

# *The Dangers of Progesterone Contraception*

*Adverse effects on women and families*

- **Oral contraceptives** Progestogen +/- oestrogen
- **Implants** Progestogen
- **Intra Uterine Systems** IUD + Progestogen
- (Intra Uterine Device - PID, ectopic pregnancy)
- **HRT – post Pill amenorrhoea**

# **Progesterone Contraception**

***Endogenous   Exogenous  
Synthetic or Natural   Bio-identical***

***Progestins, Progestogens or  
Progestagens***

**All “Act” like Progesterone (P)**

***Attach to same “receptors”***

# Progesterone Actions ?

*Progesterones attach to*



Complex Activates 1000s of Genes

*Up or Down Regulate*

# ***Progestogens used***

	<i>Androgenic</i>	<i>Pregnanes</i>
	<i>Estranes</i>	<i>Gonanes</i>
OCs	10	13 <i>MPA - depot</i>
HRT	13	5 <i>MPA in USA</i>

***MedroxyProgesterone Acetate and Megestrol Acetate (banned UK 1970s)***

***Breast cancer small or large doses***

# *Progestogen Potency*

<b>ANDROGENIC</b>		<b>PROGESTOGENIC</b>	
<i>Estrane</i>		<i>Gonane</i>	<i>Pregnane</i>
<b>Norethisterone 1 N Acetate</b>	<b>1.2</b>	<b><i>dl-Norgestrel</i></b>	<b>2.6</b>
			<b><u>MPA</u></b> 0.3 <b>MA</b> 0.4

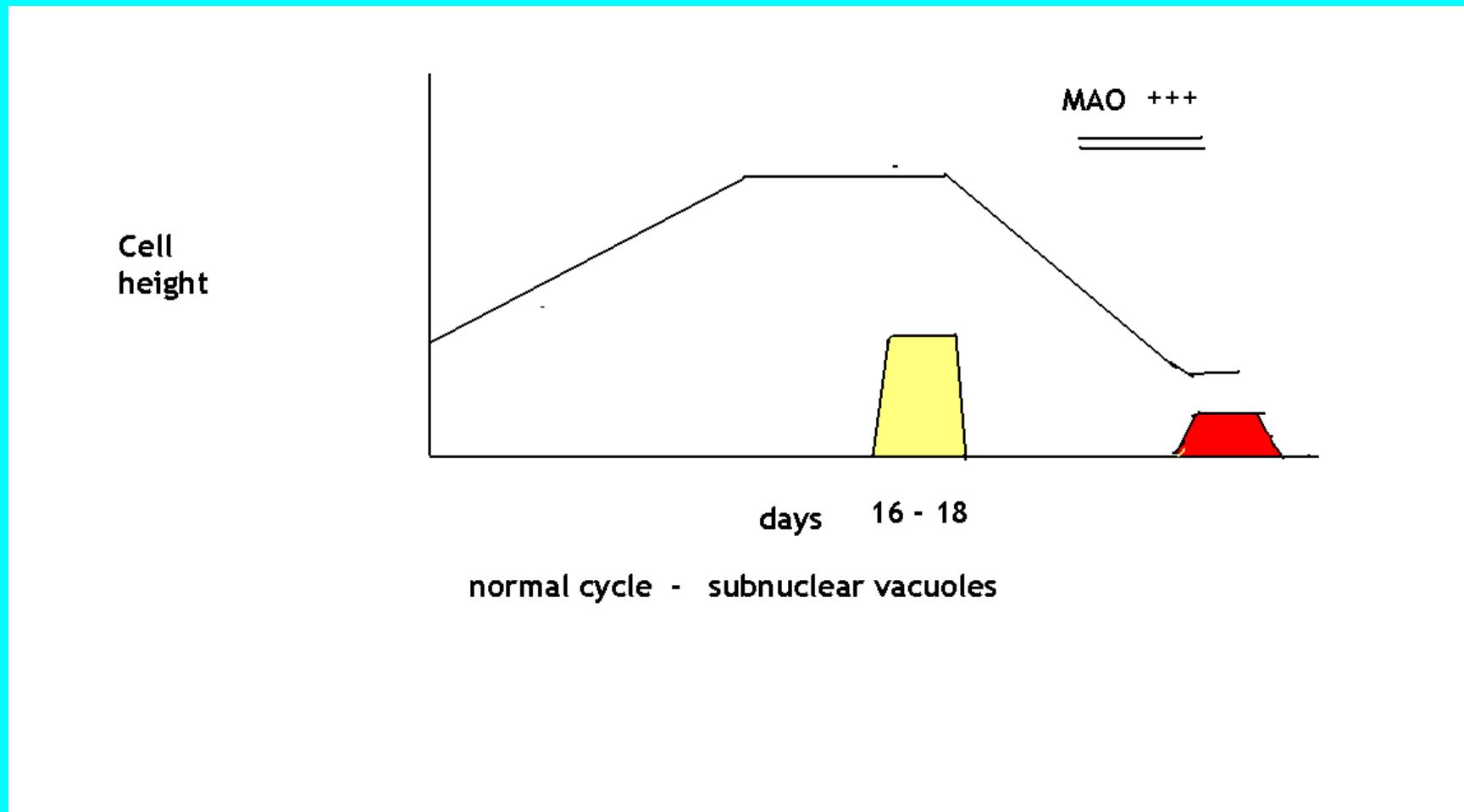
Micronised x 2 potency -

*Oral Progesterone*

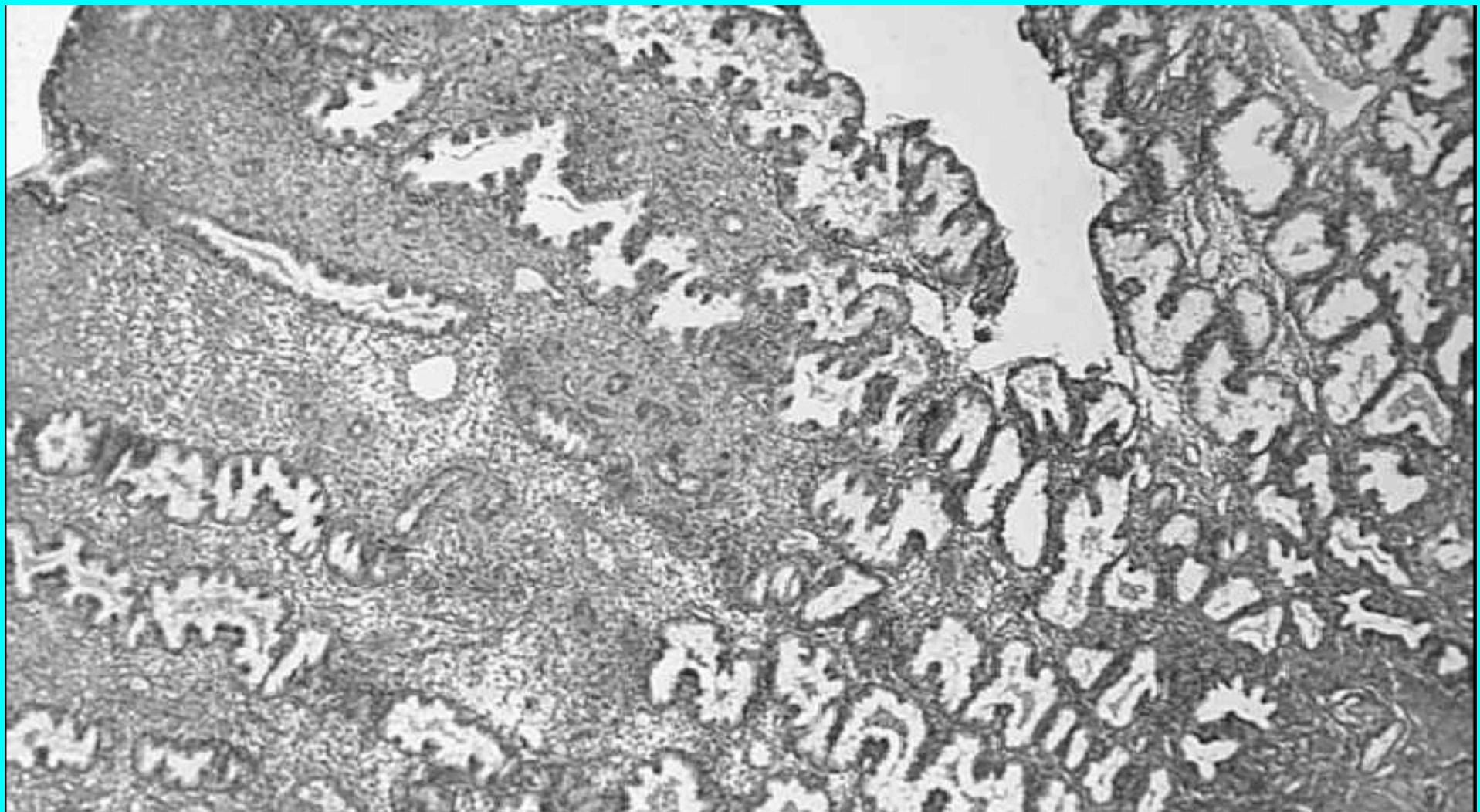
<u><i>Levonorgestrel</i></u>	5.3
<i>Norgestimate</i>	1.3
<i>Desogestrel</i>	9
<i>Gestodene</i>	12.6

