PRE-CONGRESS COURSE 3

SIG Endocrinology
"Gender specific medicine: redefining reproductive endocrinology"

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PRE-CONGRESS COURSE 3 - PROGRAMME

SIG Endocrinology

Gender specific medicine: Redefining reproductive endocrinology

Course co-ordinators: N.S. Macklon (NL), B. Tarlatzis (GR), B.Fauser (NL)

Course description: The development of Gender Specific Medicine, which recognizes the effect of the female and male endocrine environment on general as well as reproductive health, requires us to reassess the scope of our speciality and the role of the contemporary Reproductive Endocrinologist. In order to meet the lifelong health needs of patients, the modern specialist must have a broader perspective on how reproductive function can impact on well-being at different stages of life. In this course, new clinical developments in Reproductive Endocrinology are reviewed from the perspective of Gender Specific Medicine. New insights are provided, aimed at optimizing the management of patients in the three phases of reproductive health and well-being; adolescence, adulthood and old-age.

Target audience: Reproductive endocrinologists, gynaecologists and other physicians caring for women.

Programme

Session 1: Gender and development / Session Chairman: *N. Macklon (NL)*

Welcome and Introduction: ***N. Macklon (NL)***

09.00- 09.30: Women's health - ***B. Fauser (NL)***
09.30- 09.45: Discussion

09.45 - 10.15: The health needs of adolescents - ***A. Balen (UK)***
10.15 - 10.30: Discussion

10.30 - 11.00: Coffee break

Session 2: New Horizons in Reproductive Health / Session Chairman: *A. Balen (UK)*

11.00 - 11.30: Contraception: determinant of health and disease - ***A. Glasier (UK)***
11.30 - 11.45: Discussion

11.45 - 12.15: Towards freedom from menstrual bleeding disorders - ***H. Critchley (UK)***
12.15 - 12.30: Discussion

12.30 - 13.30: Lunch

Session 3: Gender Specific Determinants of Health in the Adult / Session Chairman: *B. Fauser (NL)*

13.30 - 14.00: Periconceptional determinants of health – ***N. Macklon (NL)***
14.00 - 14.15: Discussion

14.15 - 14.45: Hormonal determinants of female sexual health -***R. van Lunsen (NL)***
14.45 - 15.00: Discussion

15.00 - 15.30: Coffee break

Session 4: Gender Specific Aspects of Ageing / Chairman: *B. Tarlatzis (GR)*

15.30 - 16.05: Estrogen, cognition and the ageing brain -***A. Genazzani (I)***
16.05 - 16.15: Discussion

16.15 - 16.50: Reproductive functions in the ageing male -***E. Nieschlag (D)***
16.50 - 17.00: Discussion

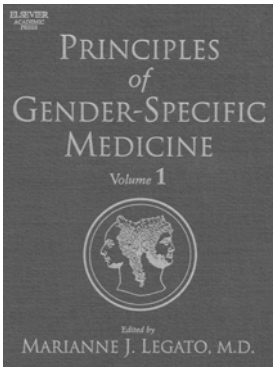
Conclusions - ***B. Fauser (NL)***

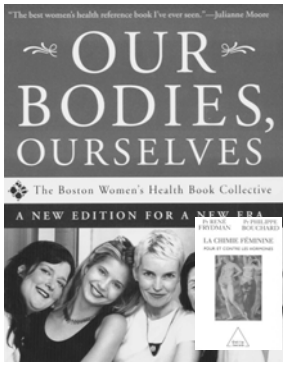
Women´s Health

Prof. Bart CJM Fauser, MD, PhD

Dept. Reprod Medicine & Gynecology
University Medical Center, Utrecht, The Netherlands

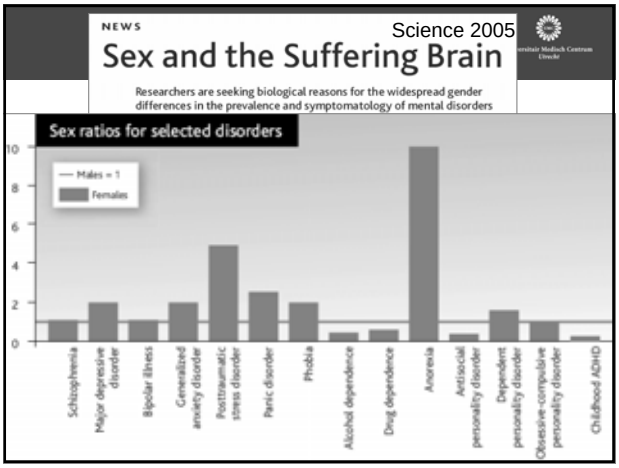
Two key Women´s Health Books



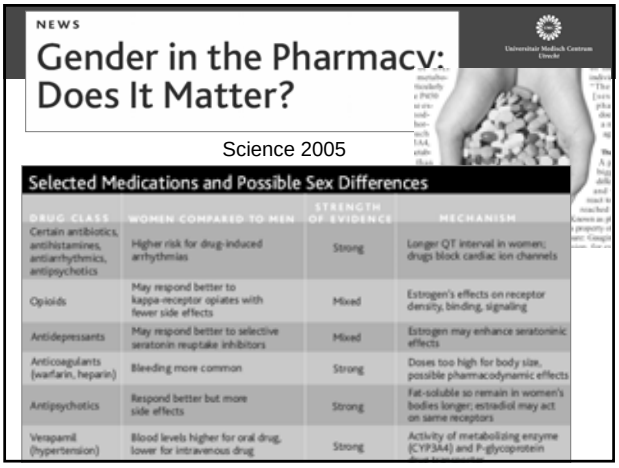


Is women's health a threat for gynecology?

Science 2005



Science 2005



Science 2005

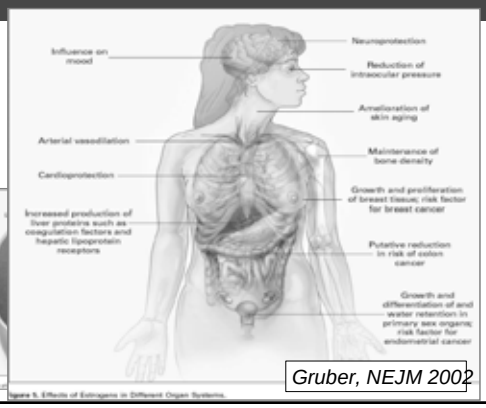

Let's Talk About Sex—and Drugs

Products for Female Sexual Dysfunction in Clinical Trials

DEVELOPING COMPANY	TREATMENT/MECHANISM	PROPOSED TRADEMARK	PHASE OF DEVELOPMENT
Acrux and Vivus	Testosterone transdermal spray	Testosterone MDTS	Phase II
Antares Pharma	Estradiol and testosterone patch		Phase I
BioSante	Testosterone gel	LibiGel	Phase III
Boehringer Ingelheim	Flibanserin, 5-HT_{1A} agonist and 5-HT_{2A} antagonist		Phase II
Cellegy	Testosterone gel	Tostrelle	Phase III
Columbia Laboratories	Intravaginal testosterone gel		Phase II
Eli Lilly	VML-670, 5-HT_{1A} agonist		Phase II
Galen Holdings	Intravaginal testosterone		Phase II
Nastech Pharmaceutical	Intranasal apomorphine		Phase II
NexMed	Alprostadil cream	Femprox	Phase II
NitroMed	NMI-870, Nitric oxide–enhanced α_2-agonist		Phase II
Novavax	Testosterone cream	Androsorb	Phase II
Palatin	PT-141, Melanocortin receptor agonist		Phase II
Procter & Gamble and Watson Laboratories	Testosterone patch	Intrinsa	Phase III
Retroactive Bioscience	Topical nitric oxide induction/lubricant	Sensual	Phase II/III
Sepracor	Didesmethylsibutramine		Phase I
Solvay	Estrogens and methyltestosterone	Estratest	Phase III
Vivus	Topical alprostadil	Alista	Phase III

Science 2005

Estrogen effects on different organ system



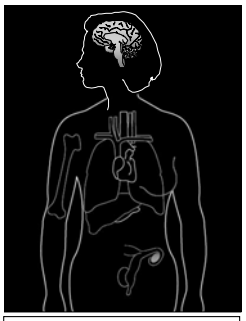
Gruber, NEJM 2002

Roles of ERα and ERβ in Organ Systems

α
- **Breast**
- **Liver**
- **Uterus**

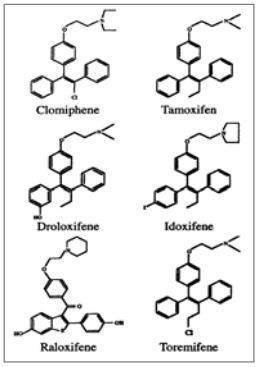
β
- **Blood vessels**
- **Bone**
- **Lungs**
- **Urogenital tract**

α and β
- **Central nervous system**
- **Ovary**



☐ alpha ☐ beta

Couse 1997, Shughrue 1996, Arts 1997



SERMs,
structure and function

Agonist
Antagonist

Cosman,
Endocr Rev 1999

SERMs
actions and clinical implications

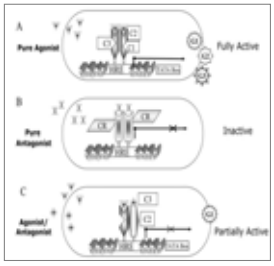
Table 3. Results of Major Trials of SERMs for the Primary Prevention of Breast Cancer.*

Variable	NSABP P-1 Study[24]	Royal Marsden Hospital Trial[27]	Italian Trial[25]	IBIS-I[24]
Primary outcome	Breast cancer	Breast cancer	Breast cancer	Breast canc
Secondary outcome	Bone, cardiovascular	—	Cardiovascular, psychometrics	Thromboem disease,
Eligibility	Age ≥60 yr, or 35–59 yr with a 5-yr predicted risk of ≥1.66%, lobular carcinoma in situ	Age 30–70 yr with a family history	Age 35–70 yr after hysterectomy	Age 35–70 y family h ular can situ or a
No. of women	13,388	2471	5408	71
Study drugs	Tamoxifen vs. placebo	Tamoxifen vs. placebo	Tamoxifen vs. placebo	Tamoxifen v
Age distribution (%)				
<50 yr	39	61	38	—
50–60 yr	31	39	50	
>60 yr	30		12	
Family history of breast cancer (%)	77	96	18	9
Mean follow-up (mo)	55	70	46	5
Effect on invasive breast cancer				
No. taking placebo in whom breast cancer developed	175	64	Not reported	8
No. taking tamoxifen in whom breast cancer developed	89	54	—	6
Relative difference (%)	−49‡	—§	—§	−2

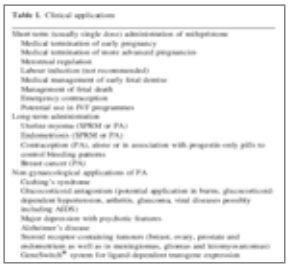
Table 1. Comparison of Selected Actions and Side Effects of Estrogen and Clinically Available SERMs.*

Side Effect	Estrogen	Tamoxifen	Toremifene	Raloxifene
Hot flushes	↓↓↓	↑↑	↑↑	↑↑
Uterine bleeding	↑↑↑	↑	↑	↔
Risk of endometrial cancer	↑↑‡	↑	?	↔
Prevention of postmenopausal bone loss	↑↑↑	↑	↔	↑↑
Risk of breast cancer	↑↑	↓↓	↓↓§	↓↓
Favorable pattern of serum lipids	↑↑↑¶	↑	↑↑	↑
Venous thrombosis	↑↑	↑↑	?	↑↑

SPRMs
potential agonist/antagonist activity

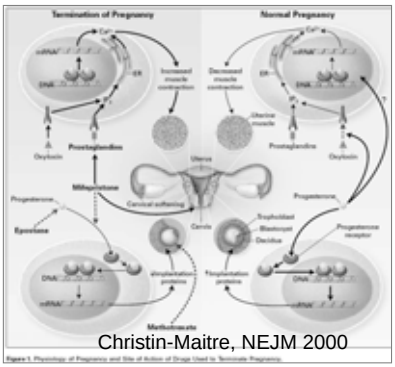


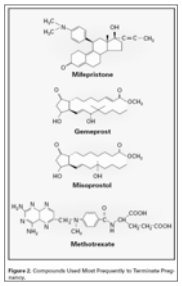
Chwalisz, Endocr Rev 2005



Chabbart-Buffet, HRU 2005

Termination of pregnancy



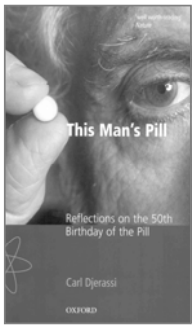


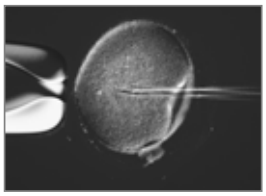
Christin-Maitre, NEJM 2000

From sex without reproduction

To

reproduction without sex





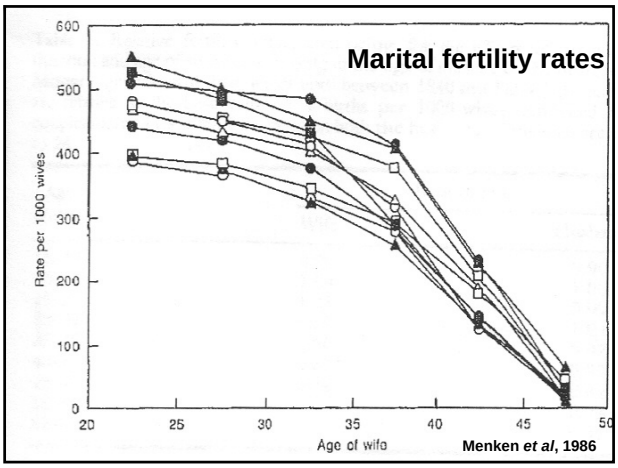
The brave new world of making babies

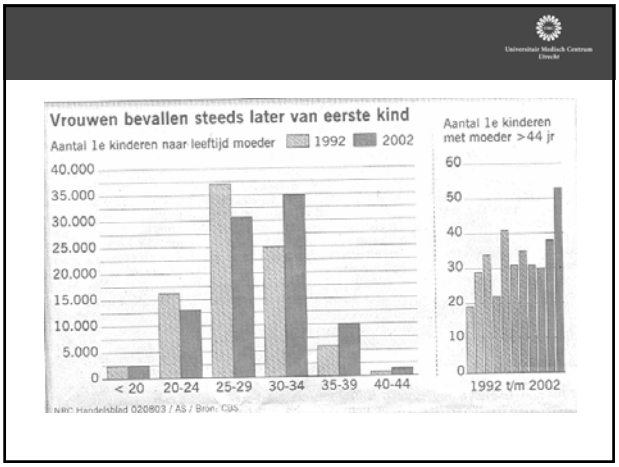
Bart C J M Fauser, Egbert R te Velde

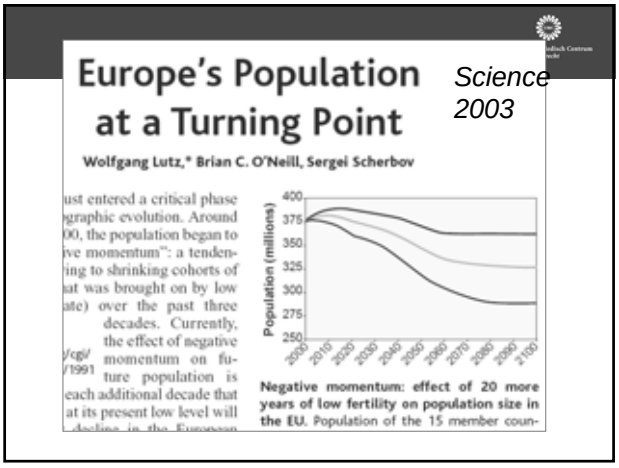
Lancet, 2000, millenium issue

Opinion

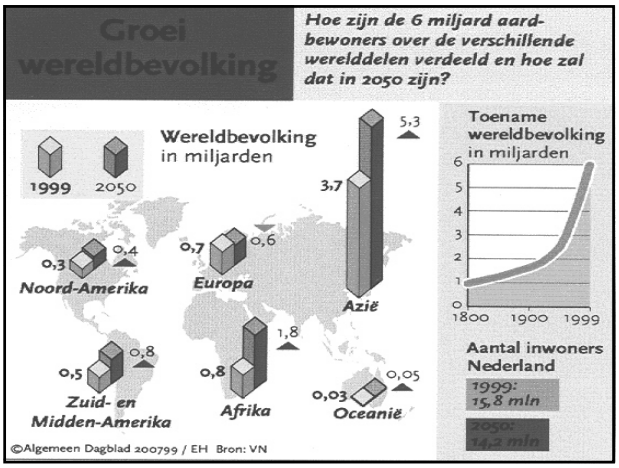
Having a baby: a 'gift from God', or a custom-made purchase?







