outpatients on Thursdays from 10am to 3pm, which is the same time as the hospital menopause clinic.

Trust Consultant Obstetrician and Gynaecologist Mr Nick Dainty is also a patron of the Daisy Network, a national charity to help women who have experienced premature menopause.

He said: "A library facility such as this for menopause patients will help to counteract some of the misinformation which often bombards women on issues such as HRT and natural alternatives."

Claire Bullock, Trust Menopause Nurse Specialist, added: "Patients often do not have a main place to go to find out about their menopause, something which this library aims to address."

Information available on self-help in the library will come from the menopause service at the clinic. The department would like to thank Ruth for her achievement in setting up this much-needed resource centre."

It took Ruth eight months to set up the library. She approached Wethers Pharmaceuticals for funding, who gave £2,500 towards the library.

Bunds were also donated to the library by nutritionist Marilyn Glavich, complementary therapist Maryon Stewart and the British Menopause Association.

For more information on the library at the Daisy Network, please email membership@daisy-network.org.uk.
European Menop Survey Genazzani, Schneider, Panay, Nijland Gyne Endocrinol 2006 Symptom prevalence

- Hot flushes
- Sleeplessness
- Mood swings
- Reduced sex drive
- Headaches/ migraine
- Depression
- Involuntary loss of urine
- Vaginal pain

94% of all women have experienced one or more menopausal symptoms
ONLY 6% haven’t experienced any symptoms at all
64% of women have experienced one or more severe menopausal symptoms

Question: Are you currently experiencing or have you experienced any of the following symptoms in the past 5 years? Can you state them as mild or severe?
84% of women agree that menopause needs to be treated. Do women suffer in silence?

Only 22% of women used an appropriate treatment for menopause related symptoms.

Question: Severe menopausal symptoms need to be treated instead of accepting them just as they are. Do you agree or disagree?
HRT: Hot off the Press
Revised BMS Consensus Statement
June 2006

- HRT is still recommended as 1st line treatment for osteoporosis in premature menopause and in the younger post-menopausal woman (50-60)

- www.the-bms.org
Putting risks into perspective
Risk for post-menopausal women (mean age 63) developing breast cancer over a five year period (15 out of 1000)

Risk to general population

Additional risk for comb HRT users: 4 out of 1000

*CEE alone – no risk

Data adapted from JAMA 2002; 288: 321-333
Take home messages
Take Home Messages

- Periods can become irregular for a number of reasons
  
- The commonest reason is hormonal imbalances in 30s and 40s
  
- The pill can restore the regularity of periods but not fertility
Take Home Messages

- Women are born with a finite number of oocytes, the loss of which can be accelerated in certain situations.

- Prediction of this loss is not always accurate so women are asked to take steps before the age of 35 (if possible) if they wish to start a family - younger if there is a family history of POF.
Take Home Messages

- Women with premature menopause should use HRT at least until the average age of the menopause

- Despite the recent media scares HRT appears to be safe in younger age group women (50-60y)

- Older age group women should use much lower doses / consider alternatives
Take Home Messages

- The fluctuations in hormone levels which occur premenstrually, postnatally and perimenopausally can lead to mood disturbances

- These disturbances respond to cycle stabilising doses of hormones such as the pill and oestrogen patches
“Longevity has no meaning without Quality of Life”
National Association for Premenstrual Syndrome - A Registered Charity

- Help-line
- Quarterly newsletter
- Annual scientific meetings
- Policy planning for PMS
- Liaison with media
- Interactive PMS diary (Femal)
- www.pms.org.uk
The Daisy Network
Premature Menopause Support Group

PO Box 183
Rossendale
BB4 6WZ

www.daisynetwork.org.uk
membership&media@daisynetwork.org.uk

In the Spring 2007 issue of The Menopause Exchange newsletter, Mr Nick Panay and Mr Emmanuel Kalu, both from the Chelsea and Westminster Hospital in London, discuss the causes, symptoms and management of premature menopause.

“A premature menopause can turn a woman’s life upside down, whether it is brought on by surgery or it occurs naturally,” says Norma Goldman, director of The Menopause Exchange.

The Menopause Exchange at PO Box 205, Bushey, Herts WD23 1ZS, call 020 8420 7245, fax 020 8954 2783 or send an e-mail to norma@menopause-exchange.co.uk
On Monday's show, Anna spoke to renowned obstetrician Nicholas Panay, from the world-famous Queen Charlotte's hospital. She also asked - what do you like about being a man or a woman, and what does the other half have which you envy?
Premenstrual Syndrome : Can a change in diet transform a woman's mood?

Three months on did the “Double D diet” have a positive improvement on the women’s lives?

According to our specialist, Nick Panay, the women on the high calcium and vitamin D diet had a one-third improvement over the placebo group.

The study was conducted by Nick Panay, consultant gynaecologist, and our dietician was Nigel Denby, senior dietician at Queen Charlotte’s & Chelsea Hospital, London.
"IS IT MY HORMONES OR IS IT ME?"

Presented by Mr. Nick Panay
Consultant Gynaecologist, Queen Charlotte's & Chelsea Hospital, Director of the West London Menopause & PMS Centre, Lecturer at Imperial College Faculty of Medicine. (Tuesday 10th July 2007 in Edgware)

Another chance to hear Mr Panay speak about understanding how your hormones affect you at various stages, including pregnancy, post-pregnancy, pre-menopause and early menopause, as well as living with PMS

For more information about this event, please call 020 8201 7101
Recommended Websites

- www.daisynetwork.org.uk
- www.the-bms.org
- www.mhra.gov.uk
- www.menopausematters.co.uk
- www.pms.org.uk
- www.nos.org.uk
- www.menopause.org
- www.imsociety.org
- www.womenshealthconcern.org.uk
- www.chana.org.uk