# ***Normal endometrial cycle***

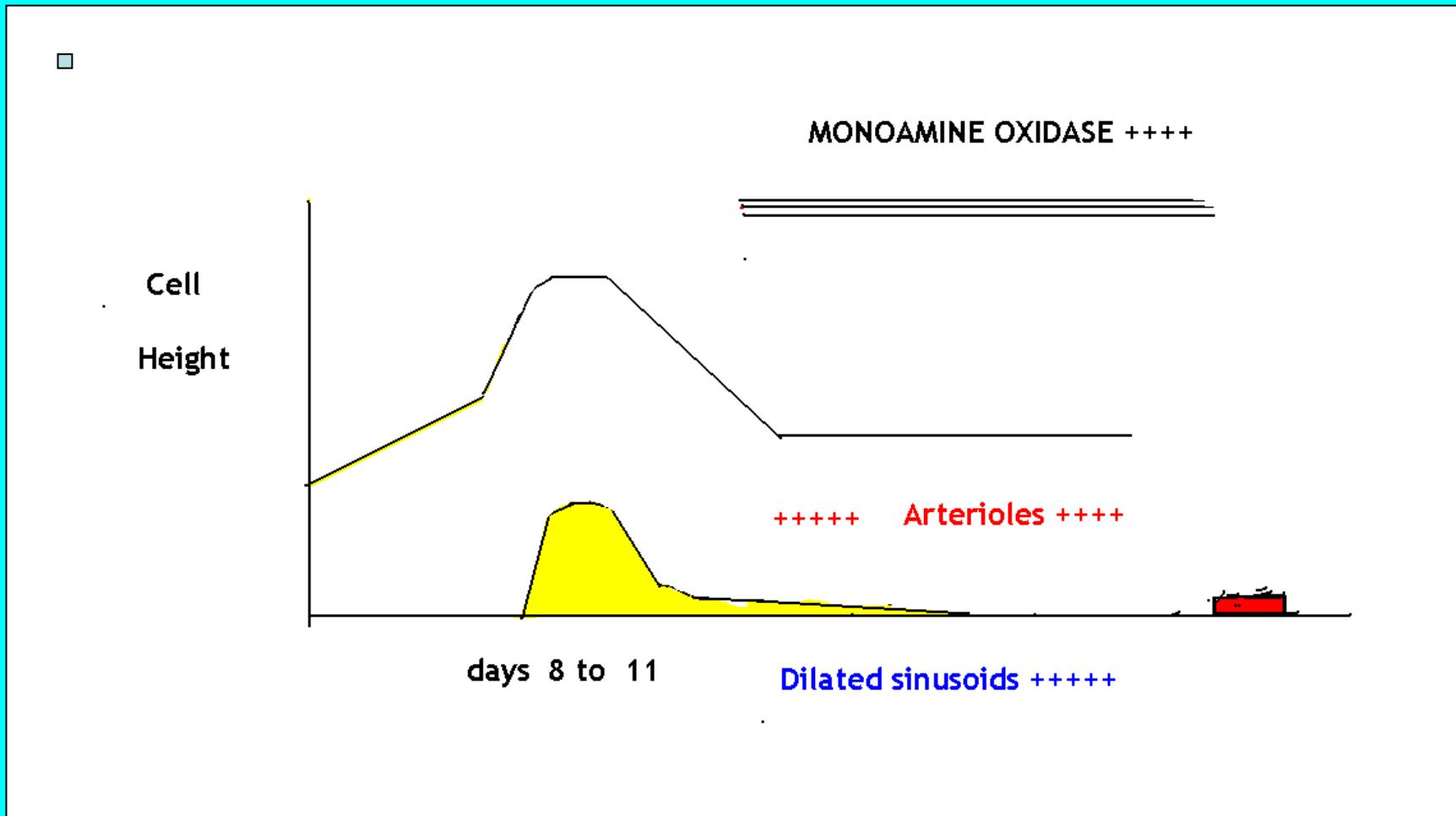
*2 days subnuclear vacuoles mid cycle*



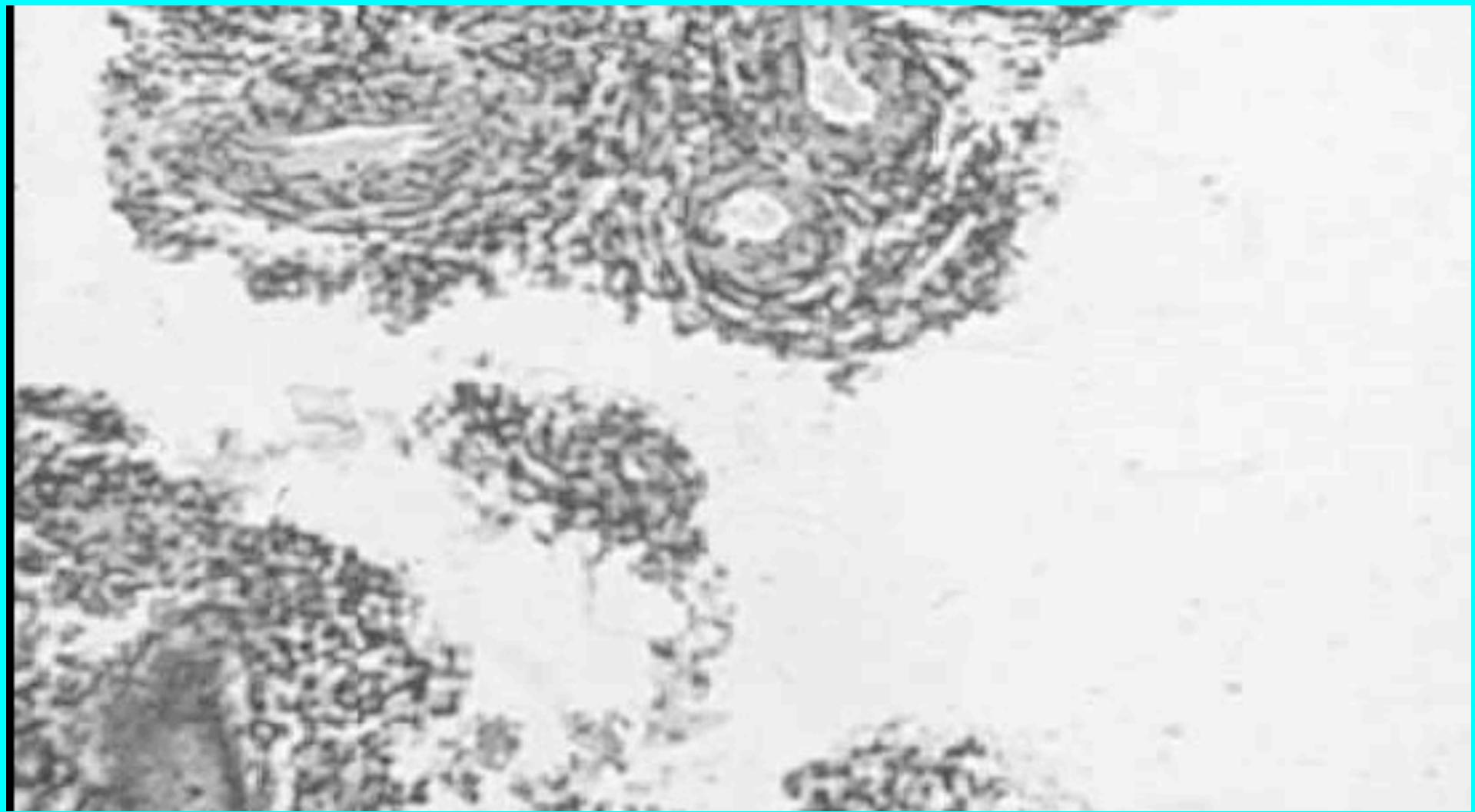
# *Normal Late Secretory*



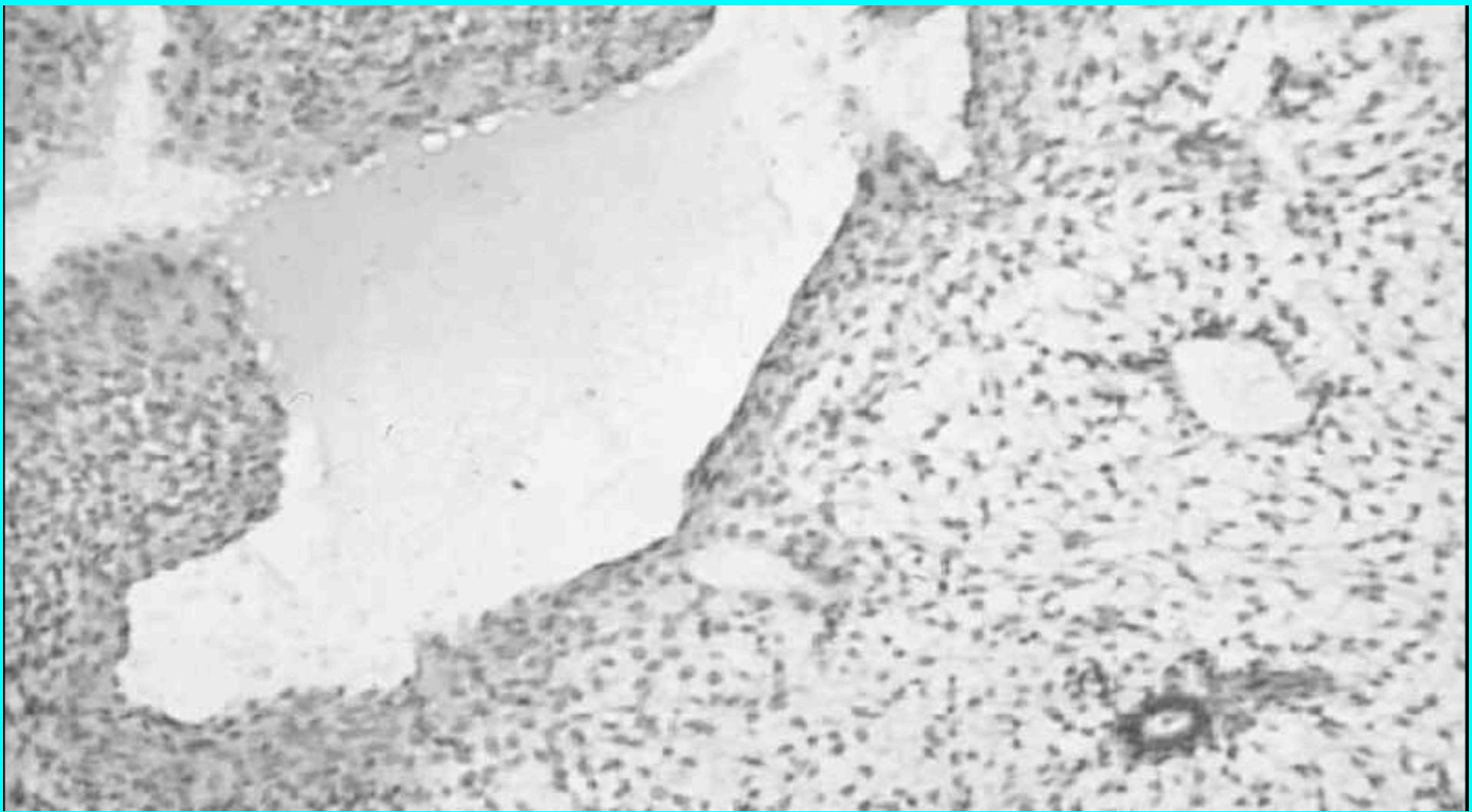
# *Progestogenic endometrium*



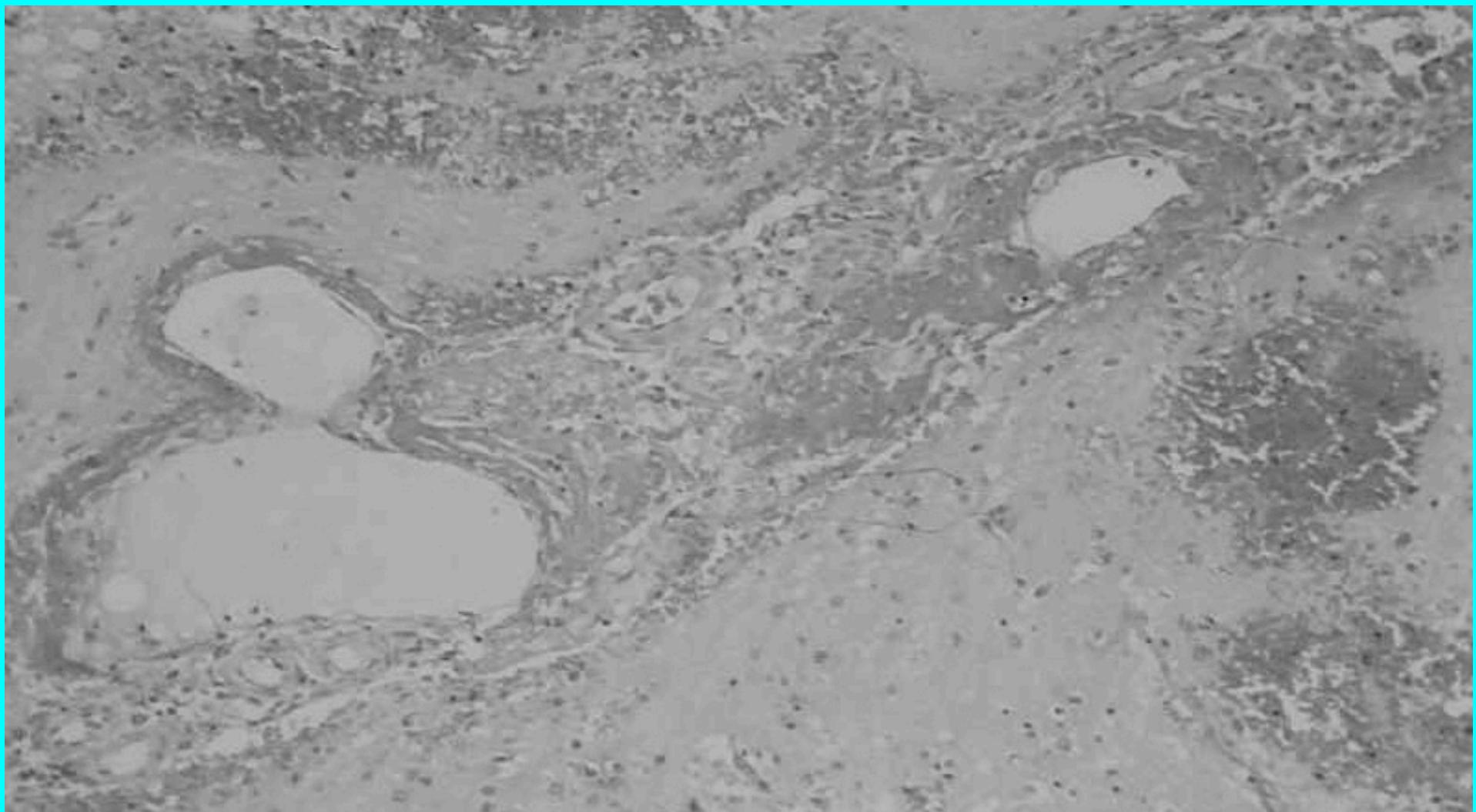
*Progesterogenic ++ arterioles ++*



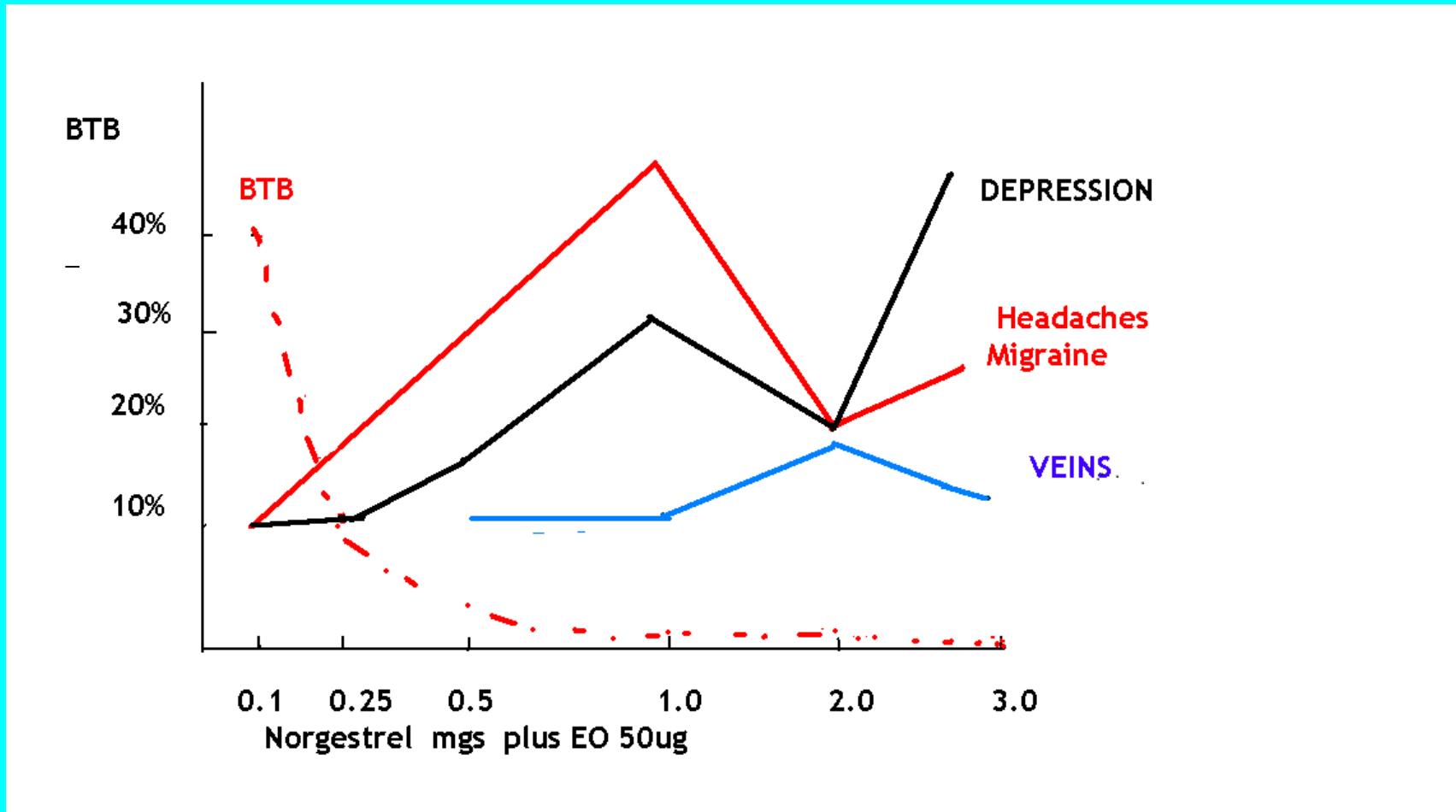