Science 2003



The relationship between contraception and fecundity

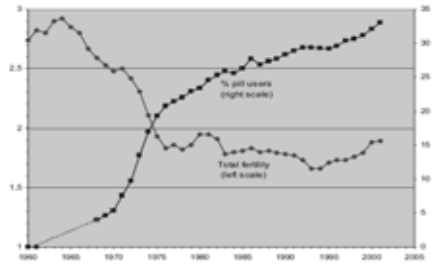


Figure 5. France: percentage of women of reproductive age using the contraceptive pill and the total fertility rate, 1960–2001. Line with squares: total

Leridon, HRU 2006

Insuffient innovation in IVF ?

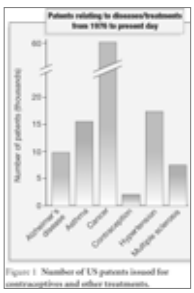
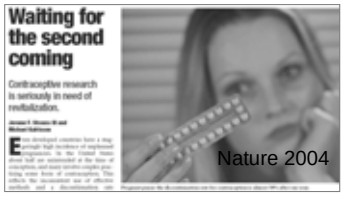


Figure 1 Number of US patents issued for contraceptives and other treatments.



Nature 2004

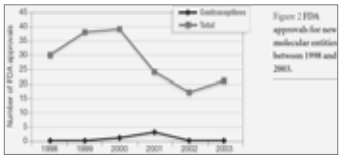
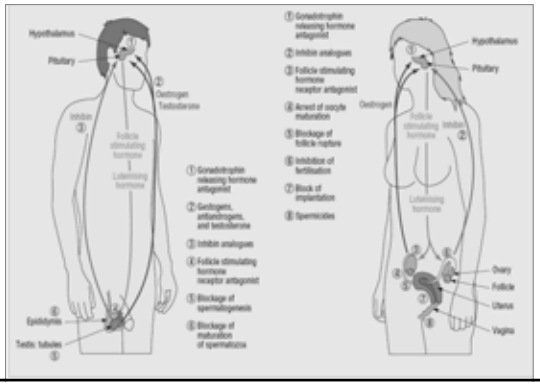
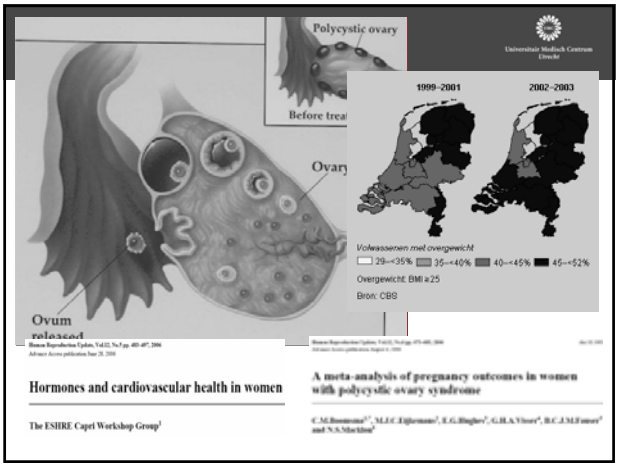


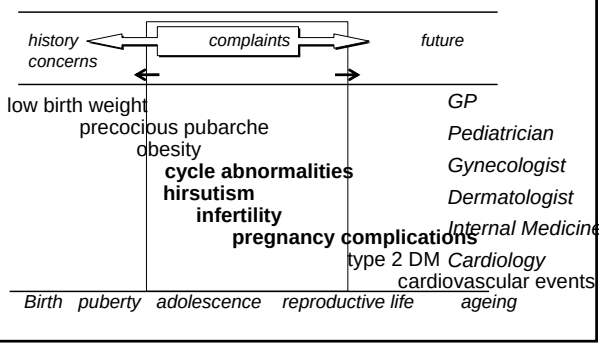
Figure 2 FDA approvals for new molecular entities between 1998 and 2003.

Targets for female and male contraception

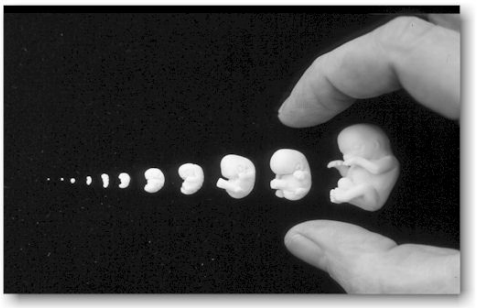




PCOS throughout life



Periconceptional medicine

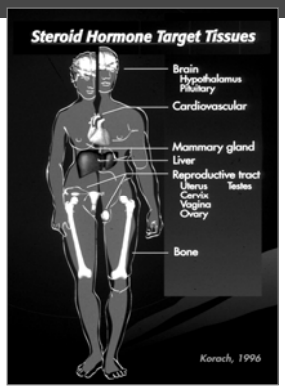


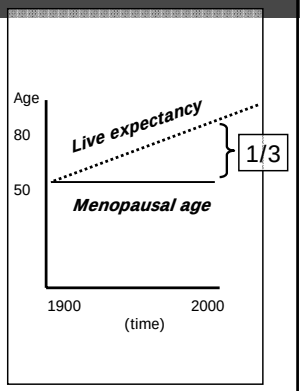
Nic

Growing old gracefully ***Nature, March 11 2004***

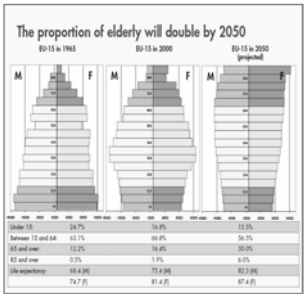
Across the industrialized world, birth rates are falling and people are living longer. This will require a new focus on research to promote healthy ageing, rather than simply treating the diseases of old age. Alison Abbott reports.

Is post-menopause a natural condition??

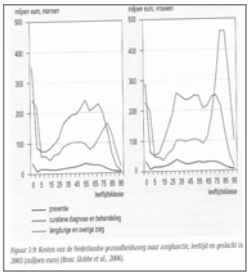


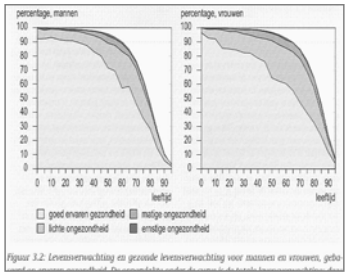


Ageing statistics in The Netherlands



Healthy ageing?

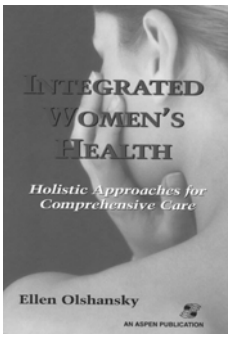




Zorg voor gezondheid, toekomstverkenning 2006. RIVM, De Hollander, e.a.

Challenges for the near future

The unmet need of women's health



The Health Needs of Adolescents

Barcelona, ESHRE, 2008

Adam Balen MD, FRCOG
Department of Reproductive Medicine
Leeds General Infirmary, U.K.

Learning Objectives

- **To understand disturbances of puberty, management of menstrual disturbance and complex disorders of sexual differentiation and development**
- **To appreciate the specific needs of the adolescent patient and appropriate environment for her care**

The Health Needs of Adolescents

- **General Principles**
- **Puberty**
- **Menstrual disturbance**
- **Sexual health / education**
- **Complex disorders of sexual differentiation and development**

General Principles

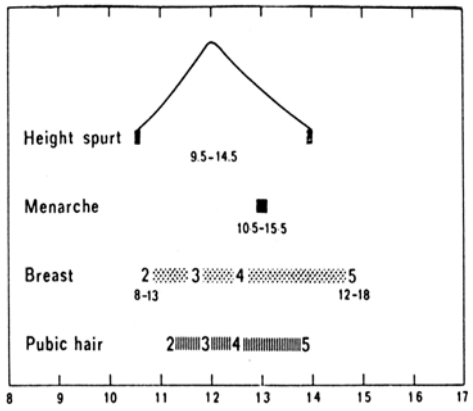
- **The adolescent clinic / ward**
- **Defining the transition from paediatrics**
  …. age vs menarche vs "maturity"

The Health Needs of Adolescents

- **General Principles**
- **Puberty**
- **Menstrual disturbance**
- **Sexual health / education**
- **Complex disorders of sexual differentiation and development**

Puberty in girls:

- **2^0 sexual characteristics appear in 95% of girls between 8.5 – 13y**
- **10 – 12.5y Breast development (average age breast stage 2 = 11.2y)**
- **Pubic hair usually 6m after breasts start, although before breasts in one third**
- **1 year later adolescent growth spurt**
- **Menarche: 12 – 15 y, as growth spurt wanes, average age 13y**



Sequence of normal puberty in girls, after Tanner 1989

Body fat and age at menarche

- **26-28% body fat required for regular ovulatory cycles**

  Frisch, Baillere's Clin Obstet Gynaecol 1990; 4:419-439

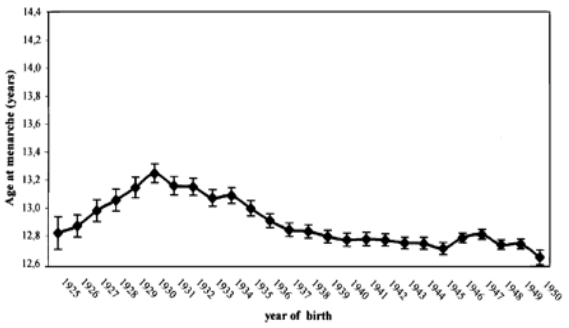
- **Obesity associated with early menarche and PCOS**

  Stoll, Cancer Res Treat 1998; 49: 187-193
  van Hoff et al, JCEM 2000; 85: 1394-1400

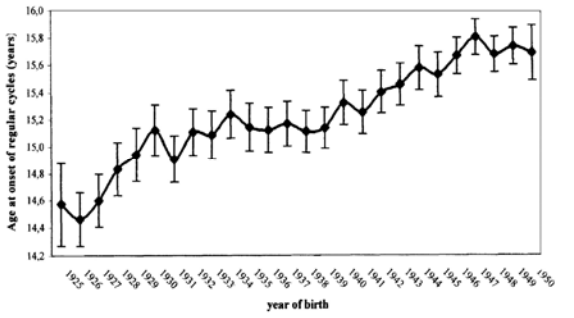
Age at menarche and at onset regular cycling:

- **85,683 questionnaires from women aged 40-65y reliable data on ~ 60,000**
- **Age menarche 7 - 20 y**
- **53,272 reported age of regular menstruation from 7- 25 y**
- **7,707 reported never having had regular menses**

Clavel-Chapelon & E3N-European Prospective Investigation into Cancer, Human Reprod 2002; 17: 228-232



Evolution of age at menarche by birth cohort in theE3N-EPIC population (*n* = 85 683).



Evolution of age at onset of regular cycles by birth cohort in the E3N-EPIC population (*n* = 53 272).

Age at Menarche

	≤ 11y	≥ 15 y
1926-30	15.6%	16.4%
1946-50	17.9%	9.4%

Age at regular cycling

	≤ 12y	≥ 19 y
1926-30	17.4%	8.4%
1946-50	17.6%	18.1%

Age of regular cycling has become older

Menarche together with regular cycles: 26%

Regular cycles within 1 year of menarche: 32%

Regular cycles 1-5 years of menarche: 26%

Regular cycles > 5 years of menarche: 16%

With younger generations decrease in rapidity of achieving regularity from 64% to 53%

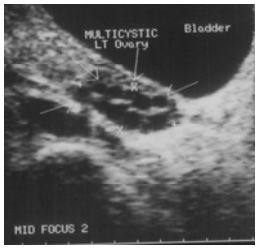
Those waiting > 5 years rose from 9% to 21% from 1925 to 1945

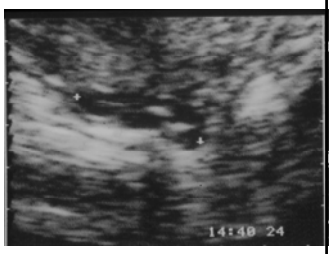
The later the onset of menarche, the longer until start of regular menses

< 11 y : 14% took > 5 y

> 17 y : 33% took > 5 y

Multicystic ovaries





Delayed puberty

Delayed onset of puberty is defined as occurring older than 2 SD after the average age

>13.4 years old in females

Causes of delayed puberty

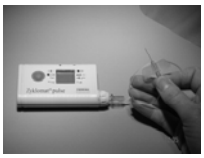
General
- **Constitutional delay of growth and puberty**
- **Malabsorption (e.g. coeliac disease, inflammatory bowel disease)**
- **Underweight (dieting/anorexia nervosa, over-exercise)**
- **Other chronic disease (malignancy, asthma, β thalassaemia major)**

Gonadal failure (Hypergonadotrophic hypogonadism)
- **Turner's Syndrome**
- **Post-malignancy (chemotherapy, local radiotherapy or surgical removal)**
- **Polyglandular autoimmune syndromes**

Gonadotrophin deficiency
- **Congenital hypogonadotrophic hypogonadism (± anosmia)**
- **Hypothalamic/pituitary lesions (tumours, post radiotherapy) Rare inactivating mutations of genes encoding LH, FSH or their receptors**

DELAYED PUBERTY: management

- **Low dose oestradiol, slowly rising**
  - **2 mcg orally**
  - **Evorel matrix patch 25mcg/d cut into 1/6**
- **For later fertility: Pulsatile GnRH or Gonadotropin (FSH+LH) therapy**



The Health Needs of Adolescents

- **General Principles**
- **Puberty**
- **Menstrual disturbance**
- **Sexual health / education**
- **Complex disorders of sexual differentiation and development**

Classification of primary amenorrhoea (1)

Hypothalamic causes *(hypog. hypog.)*	**Weight loss Intense Exercise Genetic (e.g. Kallman's syndrome)**
Delayed puberty	**Idiopathic Consitutional delay or secondary (Tumours: craniopharyngiomas, gliomas, germinomas, dermoid cysts)**
Hypothalamic/ pituitary damage	**Cranial irradiation, head injuries**
Systemic causes	**Chronic debilitating illness; Weight loss**
Endocrine disorders	**Thyroid, Cushing's syndrome....**

Classification of primary amenorrhoea (2)

Pituitary causes	**Hyperprolactinaemia; Hypopituitarism**
Ovarian causes	**Polycystic ovary syndrome** **Premature ovarian failure**
Uterine causes	**Mullerian agenesis (e.g. Rokitansky syndrome)** **Intersex conditions**

Amenorrhoea should always be investigated fully:

- **Examination: signs of sexual characteristics**
- **endocrine profile (FSH, LH, TFTs, PRL)**
- **androgen profile if indicated**
- **pelvic ultrasound (congenital anomalies)**
- **karyotype**
- **bone densitometry**
- **pregnancy test …..**

Gonadotropin measurements in amenorrhoea

FSH	LH	E2	Diagnosis
N	↑	N	PCOS
N / ↓	↓	↓	Weight-related amenorrhoea
↓	↓	↓	Hypogonadotropic hypogonadism, functional or organic
↑	↑	↓	If oligo-/amenorrhoeic: ovarian failure
↑	↑	↑	If E2 elevated think of mid-cycle surge

Exercise



Strategies to reduce risk

Multidisciplinary approach ~ include coaches and parents:

- **HRT / COC**
- **Calcium supplements**
- **↑ Calcium / nutrition beverages**
- **Vitamin supplements (iron, vit. K)**
- **Reduction exercise intensity**

- **Begin within 6 months of amenorrhoea**
- **Recovery of bone mass often incomplete**

Dueck `96; Kopp-Woodruffe `99; Haberland `95; Cumming `96




Eating disorders

The high-intensity exercise may be part of the expression of a severe eating disorder

"Undereating and over-exercising are mutually reinforcing and self-perpetuating behaviours"

Garner et al 1998

Eating disorders

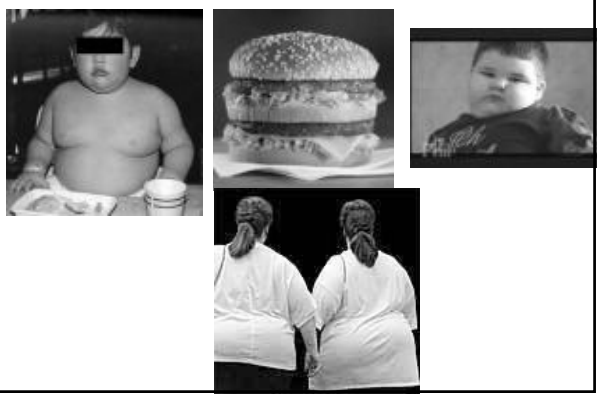
- **Common during adolescence**
- **Amplify endocrine disturbances**

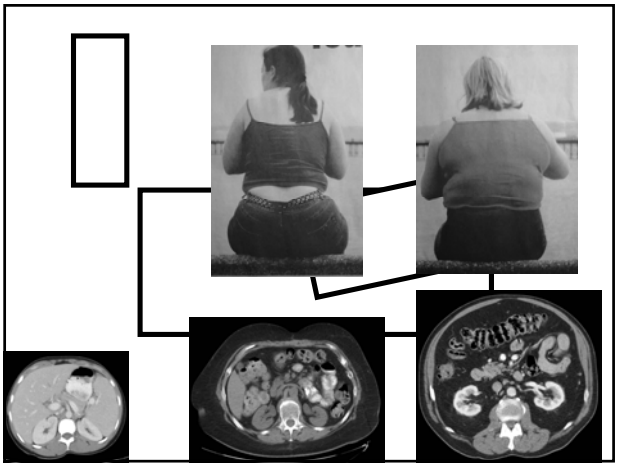
224 women 17-24 years:

30% episodes over-eating,
4% extreme methods weight control

Michelmore KF, Balen AH, Dunger DB
Human Reproduction, 2001; 16: 765-769

Obesity





Body fat and age at menarche

- **26-28% body fat required for regular ovulatory cycles**

  Frisch, Baillere's Clin Obstet Gynaecol 1990; 4:419-439

- **Obesity associated with early menarche and PCOS**

  Stoll, Cancer Res Treat 1998; 49: 187-193
  van Hoff et al, JCEM 2000; 85: 1394-1400

PCOS in Singaporean Adolescents

150 girls aged 12-22 y, "majority" 15-18y
All presented with menstrual disturbance

Mean age menarche in Singapore 12.6 ± 1.3 y

In PCOS: 53% had menarche 9 - 12 y
33% > 12y
14% primary amenorrhoea
21% secondary amenorrhoea

Dramusic et al J Ped Adol Gyn 1997; 10: 125-132

PCOS in Singaporean Adolescents

Of those with primary amenorrhoea or secondary amenorrhoa of more than 1 year duration, 43% were obese

Dramusic et al J Ped Adol Gyn 1997; 10: 125-132

Age at menarche and ovarian function

	Controls n = 957	PCOS 265	POF 98
Age at menarche			
< 11y	**12%**	**16%**	**21%***
12-14y	**74%**	**59%**	**58%**
➢15y	**14%**	**26%***	**21%**

*** Significant compared with controls**

Sadrzadeh et al Hum Reprod 2003; 10: 2225

PCOS in adolescence

Adolescents, mean age 16.7 ± 0.9 years

Regular cycle (58)	**Irreg. (50)**	**Oligomen. (29)**
PCO 9%	**PCO 28%**	**PCO 45%**

van Hoff et al F&S 2000;74:49

PCOS in adolescence

Oligomenorrhoeic adolescents (mean age 15.7 ± 0.6y) had higher LH and androgens than those with regular cycles

Proportion with irregular cycles (22-41d) declines with age; Oligomenorrhoea more constant

Oligomenorrhoea in adolescents is an early sign of PCOS and not a stage in maturation of H-P-O axis

van Hoff et al Hum Rep 1999; 14:2223

Menstrual irregularity aged 15y better predictor for later oligomenorrhoea than LH or androgens

Increased body weight contributed to predict persistent oligomenorrhoea but also normal weight oligomen adolescents have high risk of staying so

van Hoff et al Hum Rep 2004; 19:383

60% adolescents with oligomenorrhoea 2y after menarche keep this pattern for at least 8 years

Southam & Richart Am J Obstet Gynecol 1966; 94: 637

Oligomenorrhoea 2 years post menarche may be regarded as possible early clinical sign of PCOS

Homburg & Lambalk Human Reprod 2004; 19: 1039-1042

The PCOS Health-Related Quality of Life Questionnaire (PCOSQ)

Women and adolescents with PCOS

Worst health concerns:

- **weight**
- **infertility**
- **emotional limitations and poor energy**
- **hirsutism**

Jones et al Human Reprod 2004; 19:371
Hall et al ESHRE 2007

PCOS and eating disorders

- **Menstrual irregularity and acne common in PCOS and bulimia nervosa**
- **Women with PCOS more likely to have abnormal eating patterns (21% vs 2.5%)**
- **Bulimia affects insulin secretion which might promote PCOS**
- **PCOS affects body image which might promote Bulimia**

McCluskey 1991; Jahanfar 1991; Raphael 1995

Eating disorders

- **Common during adolescence**
- **Amplify endocrine disturbances**

224 women 17-24 years:
30% episodes over-eating,
4% extreme methods weight control

Michelmore KF, Balen AH, Dunger DB
Human Reproduction, 2001; 16: 765-769

Obesity and quality of life in adolescent girls with PCOS

186 healthy girls (BMI 23.5)
vs 96 with PCOS (BMI 31.7)

Body weight primary factor affecting quality of life

Trent et al, Ambul Pediatr 2005; 5: 107-11

Menorrhagia causing hospital admission in adolescents

- **1979-1995 – University of Michigan**
- **<20 years – Average age 15.9 y**
- **Causes : anovulation (46%)**
  haematological disease (33%)
  chemotherapy-related (11%)
  infection (11%)
- **Transfusion required in 63% of admissions**

Smith et al 1998

Bleeding Disorders

28 – 50% of adolescents with menorrhagia have a bleeding disorder

Ragni et al 1999 , Oral et al 2002

Bleeding Disorders

- **Check family history**
- **Look for ecchymoses, petechiae or epistaxis**
- **Investigation for a bleeding disorder should be done prior to therapy**
- **Von Willebrands may present with no history other than for profuse menstruation from the menarche**

Investigations

- **FBC**
- **Basic screening clotting assays**
  - **Platelet count**
  - **PT**
  - **APTT**
  - **Fibrinogen level**
  - **Bleeding time**
- **TFT's**
- **LH / FSH / prolactin / testosterone depending on history**
- **hCG / PID swabs / ESR if sexually active**
- **Ultrasound scan**

Menstrual Calendars

- **Often pictorial aids are helpful in guiding the adolescent to complete the calendar appropriately.**
- **Pattern, duration, quantity and colour of flow**
- **Validation study (Reid et al 2000) poor correlation between pictorial assessment and actual measured blood loss (cohort not restricted to adolescents)**

Medical conditions altering treatment

Children with complex medical conditions surviving through childhood

Usually only prevents oestrogen administration:

- **renal**
- **haematological**
- **cardiac**
- **wheelchair bound**

Acute severe menorrhagia

- **High dose oestrogen (i.v. premarin 15-25mg, repeated after 12h) or 3x COCP**
- **Cyclical progestogen / combined oral contraceptive**
- **Correct clotting abnormalities (e.g. rec factor V11a)**
- **GnRH analogue**
- **Hysteroscopy / Dilatation and Curettage**

Other Bleeding Disorders

Glanzmann's thrombasthenia – deficiency of glycoprotein IIb-IIIa complex **(Markovitch 1998)**

Factor V deficiency

Idiopathic Thrombocytopaenic Purpura

Acute promyeloctic leukaemia

Differential Diagnosis of abnormal uterine bleeding

- **Reproductive tract disease**
  e.g. pregnancy-related
- **Iatrogenic Causes**
  e.g. sex steroids, anticoagulants
- **Systemic Disease**
  e.g.hypothyroidism causing menorrhagia

Von Willebrands Disease

- **Caused by quantitative (type 1 and 3) or qualitative (type 2) defects of Von Willebrand factor.**
- **Correct dual defects of Haemostasis**
  Low levels of Factor VIII
  Abnormal platelet adhesion

Ultrasound in Menstrual Abnormalities

Potential Management Plan based on simple ultrasonic assessments:-

Endometrial thickness	Treatment
<6mm	Sequential HRT
6-12mm	Combined OCP
>12mm	Cyclical Progestogens

(Parry 1995)

Ultrasound in Menstrual Abnormalities

Familiarity with appearances of pelvic organs in adolescence in normal and pathological states.

Uterine/cervix ratios: 1:2 pre-pubertal
1:1 at puberty
2:1 after puberty

Appreciate usefulness of imaging in the management of menstrual disorders

Help with the appropriate management of anatomical abnormalities

Use serial examinations to monitor and adjust treatment as necessary

Von Willebrands Disease

Rx Desmopressin
Plasma concentrates

Tranexamic Acid (4 g/day) for menorrhagia

Inherited Bleeding Disorders

Menorrhagia confirmed objectively in:-

74% with Von Willebrand's disease
57% with haemophilia carriage
59% with Factor XI deficiency
29% in control group

Kadir et al, 1999

Bleeding Disorders

- **Approximately half of adolescents presenting with menorrhagia at menarche will have a bleeding disorder (Ragni et al 1999)**
- **Up to 19% of admissions with acute menorrhagia over 9 years due to primary coagulation disorders (Claessens et al 1981)**
- **An underlying coagulation disorder noted in 28% of adolescents with acute menorrhagia (Oral et al 2002)**

Treatment of mild/moderate DUB

Observation and reassurance if mild

Menstrual calendar
Iron supplements
Antifibrinolytics
Combined OCP
Progestogens
Mirena IUS

Pelvic Pain

- **Cyclical: primary dysmenorrhoea**
- **Endometriosis?**
- **Congenital anomaly?**

The Health Needs of Adolescents

- **General Principles**
- **Puberty**
- **Menstrual disturbance**
- **Sexual health / education**
- **Complex disorders of sexual differentiation and development**

Sexual Health

- Sex education
- Contraception
- HPV vaccination

- Sexual abuse

The Health Needs of Adolescents

- General Principles
- Puberty
- Menstrual disturbance
- Sexual health / education
- Complex disorders of sexual differentiation and development

Causes of Intersex

- **Virilised female (46,XX)**
  - Congenital Adrenal Hyperplasia (CAH)
  - mixed gonadal dysgenesis
- **Undervirilised male (46,XY)**
  - complete or partial AIS
  - testosterone synthesis defects
- **True hermaphroditism**
  (46,XX ± *SRY* or 46,XX/46,XY)

The Paediatric & Adolescent Gynaecology Clinic

Multidisciplinary multi-professional team

- **Gynaecologist**
- **Specialist nurse**
- **Clinical psychologist**
- **Psychiatrist**
- **Paediatric & adult endocrinologist**
- **Paediatric & adult urologist**
- **Plastic surgeon**
- **Radiologist**
- **Geneticist**

The Paediatric & Adolescent Gynaecology Clinic

Separate clinic and ward areas

Surgery in Infancy

- **"Normalised" genital appearance no longer thought to equate with sexual identity**
- **Surgery required if major cloacal defect**
- **Timing for intersex conditions?**