# *Dilated sinusoid - thrombosis*



*Thrombosed cerebral vessels*  
– 5 yrs OC

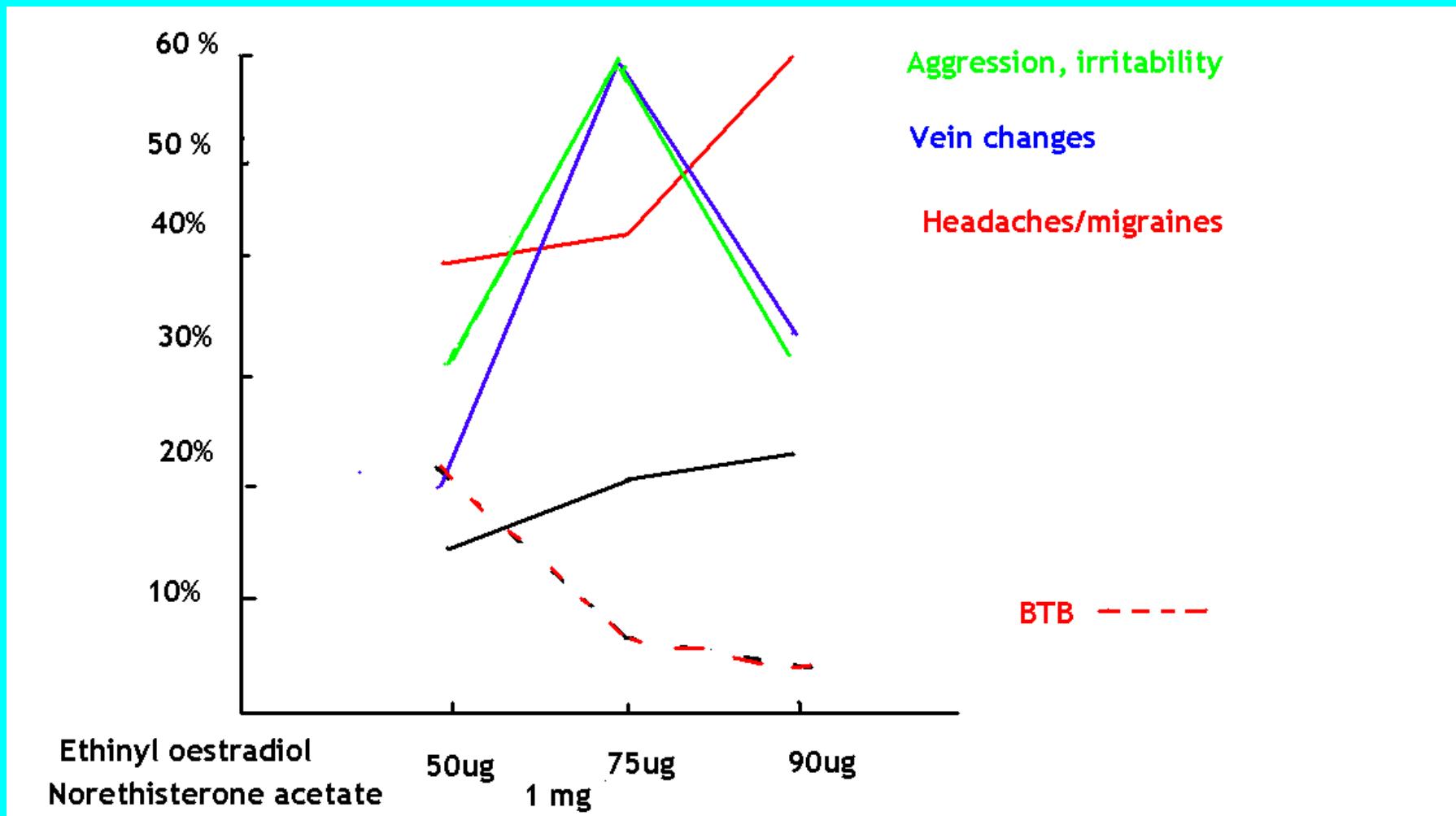


# *Norgestrel Dose Effects*



Grant ECG BJOG 1965 BMJ 1968, 1969, +Pryse-Davies J BMJ 1968

# $\uparrow\uparrow$ Aggression $\uparrow$ Vascular

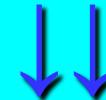


# *Actions of Progesterone*

↑ oestrogen priming