Surgery in Adolescence

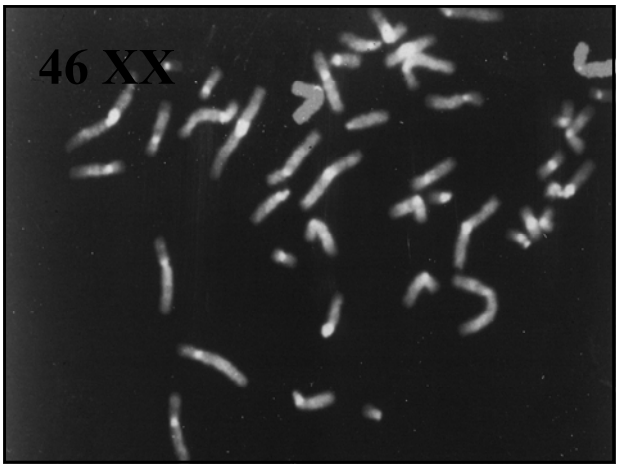
- **Timing important:**
  - **before/at start of uterine activity**
  - **psychological support**
  - **acceptance of dilators**

Aims of Surgery

- **To provide a vagina for comfortable, enjoyable penetrative intercourse**
- **If uterus present, to allow unobstructed menstrual flow**
- **Improved feeling of "normality" and confidence**

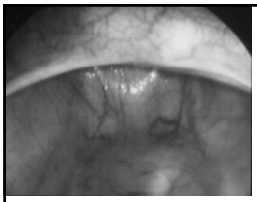
The Management of Intersex
and
Major Mullerian Anomalies

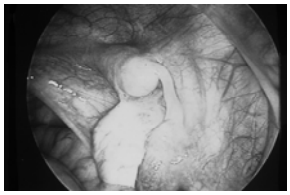
1. **Timing of treatment**
2. **Utero-vaginal anomalies**
3. **Congenital Adrenal Hyperplasia**
4. **Androgen insensitivity syndrome**

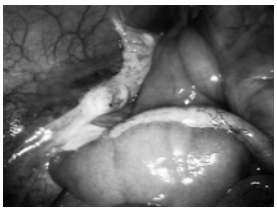


Mayer-Rokitansky-Kuster-Hauser syndrome

- **1:5,000 female births**
- **associated with renal tract anomalies (15-40%)**
- **anomalies of the skeletal system (10-20%)**



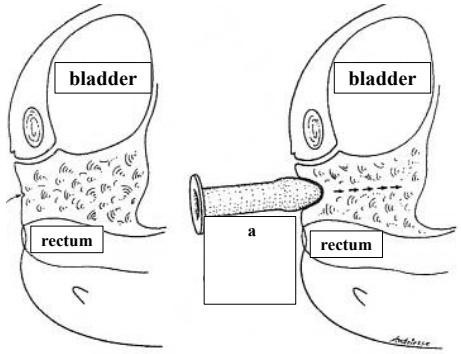




Management

- **Uterine remnant (anlagan) may require excision**
- **Vaginal dilatation** ***Franks, 1938***
- **Surrogacy**

Vaginal dilators



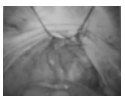
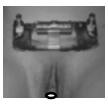
Vaginal Dilators

Width (mm)	Length (cm)
15	8
20	10
25	10
30	10
35	10

30 20 15

Vaginoplasty

- Vecchetti mechanical dilatation

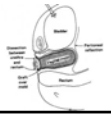
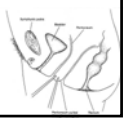



- Tissue expansion vaginoplasty



- Williams vulvo-vaginoplasty

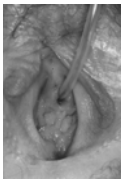
- Bowel transposition
- McIndoe – split skin graft
- Davydov vaginoplasty

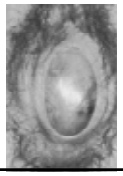
Vaginal Fusion Abnormalities

Transverse

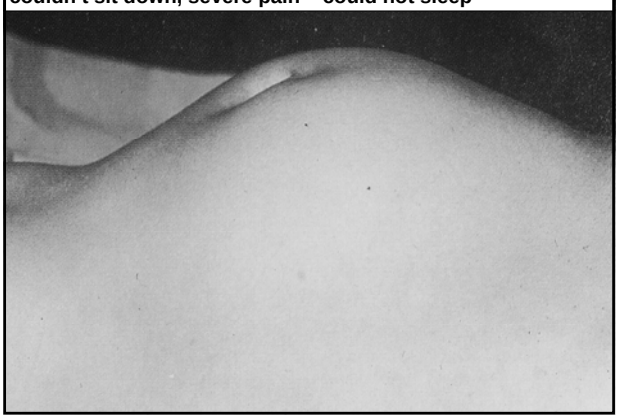
- transverse septum

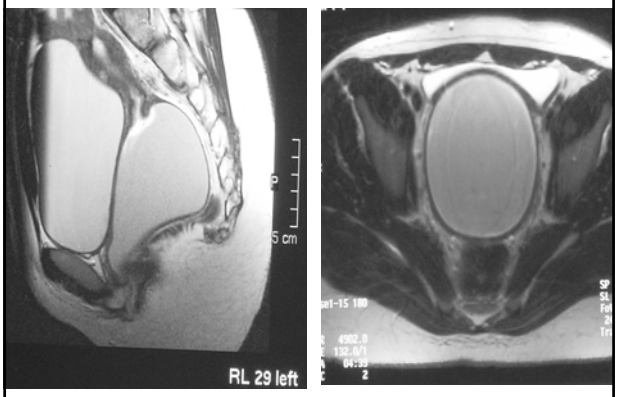


- imperforate hymen

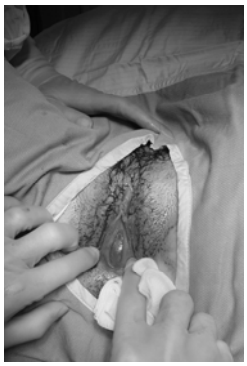


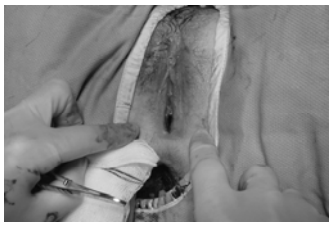
12 year old, removed from school as disruptive behaviour – couldn't sit down, severe pain – could not sleep



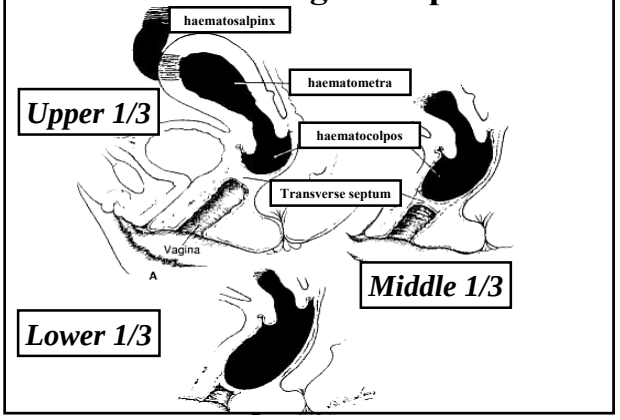


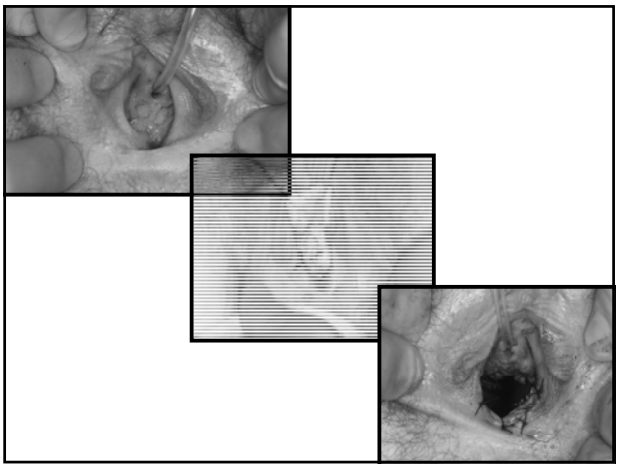
Imperforate hymen



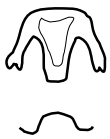


Transverse vaginal septum



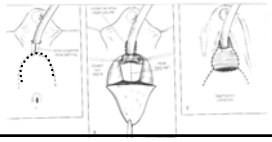


Cervical agenesis, absent vagina

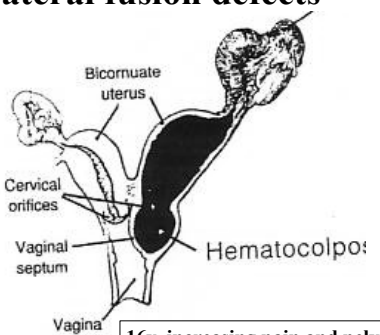


- **vaginal dimple**
- **normal uterine corpus**

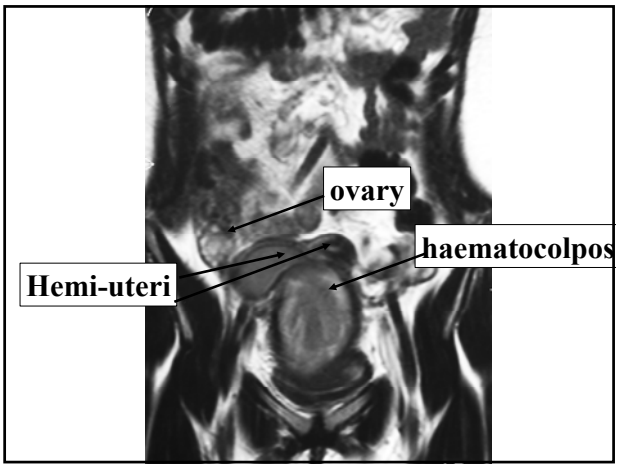
- **menstrual suppression**
- **uterine cannulation**
- **vaginal mobilisation, pull through rotational skin flaps**



Lateral fusion defects



16y, increasing pain and pelvic mass; unilateral haematocolpos on right, single kidney on left



The Management of Intersex and Major Mullerian Anomalies

1. **Timing of treatment**
2. **Utero-vaginal anomalies**
3. **Congenital Adrenal Hyperplasia**
4. **Androgen insensitivity syndrome**

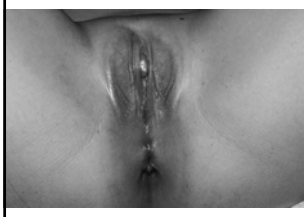
Congenital Adrenal Hyperplasia

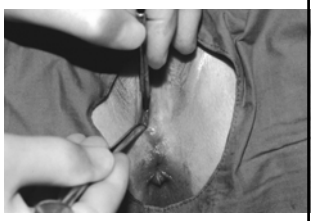
21 hydroxylase deficiency (95% of CAH)

1:5,000 – 1:20,000 births
carrier status in 1:80
racial differences

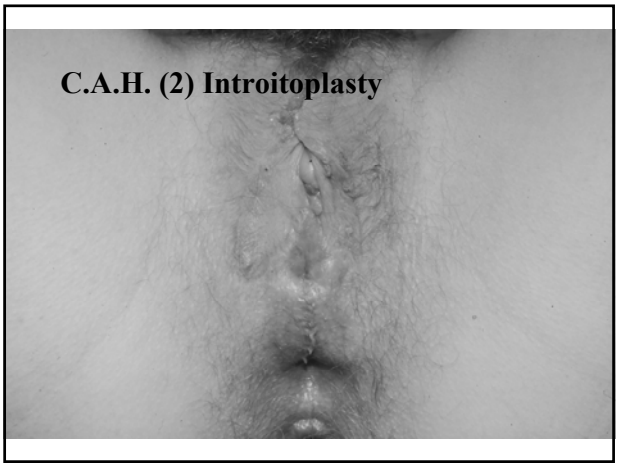
classical salt wasting ~ 60%
non-salt wasting ~ 20%
late onset ~ 20%

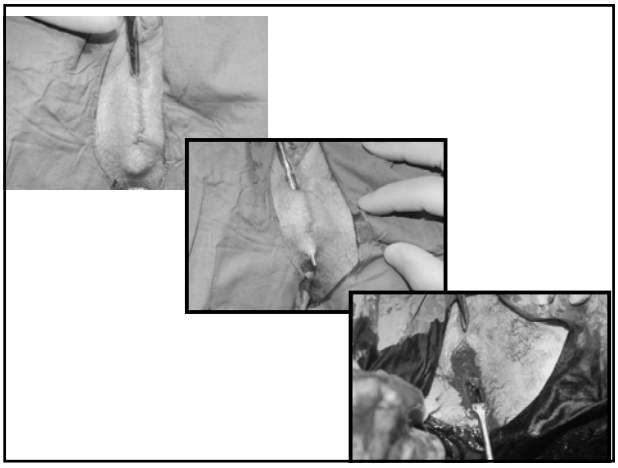
C.A.H (1)

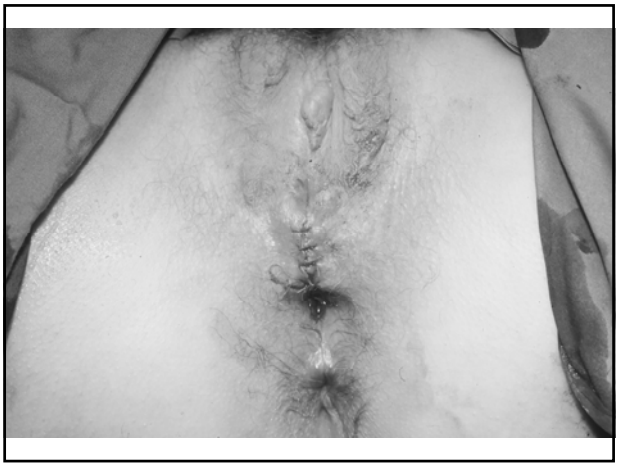




C.A.H. (2) Introitoplasty







"surgical intervention significantly increases the risk of impaired sexual function later in life"

Intersex society of North America, 2002

"patients have been saying for years – surgery can and does cause damage to sexual function….ambiguous genitalia isn't something to be ashamed of."

M Cull, response to BMJ 2001; 323: 1264-1265

Outcome of surgery in infancy

33% successful penetration (n=78)

46% not sexually active

Azziz et al, 1986

50% sexually active (n=6)

Bailez et al, 1992

44% successful penetration (n=10)

Krege et al, 2000

98% (n=44) will require further intervention for tampon use and intercourse

Dilators only 23%

Minor Surgery 7%

Major surgery 70%

Creighton et al, Lancet 2001; 358: 124-5

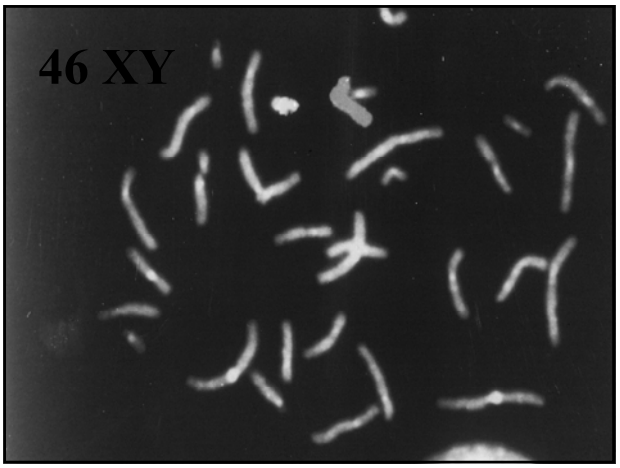
Cosmetic outcomes

clitoral recession surgery
28% unsatisfactory (n=33) ***Randolph & Hung, 1981***
clitoral reduction
0% unsatisfactory (n=4) ***Passerini-Glazel, 1989***
clitoral reduction
46% unsatisfactory clitoral appearance (n=13)
Alizai, et al, 1999

Clitoral reduction and vaginoplasty
41% poor (n=44) ***Creighton et al, 2001***

The Management of Intersex and Major Mullerian Anomalies

1. **Timing of treatment**
2. **Utero-vaginal anomalies**
3. **Congenital Adrenal Hyperplasia**
4. **Androgen insensitivity syndrome**



Androgen insensitivity syndrome - AIS
(formerly known as testicular feminisation syndrome)

- **1: 20,000 - 60,000 male births (46 XY)**
- **X-linked (androgen receptor on Xq), recessive**
- **30% result from de novo mutations**
- **anti-Müllerian factor prevents development Müllerian structures**
  - Wolffian structures do not respond to testosterone
  ∴ female external genitalia
- **Testicular descent within abdomen dependent on "insulin-3" (or Leydig insulin-like hormone) and not Testosterone**
- **Inguinoscrotal descent is T dependent**

Androgen insensitivity syndrome - AIS
(formerly testicular feminisation syndrome)

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  - Wolffian structures do not respond to testosterone
  ∴ female external genitalia

Androgen insensitivity syndrome - AIS

- **Many present with primary amenorrhoea, some breast development and no pubic hair**
- **May present with inguinal hernia or inguinal lump**
  - **occur in 90% of cases, usually bilateral**
  - **must do karyotype on any girl with hernia as 1-12% have AIS**
- **10% are partial (PAIS)**
  - **ambiguous genitalia and variable degrees of virilisation**

Type 1 (MAIS)	**Male external genitalia +/- gynecomastia, high-pitched voice, ↓ pubic hair , ↓spermatogenesis**
Type 2	**Isolated hypospadius**
Type 3	**Micropenis, perineal hypospadius, bifid scrotum, undescended testes**
Type 4 (PAIS)	**Ambiguous genitalia: Phallus, genital folds, urogenital sinus**
Type 5	**Severe abnormality in female genitalia: Posterior labial fusion, urethral and vaginal perineal openings, clitoromegaly**
Type 6	**Normal female genitalia, variable pubic hair**
Type 7 (CAIS)	**Normal female genitalia, absent pubic hair**

Gonadectomy in AIS

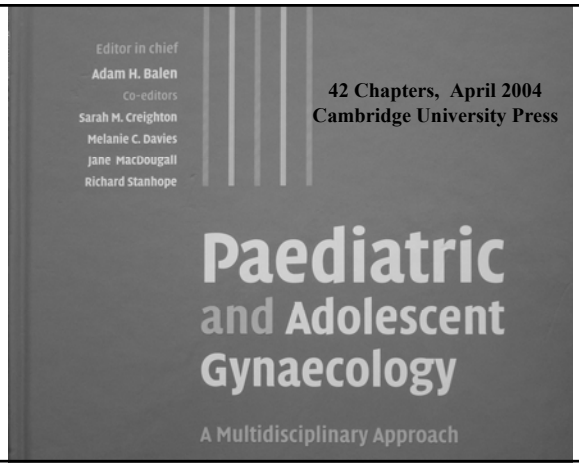
- **Risk of dysgerminoma 5-22%**
  - **unsure if similar to simple cryptorchidism**
- **carcinoma in situ found in children**
  ∴some advocate biopsy and gonadectomy if positive
- **Risk of malignancy < 5% if < 25y**

The Management of Intersex and Major Mullerian Anomalies

- **Requires a multi-disciplinary team approach**
- **Psychological support essential**
- **Timing of surgery critical for best results**
- **National networks of care, with a few specialised centres**

British Society for Paediatric & Adolescent Gynaecology

www.britspag.org
adam.balen@leedsth.nhs.uk



42 Chapters, April 2004
Cambridge University Press

Contraception: determinant of health and disease

Anna Glasier MD DSc
University of Edinburgh

Conflict of interest

There can be no pharmaceutical company marketing contraceptives nor any organisation working in contraceptive development from whom I have not indirectly benefitted (e.g. support for meetings, research grants etc). I am indiscriminate in seeking their support. However there is no company from which I receive any direct benefits. I do not believe that my relationship with the pharmaceutical industry compromises my ability to be objective in this session.

Learning objectives

This presentation should help you to

- Understand, from a global perspective, the enormous benefits of contraceptive use in preventing unintended pregnancy and its consequences and sexually transmitted infections including HIV/AIDS
- Appreciate the additional, non-contraceptive benefits of hormonal contraception for women
- Consider the possible non-contraceptive benefits of hormonal contraception for men

Most important risk factors leading to disease, disability or death

Poorest countries	Developed countries
Underweight	
Unsafe sex	
Unsafe water/sanitation	
Indoor smoke	
Zinc deficiency	
Iron deficiency	
Vit A deficiency	
Hypertension	
Tobacco	
High cholesterol	

Most important risk factors leading to disease, disability or death

Poorest countries	Developed countries
Underweight	Tobacco
Unsafe sex	Hypertension
Unsafe water/sanitation	Alcohol
Indoor smoke	High cholesterol
Zinc deficiency	High BMI
Iron deficiency	Low fibre intake
Vit A deficiency	Physical inactivity
Hypertension	Illicit drugs
Tobacco	Unsafe sex
High cholesterol	Iron deficiency

Unintended pregnancy: the statistics

- 205 million pregnancies annually worldwide
- More then one third are unintended (68 million)
- 182 million pregnancies occur in developing countries

Maternal Mortality

(Deaths/100,000 live births)
WHO/UNICEF/UNFPA estimates

Canada	6
Belgium	8
USA	12
Chad	1500
Nigeria	1100
Rwanda	2300

Maternal mortality: the statistics

- An estimated 536,000 maternal deaths in 2005
- 533,000 in developing countries
- 270,000 in sub-Saharan Africa

The adult lifetime risk of maternal death is

1 in 48,000 in Ireland
1 in 25 in Africa
I in 7 in Niger

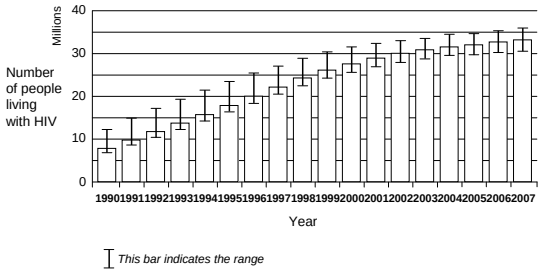
Abortion : the statistics

- 205 million pregnancies every year
- 42 million end in induced abortion
- 35 million occur in developing countries
- Worldwide 48% are unsafe

Unsafe Abortion: the statistics

- An estimated 67,000 women die
- An estimated 5 million women are hospitalized each year for treatment of abortion-related complications
- Every year approximately 220,000 children loose their mothers from abortion related deaths

Estimated number of people living with HIV globally, 1990–2007



The HIV/AIDS Epidemic by World Region, 2003

Region	People living with HIV/AIDS (million)	% Adults ages 15–49 with HIV/AIDS	% of infected who are women	Main mode of transmission
World	40.0	1.1%	50%	Heterosexual
Sub-Saharan Africa	26.6	8.0	58	Heterosexual
South/Southeast Asia	6.5	0.6	37	Heterosexual, IDU
Latin America	1.6	0.6	31	MSM, IDU, Heterosexual
Eastern Europe/Central Asia	1.5	0.7	26	IDU
East Asia/Pacific	1.0	0.1	24	IDU, MSM, Heterosexual
North America	1.0	0.1	20	MSM, IDU, Heterosexual
Western Europe	0.6	0.6	26	MSM, IDU
North Africa/Middle East	0.6	0.3	54	Heterosexual, IDU
Caribbean	0.5	2.5	53	Heterosexual, MSM

Mother to child transmission

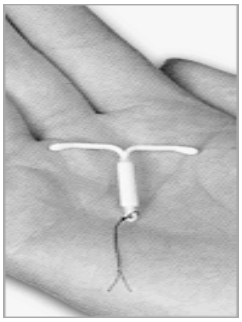
- Each day, approximately 1,800 children become infected with HIV, the vast majority of whom are newborns.
- Over 65,000 newborns become infected every year
- Many of these births result from unintended pregnancies

The non-contraceptive benefits of contraception

- Prevention and treatment of menstrual dysfunction
- Prevention & treatment of benign gynaecological conditions
- Prevention & treatment of acne
- Prevention of gynaecological cancers

The non-contraceptive benefits of contraception

- Prevention and treatment of menstrual dysfunction



Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up
(Hurskainen et al JAMA 2004)

- 236 women mean age 43 referred for HMB
- 5 university hospitals in Finland
- Randomized
- LNG-IUS (119) or Hysterectomy (117)
- Followed for 5 years
- Health Related Quality of Life

Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up
(Hurskainen et al JAMA 2004)

- 232 women completed trial
- 42% of women assigned to LNG-IUS underwent hysterectomy
- No difference in HRQL, psychosocial well-being or satisfaction
- Cost of LNG-IUS 2817 US$
- Cost of hysterectomy 4660 US$

RCGP Study incidence of menstrual dysfunction (rate/1000 woman years)

	OC users	Controls	RR
HMB	12.5	23.8	0.52
Irregular menses	5.2	13.1	0.65
IMB	3.0	5.3	0.72

Dysmenorrhoea and use of oral contraceptives in adolescent women attending a family planning clinic
(Courtland Robinson et al Am J O&G 1992)

- 430 women aged 18 or over getting OC from a clinic in Baltimore
- Followed for 6 months
- Interviews at baseline 3 and 6 months
- 382 (89%) follow-up
- 308 reported SI during follow-up

Dysmenorrhoea and use of oral contraceptives in adolescent women attending a family planning clinic
(Courtland Robinson et al Am J O&G 1992)

- 80% had dysmenorrhoea
- 46% mild
- 16% moderate
- 18% severe

Dysmenorrhoea and use of oral contraceptives in adolescent women attending a family planning clinic
(Courtland Robinson et al Am J O&G 1992)

The most statistically and clinically significant predictor of consistent oral contraceptive use was experiencing the reduction of dysmenorrhoea as a result of OC use; those with severe dysmenorrhoea who reported positive side effects of the pill were 8 times as likely to be consistent OC users as others.

The non-contraceptive benefits of contraception

- Prevention and treatment of menstrual dysfunction
- Prevention & treatment of benign gynaecological conditions
- Prevention & treatment of acne
- Prevention of gynaecological cancers

Combined oral contraceptive pills for the treatment of acne
(Arowojulo et al Cochrane Systematic Review. 2004)

- 5 placebo controlled trials
- 20-35 mcg ethinyl estradiol
- Levonorgestrel (2) norgestimate (2) NA (1)
- Lesion counts
- Self-assessment
- Physician assessment

Combined oral contraceptive pills for the treatment of acne
(Arowojulo et al Cochrane Systematic Review. 2004)

All five trials showed that combined oral contraceptives were better than placebo for the treatment of acne. Physician assessment of acne was 1.56-3.36 fold better than placebo

The non-contraceptive benefits of contraception

- Prevention and treatment of menstrual dysfunction
- Prevention & treatment of benign gynaecological conditions
- Prevention & treatment of acne
- Prevention of gynaecological cancers

Cancer risks among users of oral contraceptives: cohort data from the RCGP oral contraception study
(Hannaford et al BMJ 2007)

- Recruitment in 1968/69
- 14,000 GPs; 23,000 ever and 23,000 never users
- Mean age at recruitment 29
- Virtually all women now post-menopausal

Cancer risks among users of oral contraceptives: cohort data from the RCGP oral contraception study
(Hannaford et al BMJ 2007)

- 744,000 w. years observation for ever users
- 339,000 w. years observation for never users

Cancer risks among users of oral contraceptives: cohort data from the RCGP oral contraception study
(Hannaford et al BMJ 2007)

Cancer <u>diagnosis</u> among ever users compared with never users

- 12% reduction in the risk of any cancer diagnosis
- Reduced risk of colorectal cancer RR 0.72 (0.58-0.90)
- Reduced risk of endometrial cancer RR 0.58 (0.42-0.79)
- Reduced risk of ovarian cancer RR 0.54 (0.40-0.71)
- No difference for breast cancer RR 1.33 (0.92-1.94)

Mortality associated with OC use : 25 year follow up of RCGP study

Beral et al Lancet 1999

Current and recent (within 10 years) users versus never-users

Relative risk of death from		
Ovarian cancer	0.2	(0.1 - 0.8)
Stroke	1.9	(1.2 - 3.1)
Cervical cancer	2.5	(1.1 - 6.1)

Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23257 women with ovarian cancer and 87303 controls

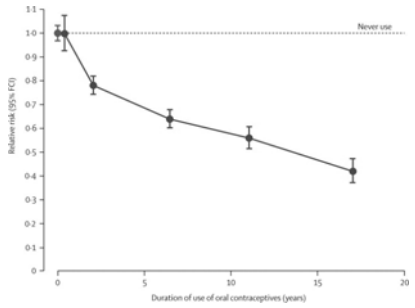
Lancet 2008

Ovarian cancer & oral contraceptives
(Lancet 2008)

- 45 studies all with at least 100 cases
- 21 countries mostly Europe and USA
- 13 prospective studies
- 19 case control studies (population controls)
- 95% combined oral contraceptives

Ovarian cancer & oral contraceptives
(Lancet 2008)

- Use of OC is associated with a reduced risk of ovarian cancer
- The longer the duration of use the lower the risk

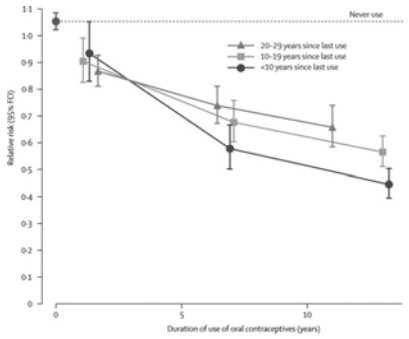


Relative risk of ovarian cancer by duration of OC use

Duration of use	Cases	RR and 99% CI
Never	14703	**1.00** (0.96-1.04)
< 1 year	1492	**1.00** (0.91-1.10)
1-4 years	2686	**0.78** (0.73-0.83)
5-9 years	1562	**0.64** (0.59-0.69)
10-14 years	655	**0.56** (0.50-0.62)
15 years or more	247	**0.42** (0.36-0.49)

Ovarian cancer & oral contraceptives
(Lancet 2008)

- Use of OC is associated with a reduced risk of ovarian cancer
- The longer the duration of use the lower the risk
- The reduction persists for 30 years after stopping the pill but the effect attenuates with longer gaps



Ovarian cancer & oral contraceptives
(Lancet 2008)

- Use of OC is associated with a reduced risk of ovarian cancer
- The longer the duration of use the lower the risk
- The reduction persists for 30 years after stopping the pill but the effect attenuates with longer gaps
- The effect does not seem to be reduced by lower dose pills
- The effect is independent of histological type of tumour apart from mucinous tumours which are not affected (and are 12% of tumours)

The Public Health Impact

In high income countries an estimated 13% of ovarian cancers are being prevented in women under 75 years of age This would amount to the prevention, by oral contraceptives, of 200,000 cases of ovarian cancer and 100,000 deaths in the last 50 years.