Early Sec Ph **Subnuclear vacuoles**

Alkaline phosphatase



Acid phosphatase, SOD, COMT



Late S Ph Monoamine oxidase Depression ↑↑

**Immediate Angiogenesis** ↑↑

**VEGF and TF - Br Ca metastasis**

# Enzymes altered by Progesterone

- ↑ Oxygen metabolism
- MAO Monoamine oxidase depression ↑
- COMT Catechol-O-methyltransferase pain ↑
- Alkaline Phosphatase ↓ osteoporosis
- SOD Superoxide dismutase Zn Cu Mn ↓
- GPx Glutathione peroxidase Se ↓
- oxidative and antioxidative capacity modulated by sexual steroid hormones mediated through antioxidant metabolizing enzymes

# *Actions of Progesterone*

*Blocks FSH and LH - prevents ovulation*

*Switches immune balance T1 → T2*

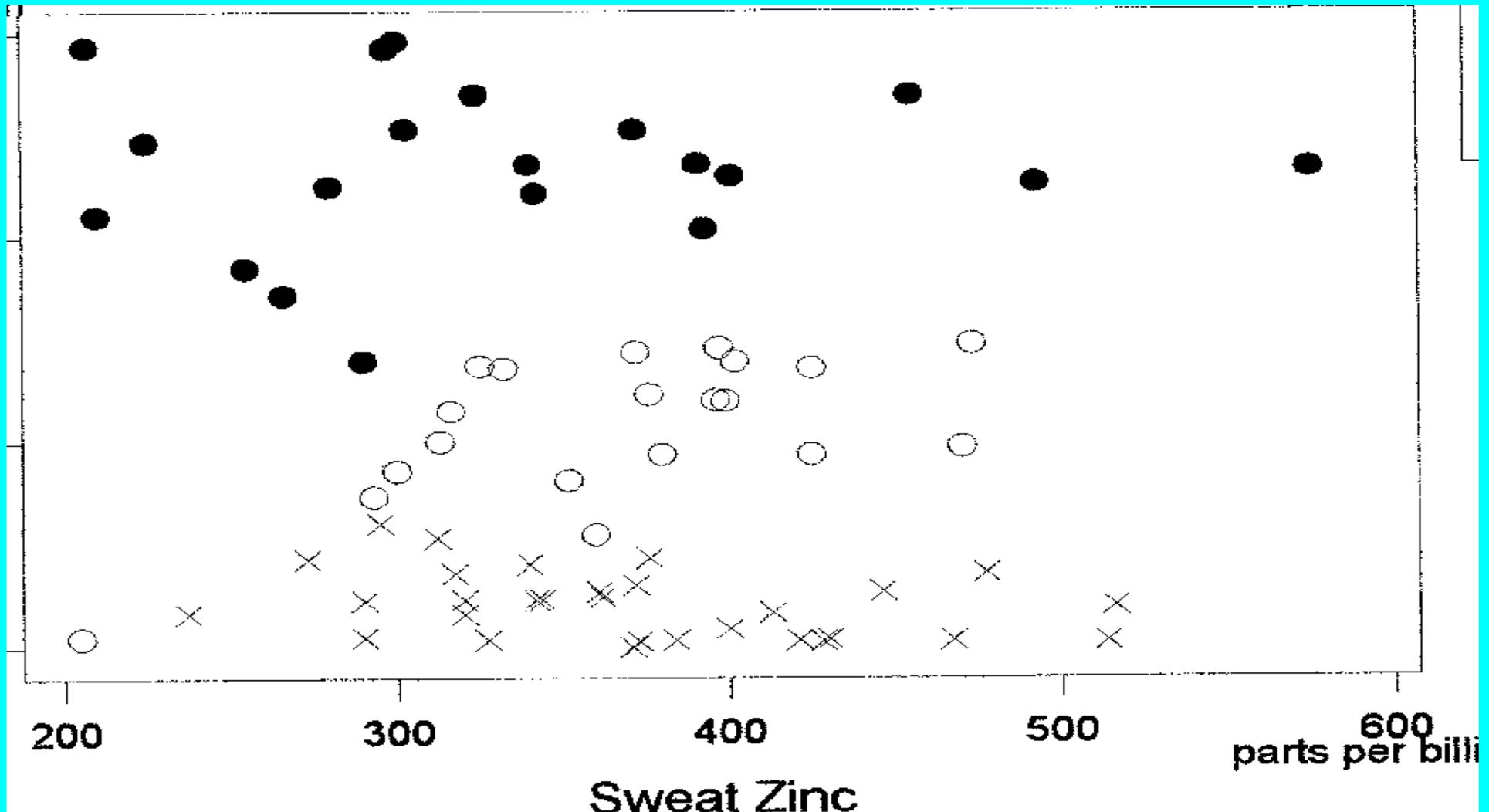
*Antibody production*                    ↓↓