Use of oral contraceptives and endometrial cancer risk (Sweden)
(Widerpass et al 1999. Cancer causes & control)

- All women born in Sweden & resident in 1994-95
- Post menopausal, intact uterus, age 50 -74
- Newly diagnosed endometrial cancer
- 1055 cases
- 4216 population controls

Use of oral contraceptives and endometrial cancer risk (Sweden)
(Widerpass et al 1999. Cancer causes & control)

- Ever use of OCs reduced endometrial cancer risk by 30%
- Independent of dose
- Reduction in risk dependent on duration of use
- Risk reduced by 10% for every year of use
- Independent of tumour stage or later HRT use
- Effect lasted 20 years

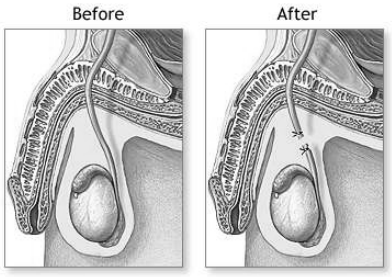
Oral contraceptive use and cancer. Findings in a large cohort study 1968-2004
(Vessey & Painter. B.J.Cancer 2006)

- 17,032 women recruited at 17 UK family planning clinics from1968-1974
- Age 25-39; annual follow up
- 187000 w.y. never use; 116,000 8+ year use

Oral contraceptive use and cancer. Findings in a large cohort study 1968-2004
(Vessey & Painter. B.J.Cancer 2006)

Endometrial cancer

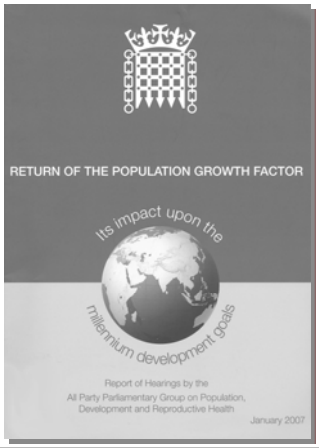
- Up to 4 years of use RR 0.6 (0.3-1.1)
- 4-8 years of use RR 0.4 (0.2-0.8)
- Over 8 years RR 0.1 (0.00-0.4)
- Effect persists for 18 years since last use



Promotion of family planning in countries with high birth rates has the potential to reduce poverty & hunger & avert 32% of all maternal deaths and nearly 10% of childhood deaths. It would also contribute substantially to women's empowerment, achievement of universal primary schooling and long-term environmental sustainability.

Cleland J et al

Lancet 2006.



Stern Review on the Economics of Climate Change 2006

- Population movement and growth will often exacerbate the impacts by increasing society's exposure to environmental stresses (for example, more people living by the coast) and reducing the amount of resource available per person (for example, less food per person).

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Gender specific medicine: Redefining reproductive endocrinology

Towards freedom from menstrual bleeding disorders

Hilary OD Critchley
Professor of Reproductive Medicine
Centre for Reproductive Biology
University of Edinburgh

ESHRE Pre-congress Course
Barcelona, July 2008

- Studies shown herein include studies undertaken with research grant support from TAP Pharmaceuticals.
- Research Grant support from Medical Research Council

Overview
"Towards freedom from menstrual bleeding disorders"

- **Problem - prevalence of menstrual disorders**
- **Terminologies and aetiologies**
- **Predictors of hysterectomy**
- **Current medical strategies to reduce menstrual bleeding**
- **Is menstruation "obsolete"?**
- **Progesterone receptor modulators – mifepristone; asoprisnil**
- **Clinical applications: endometrial contraception; heavy menstrual bleeding; fibroids**
- **Do women want amenorrhoea?**
- **Health benefits of amenorrhoea**

Menstrual disorders

- Increasing prevalence due to:
  - More periods per lifetime
    - Earlier menarche
    - Increased life expectancy
    - Ability to regulate fertility
    - Less time spent breastfeeding
  - More demanding lifestyles and reduced tolerance of troublesome periods

Scale of the problem

- Menstrual disorders impose a significant impact on quality of life

  [Sculpher. Int J Technol Asses Health Care, 1998; 14:302]
- Disruption to personal & professional life
- Sensitive nature of period problems may delay presentation
- Discordance between symptoms reported by women & reason for referral by GP – disproportionate focus on excessive bleeding

[Warner et al. BMJ, 2001]

The cost (UK)

- Major public health problem with invasive treatments and significant cost
- £7m is spent per year on primary care prescriptions
- Annual treatment costs exceed £65m and an estimated annual 3.5 million work-days lost

[Weeks et al. BJOG, 2000;107: 323]

The surgical workload

- In England during 2002-3, over 13,000 surgical procedures (hysterectomy and endometrial ablation) for HMB

[Reid et al. BMJ, 2005]

- 1 in 5 women have a hysterectomy by the age of 60, mainly for HMB; 40% have a normal uterus on histological examination

[Maresh et al. BJOG, 2002;109:302]

Terminology

- Terminology – "DUB"
  "Menorrhagia"
  "Heavy menstrual bleeding"

- Simple terminologies should be used for a description of symptoms, signs and causes of abnormal uterine bleeding
  ("Heavy menstrual bleeding" = HMB)

Analysis of the apparent meaning of usage of the term *menorrhagia* in 100 publications between 2000 and 2006, where the term *menorrhagia* appeared in the title of the publication
[Adapted from Woolcock et al 2008]

• **1**	(a)	Defined	56	
	(b)	Undefined	44	*n = 100*
• **2**		Used as ***symptom*** of heavy uterine bleeding		
	(a)	irregular, with or without pathology	34	
	(b)	regular, with or without pathology	28	
	(c)	regular with no detectable pathology	16	*n* = 78
• **3**	(a)	Primarily reflecting ***patient complaint***	59	
	(b)	Primarily reflecting the ***doctor's definition***	19	*n* = 78
• **4**		Used as ***diagnosis***		
	(a)	on its own	5	
	(b)	combined with another term (eg 'idiopathic')	17	*n = 22*

Heavy Menstrual Bleeding (HMB)			
Local uterine causes	**Iatrogenic causes**	**Systemic causes**	**Idiopathic causes**
Leiomyoma	Anticoagulants	Coagulation disorders	Altered synthesis of uterine vasodilatory prostanoids
Polyp	Copper intrauterine device	Hypothyroidism	Reduced endothelin expression
Infection		Chronic liver disease	Increased fibrinolysis
Carcinoma		Chronic cardiac or renal disease	Perturbed endometrial angiogenesis
Adenomyosis			Perturbed endometrial regeneration
Pelvic A-V malformation			Overproduction of nitrogen oxide

Natural History of Menstrual Cycles

- 1934 Miss Esther Doerr (Graduate student) invited her friends and staff to record menses prospectively
- Only half agreed; half returned menstrual card;big drop off at presumed menopause
- By 1961 25,825 person years of menstrual experience from 2700"colleagues"
- Data bank of 250,000 menstrual interval records

Classic Longitudinal Study: Alan Treloar and colleagues in USA
Treloar et al 1967 Inter J Fertility 12:77-113

Predictors of hysterectomy: An Australian study (1)

(Treloar et al. Am J Obstet Gynecol 1999; 180: 945-954)

- Evaluated the relative importance of predictors of hysterectomy
- Questionnaire survey of adult female twins Participants - a cohort of 1979 female twin pairs from the Australian Twin Register
- Participants completed a 4-page questionnaire ("Gynaecological Health Study")
- Self-report data validated against reports from treating physicians
- 3096 women (94%) and 366 physicians (87%) responded

Predictors of hysterectomy: An Australian study (2)

(Treloar et al. Am J Obstet Gynecol 1999; 180: 945-954)

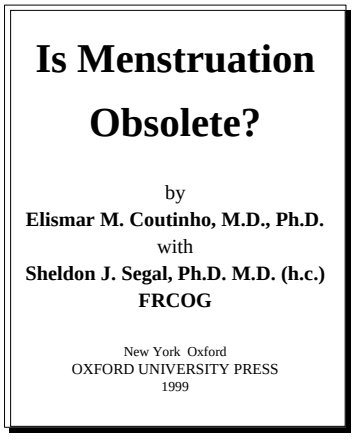
Predictor of hysterectomy	Odds ratio	95% Confidence interval
Endometriosis	3.55	3.17 – 7.43
Medical consultation for menorrhagia	3.55	2.47 – 5.12
Joint effect of fibroids with medical consultation for chronic or persisting pelvic pain	3.34	1.42 – 7.87
Smoking > 40 cigarettes per day	3.24	1.10 – 9.55
Joint effect of fibroids with consultation for menstrual problems	2.61	1.36 – 5.01
Tubal ligation	1.77	1.31 – 2.39

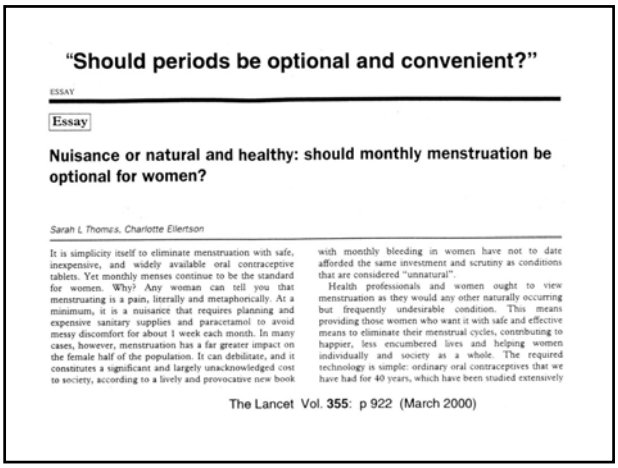
Predictors of hysterectomy: An Australian study (3)

(Treloar et al. Am J Obstet Gynecol 1999; 180: 945-954)

Conclusion

- Pelvic pain, menstrual problems, heavy bleeding are recognised steps → hysterectomy
- Future genetic analyses: high odds of hysterectomy for women with endometriosis, fibroids, or heavy menses.





"Should periods be optional and convenient?"

ESSAY

Essay

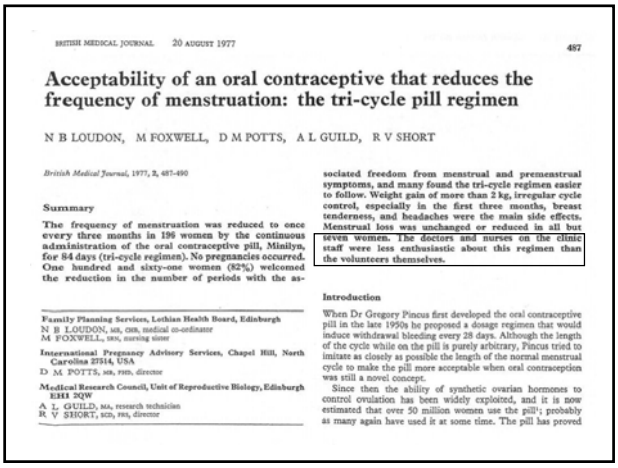
Nuisance or natural and healthy: should monthly menstruation be optional for women?

Sarah L Thomas, Charlotte Ellertson

It is simplicity itself to eliminate menstruation with safe, inexpensive, and widely available oral contraceptive tablets. Yet monthly menses continue to be the standard for women. Why? Any woman can tell you that menstruating is a pain, literally and metaphorically. At a minimum, it is a nuisance that requires planning and expensive sanitary supplies and paracetamol to avoid messy discomfort for about 1 week each month. In many cases, however, menstruation has a far greater impact on the female half of the population. It can debilitate, and it constitutes a significant and largely unacknowledged cost to society, according to a lively and provocative new book with monthly bleeding in women have not to date afforded the same investment and scrutiny as conditions that are considered "unnatural".

Health professionals and women ought to view menstruation as they would any other naturally occurring but frequently undesirable condition. This means providing those women who want it with safe and effective means to eliminate their menstrual cycles, contributing to happier, less encumbered lives and helping women individually and society as a whole. The required technology is simple: ordinary oral contraceptives that we have had for 40 years, which have been studied extensively

The Lancet Vol. 355: p 922 (March 2000)



BRITISH MEDICAL JOURNAL 20 AUGUST 1977 487

Acceptability of an oral contraceptive that reduces the frequency of menstruation: the tri-cycle pill regimen

N B LOUDON, M FOXWELL, D M POTTS, A L GUILD, R V SHORT

British Medical Journal, 1977, 2, 487-490

Summary

The frequency of menstruation was reduced to once every three months in 196 women by the continuous administration of the oral contraceptive pill, Minilyn, for 84 days (tri-cycle regimen). No pregnancies occurred. One hundred and sixty-one women (82%) welcomed the reduction in the number of periods with the associated freedom from menstrual and premenstrual symptoms, and many found the tri-cycle regimen easier to follow. Weight gain of more than 2 kg, irregular cycle control, especially in the first three months, breast tenderness, and headaches were the main side effects. Menstrual loss was unchanged or reduced in all but seven women. The doctors and nurses on the clinic staff were less enthusiastic about this regimen than the volunteers themselves.

Family Planning Services, Lothian Health Board, Edinburgh
N B LOUDON, MB, ChB, medical co-ordinator
M FOXWELL, SRN, nursing sister
International Pregnancy Advisory Services, Chapel Hill, North Carolina 27514, USA
D M POTTS, MB, FRCS, director
Medical Research Council, Unit of Reproductive Biology, Edinburgh EH1 2QW
A L GUILD, MA, research technician
R V SHORT, SCD, FRS, director

Introduction

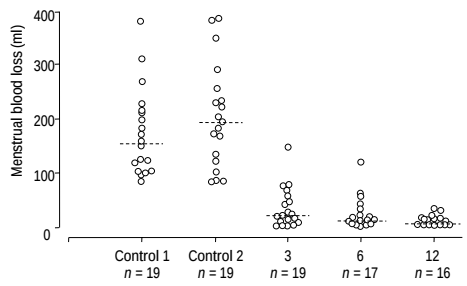
When Dr Gregory Pincus first developed the oral contraceptive pill in the late 1950s he proposed a dosage regimen that would induce withdrawal bleeding every 28 days. Although the length of the cycle while on the pill is purely arbitrary, Pincus tried to imitate as closely as possible the length of the normal menstrual cycle to make the pill more acceptable when oral contraception was still a novel concept.