*Symptoms – increased - decreased*

*Immune diseases - MS, SLE x10*

↑↑ Cu/Zn ratios in sweat (& serum and hair)

Men X Women Past Users O Current Users ●



# **RCGP OC STUDY 1974**

**NOT “ALL CLEAR”**

**Over 60 conditions**

**“significantly increased”**  
**in *takers* / non takers**

**(immune diseases, infections and allergies)**

**SERIOUS IMMUNE  
DYSFUNCTION**

# **RCGP OC Study Vascular**



1974	<b>DVT/HROMBOSIS /PE</b>	<b>5.66</b>	
	Heart disease	5.2	
	Cerebrovascular	4.1	<b>Deaths</b>
1981	<b>Vascular</b>		<b>4.2</b>
	non smoker	1.6 - 4.6	
	smoker	3.4 - 7.4	
1983	AMI +Toxaemia history	41.0	
1999	<b>Cerebrovascular +10 years</b>		<b>2.7</b>

# *RCGP OC Study Depression*



	Takers	Ex-takers
1968 – 1972		
Depressive neurosis	1.3	1.28
Hospital admissions		3.61
<b>Suicide commonest death</b>		
1984 Attempted suicide	1.42	2.12
2010 <b>Death &lt; age 30</b>	<b>3.0 ever takers</b>	
<b>Violent deaths</b>	<b>1.28</b>	

# **RCGP OC Study Cancers**



Breast cancer	age 25-29	2.53
Breast cancer	age 30-34	3.33
Breast cancer	taking for 10 yrs +	10.17
Breast cancer	8-9 years after stopping	15.8
<b>Breast cancer deaths</b>	<b>154</b> 5- 9 yrs later	<b>1.5</b>
<b>Lung cancer deaths</b>	<b>75</b> 1.3 + 10 yrs	<b>1.6</b>
<b>Liver cancer deaths</b>	<b>5</b>	<b>5.0</b>



# RCGP OC Study

<b>Cervical cancer</b>	$\times 2-3$	<b>Deaths &gt; 10yrs</b>	<b>5.3</b>
<b>Pruritis, vaginitis</b>			<b>2</b>
<b>Trichomonas, leukorrhoea, cervicitis</b>			<b>1.6</b>
<b>Ex OC</b>	<b>Irregular bleeding</b>		<b>1.55</b>
<b>Fibroids</b>			<b>2.5</b>
<b>Post Pill amenorrhoea - infertility</b>			<b>3.2</b>
<b>Abortions</b>		<b>13.3% → 30.61%</b>	
<b>*Congenital abnormalities</b>		<b>0.4% → 3.8%</b>	

Oxford/FPA contraception study 1976 never / nulliparous ever users

The Royal College of General Practitioners. Oral Contraception and Health: An Interim Report. London: Pitman Medical 1974

\*Vessey et al. Long-term follow-up study of women using different methods of contraception--an interim report. *J Biosoc Sci.* 1976 Oct;8(4):373–427.

# **“Walnut Creek” Contraceptive Drug Study**

**Cervical cancer** **x12**

**Ovarian retention cysts**

**Severe acute iron deficiency anaemia**

**Fibroids (vascular)**

**Adenomyosis (endometriosis)**

**Hysterectomies < age 40 6.3% x2.5**

**All Significantly Increased Reasons for HRT**

# Breast cancer ↑↑ with P +/- E use

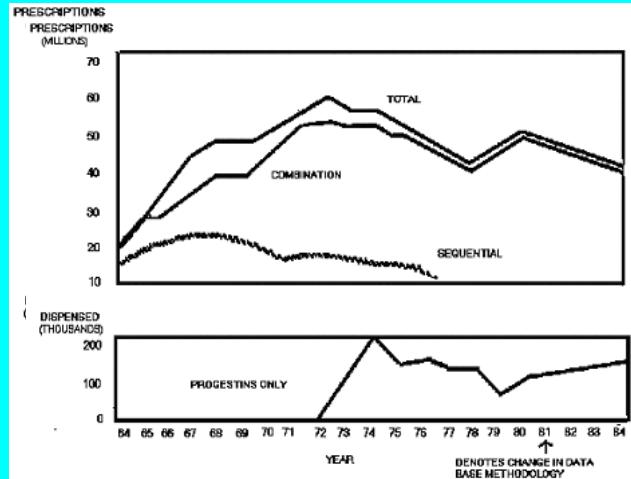


Fig 1.a. OC use in USA, 1964-84. [8]

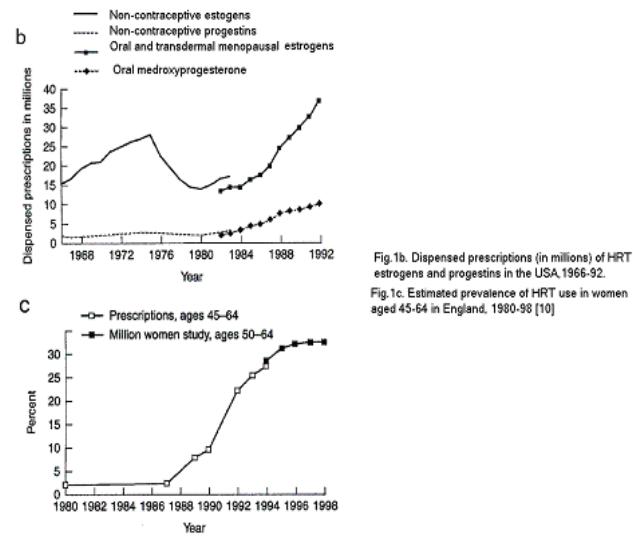
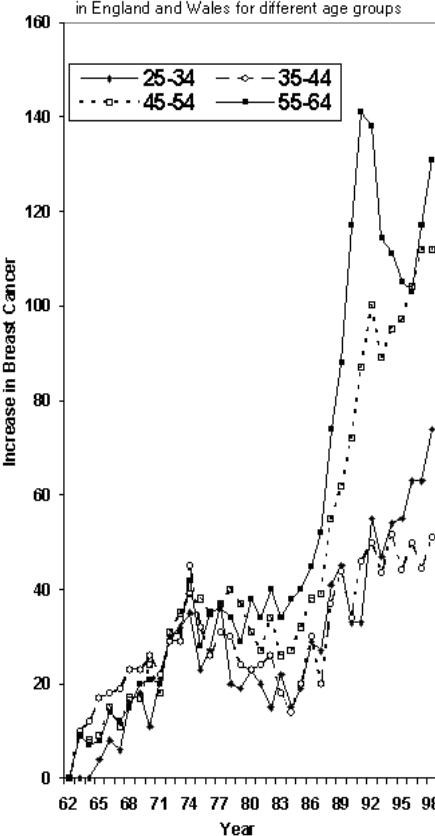