Since then the ability of synthetic ovarian hormones to control ovulation has been widely exploited, and it is now estimated that over 50 million women use the pill¹; probably as many again have used it at some time. The pill has proved

LNG - IUS provides

- Excellent contraception
- Reduction in menstrual blood loss
- Progestogen in hormone replacement therapy

Menstrual blood loss before and after LNG-IUS



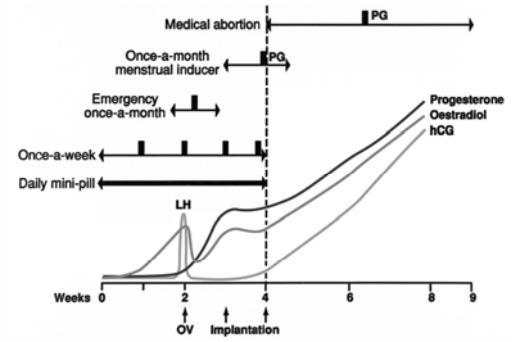
From Andersson and Rybo, 1990

Progesterone Receptor Modulators (PRMs)

- A family of compounds binding PR
- Pure agonists (e.g. progesterone)
- Pure antagonists (e.g. onapristone)
- SPRMs – mixed agonist-antagonist properties (e.g. asoprisnil)
- Wide range of potential clinical applications
- Effects on endometrium not fully understood

Contraceptive approaches

(from Baird and Glasier)



Chronic administration of PRMs

- **Several studies indicate that many PRMs have unexpected ability to block endometrial proliferation – the mechanism of this action is not clear**
- **Chronic administration of low doses of RU486 to women (2mg per day for 30 days) inhibits glandular mitosis and increases stromal density in the endometrium**
  (Cameron *et al*. 1996 Hum Rep 11: 2518)

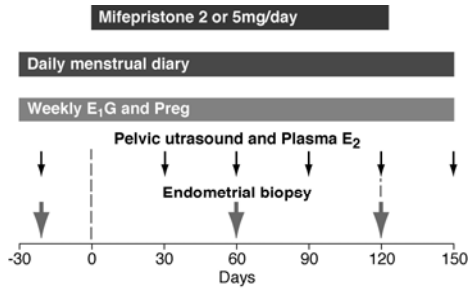
Mifepristone

Daily low-dose estrogen-free contraceptive

- 90 women, Edinburgh and Shanghai
- 2 mg or 5 mg daily for 120 days
- 90% of women anovulatory and amenorrhoeic
- E2 levels remained within mid-follicular range
- Endometrial biopsies at 60 and 120 days

Baird, Williams et al. Hum. Reprod. 2003 18:61-68

Daily low-dose mifepristone



Mifepristone: concept of a novel estrogen-free daily contraceptive pill

(Baird et al 2003; *Steroids* 68:1099; Lakha et al 2007; *Hum Rep* 22: 2428)

- **Daily doses 2 and 5mg inhibit ovulation and menstruation in over 90% subjects & maintain follicular phase levels of serum estradiol.**
- **There is an absence of proliferative activity: reduced mitotic index; reduced H3 and Ki67 immunostaining.**
- **Daily mifepristone (5 mg) is an effective oral contraceptive pill which has a better pattern of menstrual bleeding than an existing POP (LNG)**
  Lakha et al 2007; *Hum Rep* 22: 2428.

A novel estrogen-free oral contraceptive pill for women: multicentre, double-blind, randomized controlled trial of mifepristone and progestogen-only pill (levonorgestrel)* *Lakha et al 2007 Hum Rep 22: 2428

Compared - frequency of amenorrhoea (primary outcome), bleeding patterns, side effects and efficacy in women taking daily 5 mg mifepristone (n = 73) or 0.03 mg levonorgestrel (progestogen-only pill; POP, n = 23) for 24 weeks.

Amenorrhoea with mifepristone (49%) vs. POP 0% (P < 0.001)
Fewer women bled or spotted for >5 days per month
(4% vs 39% P < 0.001).

No pregnancies in 356 months of exposure in women who used only mifepristone for contraception.

The acceptability and continuation rate of oral contraceptive steroids are limited by unpredictable bleeding and the fear of long-term risks such as breast cancer.

By inhibiting ovulation and altering the receptivity of the endometrium, antagonists of progesterone, such as mifepristone, could be developed as estrogen-free novel contraceptives.

- **Uterine fibroids (leiomyomata) affect 20-25% of all women of reproductive age.**

  ….."local dysregulation of vascular structures in the uterus repsonsible for abnormal bleeding"
  (Sampson 1912 *Surg Gynecol Obstet* 14:215; Stewart & Nowak 1996 *Hum Reprod Update* 2:295)
- **No correlation between MBL and number, size and location of fibroids. Submucous fibroids consistently associated with HMB.**
  (Sulaiman et al 2004 *Eur J Obstet Gynecol Reprod Biol* 115:85)
- **Unknown how uterine fibroids cause abnormal endometrial bleeding.**
- Several vasoactive growth factors e.g. bFGF; VEGF; H-B EGF; PDGF; TGFβ; Prl are differentially regulated in fibroids.
  (Stewart & Nowak 1996 *Hum Reprod Update* 2:295)

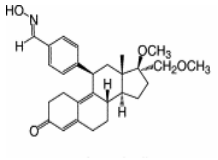
Use of the LNG-IUS in management of women with uterine fibroids and HMB

- appear in reproductive years & regress after menopause
- ovarian steroid-dependent growth potential
- LNG-IUS may have a role in management of HMB & long term contraception in women with fibroids - marked reduction in MBL
- significant increases in Hb levels after insertion of IUS
- no significant differences in myoma volume & uterine volume (MRI) between pretreatment and after 12 months use of IUS

(Maruo, T et al. (2000) Steroids 65: 585-592)

Asoprisnil (J867)

- Tissue selective PR effects
- Major target tissue - *endometrium*
  - Induces amenorrhea without suppression of estradiol
  - Dose dependent antiproliferative effect
  - Independent of effect on ovulation



Asoprisnil

Selective progesterone receptor modulators (SPRMs) -clinical effects

- **Mixed agonist and antagonist properties** (*Chwalisz et al, Endocrine Reviews, 26: 423-38. 2005*)
- **SPRMs reduce menstrual blood loss in women with fibroids and regular menses** (Chwalisz et al 2005 *Hum Reprod* 20:1090)
- **SPRM asoprisnil (J867): dose-dependent reversible suppression of menstruation (an endometrial effect), in absence of estrogen deprivation as follicular phase estrogen concentrations maintained** (DeManno et al 2003 *Steroids* 68:1019; *Chwalisz et al, Endocrine Reviews, 26: 423-38. 2005*)
- **Mechanism of suppressed endometrial growth not yet elucidated; likely direct effect on the endometrial vasculature.**

The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata

Asoprisnil induces unique morphological changes and is associated with low levels of glandular and stromal proliferation in endometrium, and in leiomyomata. These changes are likely to contribute to the amenorrhoea experienced after exposure to medication.

Williams et al 2007. Human Reproduction 22: 1696 - 1704

Do women want amenorrhoea?

Amenorrhea associated with contraception

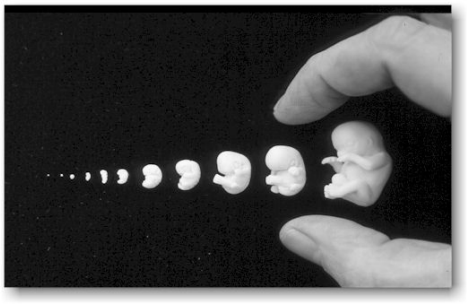
- Questionnaire survey 1001 women attending FPC
- 290 contraceptive providers - (China; South Africa; Nigeria; Scotland)
  - Most women disliked periods
  - Absence of periods highly acceptable to the majority of women in Edinburgh, Capetown, HongKong and Shanghai
- Providers over-estimate importance of regular periods to their clients

Glasier *et al* Contraception 2003 67:1-8

Potential health benefits of amenorrhoea

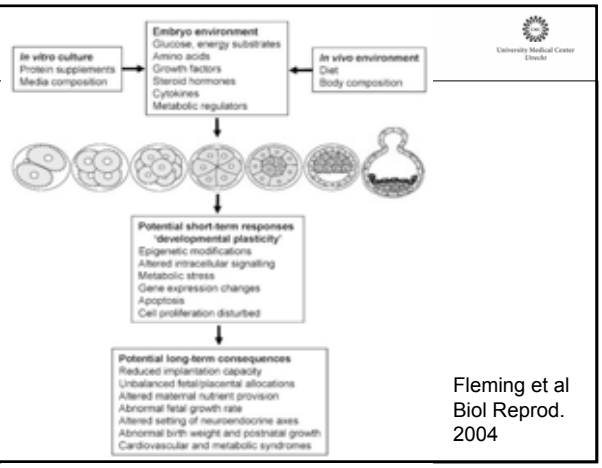
- Abolition of problematic bleeding
- Abolition of dysmenorrhoea
- Maintained iron status

Periconceptional Determinants of Health



University Medical Center
Utrecht

Nick Macklon



Fleming et al
Biol Reprod.
2004

Focus on 3 Periconceptional Factors

- Nutrition
- Toxins
- Ovarian Stimulation

Ovarian stimulation the nutritional environment of the oocyte

Correlations between follicular fluid biomarkers and follicular diameter stratified for folic acid supplement use

	Total group (*n* = 279 samples)	Supplement use (*n* = 175 samples)	Non-supplement use (*n* = 51 samples)
tHcy (µmol/g)	-0.06 s.*	-0.15 n.s.	-1.64 s.**
Folate (nmol/g)	-0.17 n.s.	-0.74 s.*	0.44 n.s.

Boxmeer et al, 2008

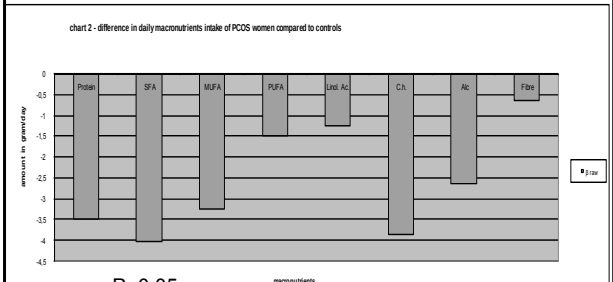
A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome

C.M.Boomsma[1,7], M.J.C.Eijkemans[2], E.G.Hughes[3], G.H.A.Visser[4], B.C.J.M.Fauser[5] and N.S.Macklon[6]

Meta-analysis: 720 women with PCOS vs 4505 controls

	OR	95% CI
Gestational Diabetes:	2.94	1.70-5.08
Pregnancy induced hypertension:	3.67	1.98-6.81
pre-eclampsia	3.47	1.95-6.17
Pre-term birth	1.75	1.16-2.62
Peri-natal mortality	3.07	1.03-9.21

Does preconceptional diet in women about to undergo IVF treatment differ in women with PCOS compared to controls?



P=0.05

Van Brussel et al 2008

Maternal Diet and Amino acid environment

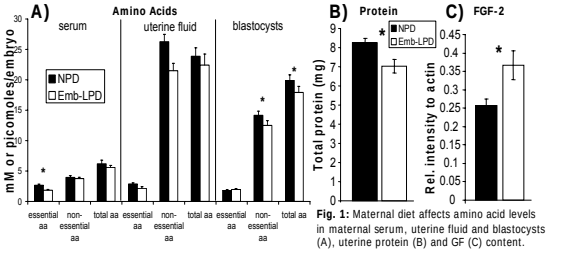
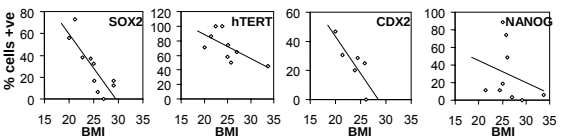


Fig. 1: Maternal diet affects amino acid levels in maternal serum, uterine fluid and blastocysts (A), uterine protein (B) and GF (C) content.

Eckert et al

Maternal BMI and early embryo phenotype



Relationship between embryonic potency protein marker expression and maternal BMI

Eckert et al

Focus on 3 Periconceptional Factors

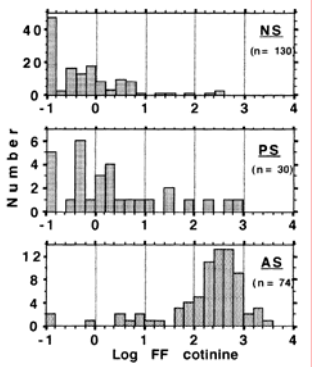
- Nutrition
- Toxins
- Ovarian Stimulation

Smoking

Smoking & Female Infertility

- **Meta analysis (21 studies)** ***(Augood et all, 1998)***
  - **Smoking reduce the natural fertility**
  - **Earlier menopause (average 2 years).**
  - **Damage of ovarian reserve increase with smoking (the amount and the period of smoking).**
  - **Increase in risks for ectopic pregnancy and spontaneous abortion.**

Nicotine in the oocyte follicle



Non smokers

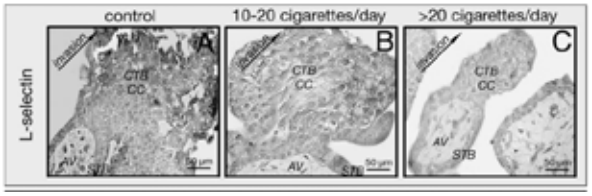
Passive smokers

Active smokers

Zenzes et al,
Hum Reprod 1997

Nicotine downregulates the L-selectin system that mediates cytotrophoblast emigration from cell columns and attachment to the uterine wall

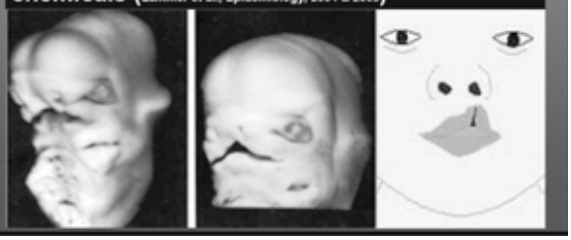
Tamara Zdravkovic [a], Olga Genbacev [a], Akraporn Prakobphol [a], Milos Cvetkovic [d], Andrea Schanz [a], Michael McMaster [a], Susan J. Fisher [a,b,c,*]



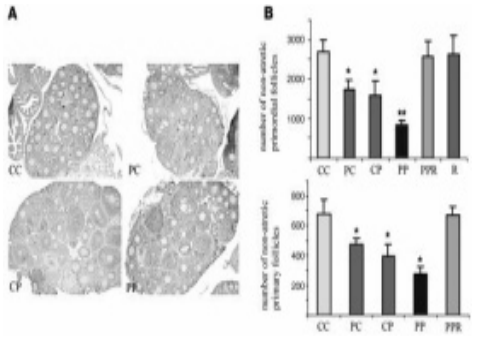
Reprod Toxicology 2006, 22;69-76

OROFACIAL CLEFTS

Among fetuses lacking enzymes involved in the detoxification of tobacco-derived chemicals (Lammer et al., Epidemiology, 2004 & 2005)



Effect of maternal treatment with PAHs on the ovarian follicle endowment in female offspring.