Fig.1b. Dispensed prescriptions (in millions) of HRT estrogens and progestins in the USA, 1966-92.  
Fig.1c. Estimated prevalence of HRT use in women aged 45-64 in England, 1980-98 [10]

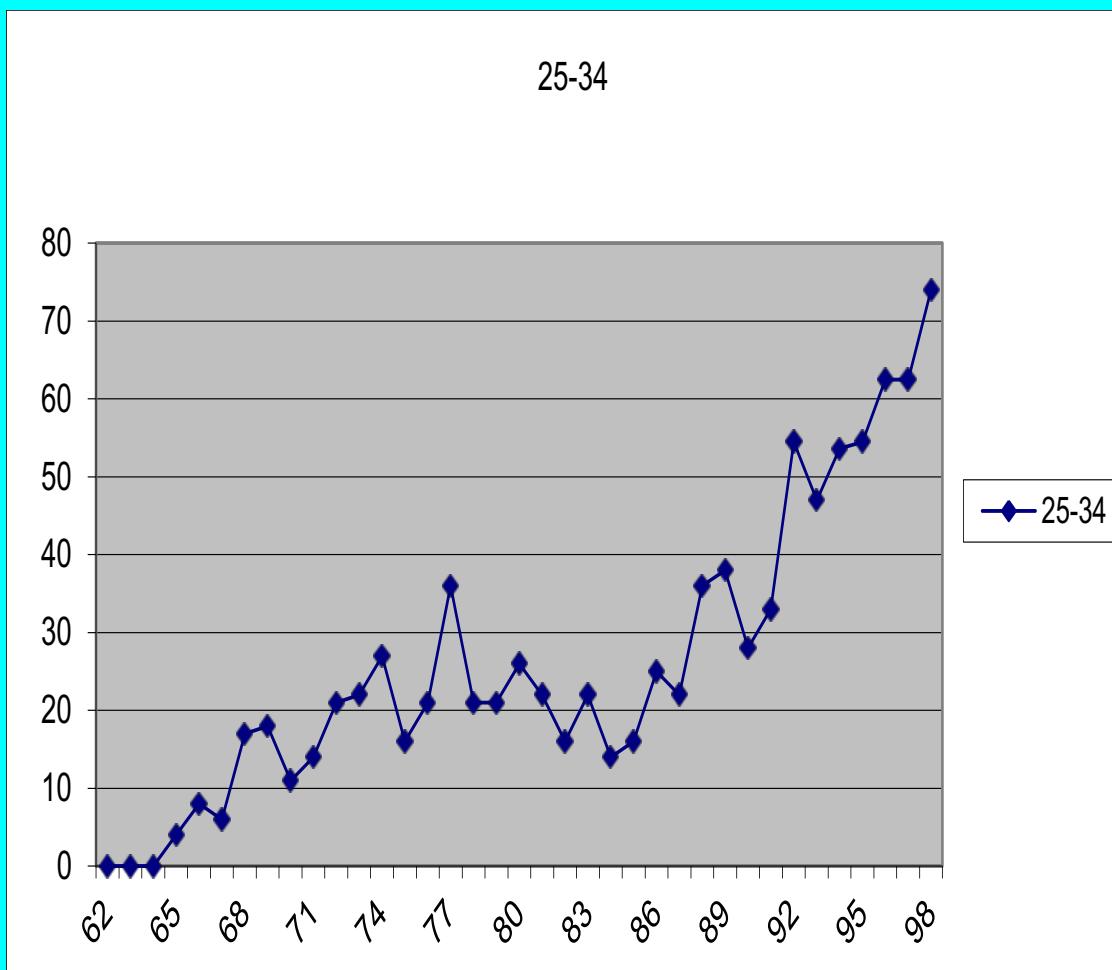
Figure 2. Percentage increases from 1962 in annual breast cancer registration rates in England and Wales for different age groups



Piper JM Int J Epidemiol 1987. Hemminki E, Topo P. J Psychosom Obstet Gynaecol 1997;18:145-157. . Beral V J Epid Biostat 1999; 4: 91-115. Grant ECG BMJ 2007

Figure: Percentage increases from 1962- 1998 in annual breast cancer registration rates in England and Wales with increased hormone use

## Age group 25 -34



Grant ECG BMJ 2007

Collated from epidemiological data NOS England and Wales data

# Longer use of OCs before FFTP

1989 UK study

*Breast cancer by age 36*  
*% taking OCs  $\geq$  4 years*

Starting age	Br Ca	No Br Ca
Up to 18	80	71
19-21	71	61
22-24	57	48
25+	50	30

# Contraceptive Breast Cancer Risks

**OESTROGEN + PROGESTOGEN**

Combined OCs (1.6 - 7.8) 2 - 5

*By age 50 - Ever use ≥ 4yrs before FFTP* 1.52

*Kahlenborn, 2006*

Combined OCs + *Ethinyl oestradiol* 35 mcg 2  
   >35 mcg 4

**PROGESTOGEN only** 1.6 - 6  
(UK study, P mostly lactation 1 – 12 months)

*51 studies, Million Women Study, Women's Health Initiative*

<i>xs Breast Ca</i>	<i>5 yr</i>	<i>10 yr</i>	<i>Study</i>
<i>Oestrogen HRT</i>	2	6	<i>Collab</i>
	1.5	5	<i>MWS</i>
<i>P plus O HRT</i>	6	19	<i>MWS</i>
	6	18	<i>WHI</i>

*Beral Lancet 2003*

HRT Studies      **2 – 8** (1.09 – 19)

# *Contraceptive and Menopausal Progestogens and Oestrogens*

*W H O International Agency for Research in  
Cancer (IARC monograph, 2005)*

**“Group 1 Carcinogen”**

**Highest level (dioxin, mycotoxins)**

**Direct Genotoxins**

# *Progesterone carcinogenesis*

*A Preventable Epidemic ?*

WHI, MWS and WISDOM HRT trials  
terminated early

*but very young OC use  
off prescription very high doses ECs  
depot MPA still vigorously promoted*

Rossouw JE JAMA 2002 Jul 17;288(3):321-33.  
Vickers M, Climacteric 2002 Climacteric. 2002 Dec;5(4):317-25.

# **Progesterone carcinogenesis**

Why does **Progesterone** cause – **3-4 x more breast cancers** than **Oestrogen?**

**4 x more genes up or down regulated**

**All tissues Carcinogenic Metabolites**  
**+ or - Progesterone Receptors**

**Angiogenesis ↑↑ Immune diseases ↑↑ (x9)**

# ***Genetics and Epigenetics***

***Epigenetics – changes in gene function***

***12,686 genes implantation window*** Kao 2002

***Progesterone 4 x genes cf Oestrogen***

Kao. 2002 Jun;143(6):2119-38

# *Progesterone –activated genes*

*377 up regulated*

*156 down regulated*

***Striking Regulation of Secretory Proteins***

***Water and Ion Channels***

***Signalling Molecules***

***Immune Modulators***

***Endometrial Development***

***Embryonic Interactions.***

Kao. 2002 Jun;143(6):2119-38

# *Endocrine-disrupting chemicals*

*Over 70 years of animal research*

**Hormones organise the brain**

**Peri-natally - critical timing**

*Modify sexuality, perception and learning*

**Endogenous - twins - risk taking – aggression**

**Aromatase inhibitors , pesticides, fungicides**

# **Genotoxic damage**

**Progestins** - acting like xs Progesterone

Animals - Chromosomal aberrations Sister chromatid exchanges  
Vitamin C prevents

In vitro - Free oxygen radicals Siddique 2005

In women - *Mitochondrial dysfunction* Ni/Lindane TL gene  
ATP →ADP blocks x2 McLaren-Howard 2006

ASD *Mitochondrial dysfunction* Giulivi 2010

mDNA over-replication & deletions

# **P down regulated genes**

- ***Intestinal Trefoil Factor (ITF) - 50-fold***
- matrilysin, members of the G protein-coupled receptor signaling pathway, frizzled-related protein (FrpHE, a Wnt antagonist)
- ***Transcription Factors, TGF-beta signaling pathway members***
- ***Immune Modulators (major histocompatibility complex class II subunits) and other cellular functions***

# *P up regulated genes*

Numerous *Immune Modulators*

*Detoxification genes*

*Metallothioneins*

*Genes involved in water and ion transport - K(+) ion channel*

*Genes corresponding to IGFBP-1, glycodelin, CPE1-R, Dkk-1, gammaglobin, and ApoD.*

# *P upregulated genes*

- *cholesterol trafficking and transport*
- *apolipoprotein E 100-fold*
- *prostaglandin (PG) biosynthesis (PLA2) and action (PGE2 receptor)*
- *proteoglycan synthesis (glucuronyltransferase), secretory proteins (glycodelin, gammaglobin, Dickkopf-1 - a Wnt inhibitor), IGF binding protein and TGF-beta superfamilies, signal transduction, extracellular matrix components (osteopontin, laminin)*
- *neurotransmitter synthesis -MAO, receptors*

# *Fertility and pregnancy hormonal “treatments”*

**de novo Y-chromosome microdeletion** 10.8% vs 0  
Feng 2008 boys ICSI or IVF (+ hypospadias)

**Genital organ malformations** 2.32

Zhu JL, BMJ, 2006 Danish national birth cohort.

**HYPOSPADIAS Progesterone /progestogens**

**4 weeks before to 14 weeks after conception** 3.7

Carmichael 2005

**BUPA** 5.0

Feng et al. Fertility and Sterility 2008; 90;1; 92-96. Zhu. BMJ. 2006 Sep 30;333(7570):679.  
Carmichael et al. Arch.Pediatr Adolesc Med. 2005 Oct;159(10):957-62.

# *Progesterone & development*

*Most pregnancy Progesterone use now*

↑ *Cancers in children, DES breast, vaginal*

**Testicular Leukaemia Neuroblastomas**

*Brain Development* ↓ *Stress coping*

↑ *Mental illness*                      ↑ *Autism x4*

*Sexual Orientation - Organ Abnormalities*

**Immune Dysfunction** ↑ *Allergies*

McLaren-Howard

## WBC DNA adducts

Women

OCs/HRT

Never hormones?

356

182

Nickel

12.5%

7.1%

Lindane -estrogen

8.7%

5%

27 Patients

Cancer

Controls

Age & Sex matched

Malondialdehyde

18.5%

3.7%

Nickel

18.5%

0%

# Why Autism increases 1987- 98?

Matching increases in Progesterone use  
Genotoxic Cancer Developmental disorders

Current and Longer use

*Before a First Full Term Pregnancy*

*In Pregnancy* - fertility treatments

miscarriage prevention premature labour

↑ Breast Cervix Ovary Lung Cancers

Beral Lancet 2007 May 19;369(9574):1703-10., Dooren BMC Womens Health. 2007; 7: 19. Tsilidis Br J Cancer. 2011 Oct 25;105(9):1436-42.

McLaren-Howard 2004 BMJ -

**61 autistic children**

**Deficiencies - Zn, Mg, Cr, Se, Mn, Cu, Mb, B vits & EFAs**

**WBC DNA adducts**

16	<b>Malondialdehyde (from lipid peroxidation)</b>	<b>26%</b>
12	<b>Cadmium</b>	<b>20%</b>
9	<b>Nickel</b>	<b>15%</b>
3	<b>Mercury</b>	<b>5%</b>
1	<b>Lead</b>	<b>1.6%</b>

# *The AUTISM Epidemic & the Pill*

- ↑ Genotoxic PROGESTERONE contraceptives
  - ↑ Maternal / ASD mitochondrial dysfunctions
  - ↑ Maternal /ASD DNA toxic adducts
  - ↑ Maternal /ASD Depression and antidepressants
- Brain function damage toxins ↑ Zn ↓ EFAs ↓
- Replete deficiencies and remove toxins
- Non-hormonal contraception

# **“Safe” Contraception**

**Fool proof pregnancy prevention**

***Typical*** Use



***“Perfect” use***

Disregard of ***adverse health effects***

# Newer Hormonal Contraceptives

Bateson BMJ 2013

Pregnancies / yr with		Typical use	Perfect use	
Implanon or Nexplanon etonogestrel implant		<u>0.05</u>	0.05	Depr↑
Intra Uterine System <u>levonorgestrel</u> IUD		<u>0.2</u>	0.2	D↑
Depo Provera <u>medroxyprogesterone acetate</u>		6	0.2	D↑
Evra norelgestromin and ethynodiol diol patch		9	0.3	D↑
Nuva etonogestrel and ethynodiol diol ring		9	0.3	
Ocs/POPs oral contraceptives /progestogen only pills		9	0.3	
NFP natural family planning		24	0.04 - 5	

# Other Contraceptive Methods /year

<u>Pregnancy “risk”/year</u>	<u>Typical</u>	<u>“Perfect”</u>
Vasectomy	<u>0.15</u>	<u>0.1</u>
Female sterilization	0.5	0.5
Copper IUD	0.8	0.6
Male condom	18	2
Diaphragm	12	6
Withdrawal	22	4
Nat Fam Plan	24	0.04 - 5
None	85	85

# Latest increases

- Irregular bleeding    Weight gain
- Depression      Autism
- Breast and Cervical cancers
- HPV                          HIV transmission X2
- Thrombosis    IVF    Migraine    Strokes
- Autoimmune diseases ME, MS, SLE, APS
- Grant ECG Lancet 2001
- Miscarriages and mortality Jurkovic D BMJ 2013



In younger women

**USA** 78-09 (IV) metastatic **Br Ca**

Johnson RH JAMA 2013

Age 25-39 5-yr survival 31% 10-yr ↓20%

78%↑

**England** 92-06 age 20-29 **Ca Cx**

Foley G Br J Ca 2011

2.16↑

**Africa** **DMPA** HIV transmission

Heffron R Lancet Infect Diseases 2012

2 ↑

**Sweden** MWS **POP** Antidepressants (age16-19)

Wiréhn AB Eur J Contracept Reprod Health Care 2010

↑

**World** 1 in 10,000 - 1 in 88 **Autism** **P use** antidepressants ↑ ↑ ↑

Rai D BMJ 2013 Grant BMJ 2013

↑ ↑ ↑

# **Dr Ellen Grant on line**

[www.harmfromhormones.co.uk](http://www.harmfromhormones.co.uk)

[www.bmjjournals.com](http://www.bmjjournals.com) Search – Ellen CG Grant  
Articles and Rapid Responses

NCBI [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov/pubmed) - grant ec [AU]

[www.tandf.co.uk/journals](http://www.tandf.co.uk/journals)

**J Nutr Environ Med June 1998**