Juriscova et al JCI 2007

Focus on 3 Periconceptional Factors

- Nutrition
- Toxins
- Ovarian Stimulation

Ovarian Stimulation, the Oocyte and the Embryo

MOUSE

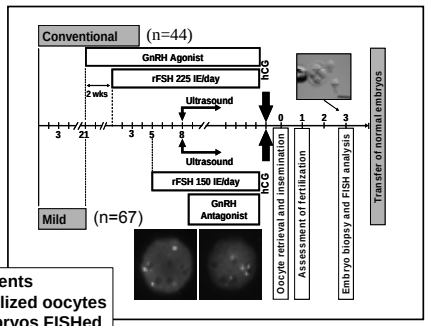
- Delays blastocyst development
- Reduces number of cells in blastocyst
- Causes a decrease in VEGF expression at implantation sites
- Causes reduction in fetal growth
- Increases frequency of chromosomal abnormalities

HUMAN

- Effect on morphology?
- Effect on chromosomal abnormalities?

Macklon et al, Endocr Rev 2006

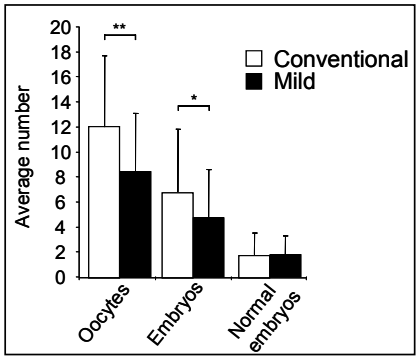
Effect of ovarian stimulation on embryo aneuploidy



111 patients
528 fertilized oocytes
302 embryos FISHed

Baart, Human Reproduction 2007

Chromosomally competent embryos generated after mild versus conventional stimulation



Baart, Human Reproduction 2007

Could embryo mosaicism be a mechanism underlying perinatal morbidity?

- Mosaicism more frequent following ovarian stimulation
- Aneuploid blastomeres more prevalent in trophoblast
- Confined placental mosaicism associated with lower birthwight and miscarriage

⇨ Is the rate of CPM higher in IVF pregnancies?

Multicentre matched cohort study

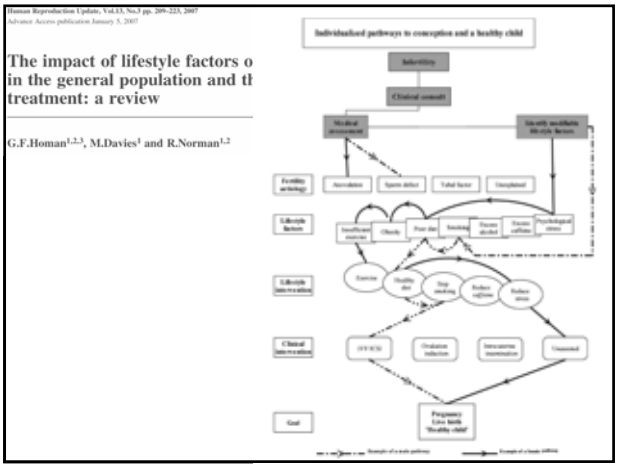
- Data from all Dutch University IVF and Genetic Centres
- Rate of CPM in IVF pregnancies versus match controls

	IVF/ICSI	Controls	OR (95% CI)
Pregnancies in women >36	9408	312838	
CVS procedures for age	235 (2.5%)	20650 (6.6%)	0.36 (0.32-0.41)
Mean age (SD)	38.4 (1.8)	38.4 (2.1)	
Abnormal karyotype at CVS	5.5%	4.6%	1.22(0.70-2.15)
Foetal anomalies (%)	4.3%	2.0%	2.17 (1.14 – 4.11)
CPM (%)	1.3%	1.8%	0.69(0.22 – 2.25)

Jacod et al, Hum Reprod 2008

Superovulation alters the expression of imprinted genes in the placenta

Fortier et al Hum Molec Genet 2008



Integrating Preconception Care

The 'PROCONCEPTION' Clinic

- **Preconceptional appointment 4 months before IVF**
- **Screening by website and nurse**
- **Personalised preconception plan**
- **Interventions**
- **Follow up**
- **RCTs**

THE ROLE OF EDUCATION CAMPAIGNS

Acknowledgements

A. Van Brussel
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A Goverde

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Y van der Schouw (Utrecht)
J. Eckert (DoHAD, Southampton)

Bart Fauser

Pre-congress Course - 6 July 2008

Course 3 - Organised by the Special Interest Group Endocrinology
Gender specific medicine: Redefining reproductive endocrinology

Session 3: Gender Specific Determinants of Health in the Adult

Hormonal determinants of female sexual health

Rik HW van Lunsen MD PhD & Ellen Laan PhD
Department of Sexology & Psychosomatic Ob/Gyn
Division Obstetrics &Gynaecology
Academic Medical Center
University of Amsterdam
The Netherlands

Learning Objectives

- Appreciate the importance of Sexual Heath as an important aspect of QOL of women of all ages
- Effectively identify and explore issues to be addressed in patients with sexual problems including the patient's context and preferences
- Select appropriate investigative methods in a resource-effective and ethical manner
- Acknowledge all bio-psychosocial variables in sexual functioning, including hormonal parameters
- Improve effective clinical problem solving and judgment to address sexual problems, including interpreting available hormonal data and integrating information to generate differential diagnoses and multifaceted management plans

Commercial Relationships

Rik HW van Lunsen and Ellen Laan conducted as PI's research in the field of female sexual health sponsored by:

- Bayer Schering Pharma
- Boehringer-Ingelheim
- Organon
- Pantarhei Bioscience
- Pfizer
- Procter & Gamble

Outline

1. Sexual Health
2. Libido does not exist. Sexual desire is part of the process of sexual arousal
3. Key words of sexual “intelligence”:
   Stimuli, context and communication
4. Hormonal aspects of sexual functioning
5. Sexual aspects of hormonal contraception
6. Sex, hormones and the menopause

1. Sexual Health

- Sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. *Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence.* For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled.

World Health Organization

5

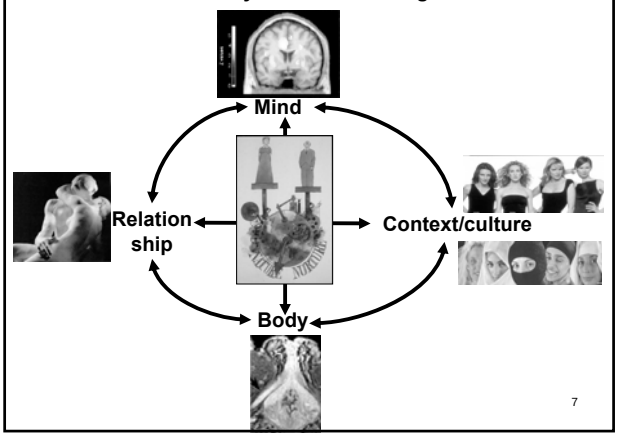
Sexual health—a new focus for WHO 2005

Prerequisites for sexual well being

- Psychological
- Social
- Relational
- Physical

→ Sexuality is a Bio-PsychoSocial Phenomenon

The Bio-Psychosocial Paradigm



7

Physiologic requirements in women's sexual function

- *intact sex steroids*
- intact autonomic/somatic nerves
- adequate arterial inflow/perfusion pressure to genital organs

van Lunsen & Laan ESHRE 2008 8

Hormones and Sexuallity

Myth:

- Libido is determined by sex hormones

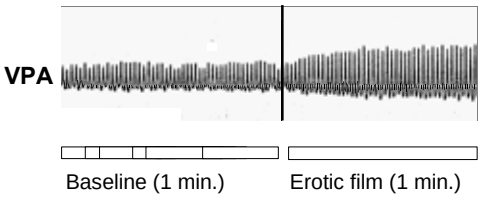
van Lunsen & Laan ESHRE 2008 9

2. Libido does not exist

- **Sexual arousability** (responsivity)
- **Sexual motivation**

} **Sexual desire**

EFA: Evaluation of Female Arousal



Sexual Processing

- Sexual responses start automatically
- Sexual desire is the result of positive cognitive elaboration (motivation) of preconsciously perceived starting responses (arousability)
- Ongoing sexual responses are related to motivated behaviour based on appraisal of context, stimulation and expected outcome

3.Stimuli, context and communication

DSM-IV-R:

If sexual stimulation is inadequate……

the diagnosis of sexual dysfunction involving excitement or orgasm is not made.

Because sexual desire is an aspect of sexual arousal we propose the same exclusion for the diagnosis of HSDD

Women with FSAD are hard to find

- Women tend to describe arousal in subjective, cognitive terms
- Women rarely present complaints about their genital responses
- A lack of physical responses is only noticed when it's virtually absent

Selection of a group of healthy women with FSAD meeting all DSM-IV criteria

Mean scores (± SD) on the 5 scales of the sexual feelings and affect-questionnaire (range 1-7), and the sexual lubrication estimate (range 1-10) of the FSAD group and the no-FSAD group, by menopausal status.

	FSAD group		no-FSAD group	
	Premeno-pausal (N=15)	Postmen o-pausal (N=14)	Premeno-pausal (N=16)	Postmen o-pausal (N=14)
Sexual arousal	3.24 (1.36)	3.50 (1.05)	5.04 (0.73)	4.17 (1.19)
Genital sensations	2.94 (1.20)	3.43 (1.53)	5.02 (0.89)	4.31 (1.35)
Sensuality	2.89 (1.29)	2.97 (1.05)	3.81 (0.92)	3.71 (1.25)
Positive affect	3.13 (1.37)	3.36 (1.35)	4.89 (0.95)	4.38 (1.41)
Negative affect	1.31 (0.50)	1.38 (0.50)	1.10 (0.20)	1.17 (0.33)
Sexual lubrication estimate	4.57 (2.13)	4.71 (1.98)	6.44 (1.90)	5.82 (1.93)

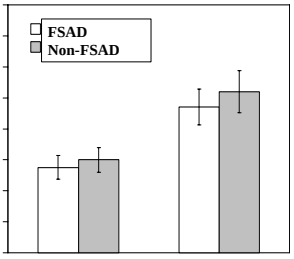
Laan E, Van Driel E,van Lunsen RHW (2008) Genital responsiveness in healthy women with and without sexual arousal disorder. J Sex Med

***Note*: significant differences between the FSAD group and no-FSAD group for all scales (*p*s < 0.001, except for negative affect, p < 0.05, and the sexual lubrication estimate, p < 0.01).**

15

Genital responsivity of women with FSAD(N=59) does not differ from that of women without SD

(Laan, van Driel, van Lunsen, 2008)



Disease Mongering?

FSAD: a disease invented by the pharmaceutical industry?

- Medically healthy women with FSAD according to DSM IV criteria have similar genital arousal response to sexual stimuli as women without sexual problems (Laan,van Driel, van Lunsen 2008)
- The only studies showing significant impairment of psychophysiological genital responses are studies of women with FSAD who have a medical condition that is known to have a potentially negative impact on genital neuro-vascular and/or neuro-endocrine functions (hypothalamic amenorrhea, radical hysterectomy, diabetes, spinal cord injury)

A complete sexual response is always possible as long as

- There is no major vascular and/or neurological disease
- Sexual stimuli are adequate
- The subject is sexually motivated
- The sexual event occurs in a suitable context

But….

Many women engage in coital activity when their prerequisites for sexual arousal are not met, resulting in unaroused intercourse

"Do you understand? I can do something that you can't and that I shouldn't do!"

4. Hormonal aspects of sexual functioning

In general "sex" hormones do not influence the sexual response itself, but determine how responsive "the sexual system" is to sexual stimuli both on a central and a peripheral level

The role of estrogens

- Estrogens have effects on the trophic state of the urogenital system
- Estrogens have effects on mood
- But estrogens do not have a direct effect on the sexual response cycle

→ E makes the brain and the body ready for Testosterone

The role of androgens

Testosterone enhances:

- Sexual arousability, responsivity
- Sexual thoughts and fantasies
- Nocturnal responses
- Genital sensitivity

→ T makes the brain and the genitals ready for sex

Testosterone Insufficiency Syndrome
(mimicking depression!)

- Declined sexual arousability
- Decreased frequency of sexual thoughts and fantasies
- Decreased nocturnal responses
- Decreased genital sensitivity
- Loss of vitality
- Fatigue
- Loss of muscle strength and volume

Possible causes of testosterone insufficiency

- Idiopathic *(sexual inactivity:use it or lose it ?)*
- Surgical/ chemical / radiotherapeutic castration
- Pituitary
- Hypothalamic
- Hyperprolactinemia
- Anti-androgenic medication
- **SHBG↑(Estrogens,Glucocortoids,Thyroid)**
- Poor general condition
- HIV & HAART

Some women may be more sensitive to *changes in T* than others

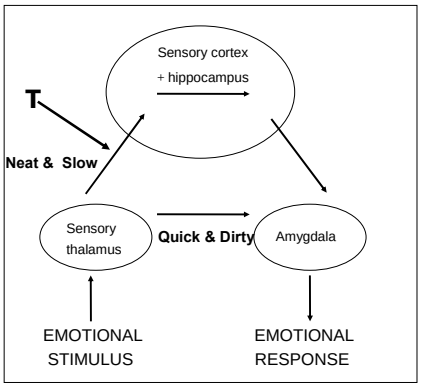
To measure effects of hormones on sexuality, assessment should include:

- *Sexual arousability* = (frequency of) responsiveness to sexual stimuli (diaries)
- *Psychophysiological studies:*
  This assessment should not be done as a response to visual stimuli only, because the “quick and dirty” route is not androgen dependent whereas the “slow and neat” route (thoughts and fantasies) is!

In several psychophysiological studies fantasy-provoked sexual responses showed to be androgen dependent, while responses provoked by visual stimuli are not

Two pathways:

1. Quick & Dirty (Ledoux 1996)
2. Neat & Slow (van Lunsen & Laan 2004)



Adapted from Ledoux, 1996

Androgen replacement?

- ❑ Some are against it (Wierman et al J Clin Endocrinol Metab 2006)
- ❑ Some want all women on T (some industries and Oprah Winfrey)
- ❑ We think there are clear but limited indications:

- Only in women who are adequately estrogenized
- Only when there are clinical signs/complaints related to androgen insufficiency
- Only if levels of bioavailable T (measurement of at least Total T and SHBG) are in the lower quartile of normal T ranges assessed by means of RIA and extraction, blood sampling before 10 AM

➢ Side effects are rare if androgen levels are maintained within normal physiological ranges.

The role of prolactin

Hyperprolactinemia causes a considerable decrease in sexual desire

A patient with hyperprolactinemia once described the effects of the disease on her sexuality as follows:

"*You are in the honeymoon suite of the Waldorf Astoria hotel, along with Brad Pitt, George Clooney and Robert Redford, all of whom are naked and fighting for the honor of getting into your bed, although you would prefer that they leave you alone in the room to watch television in peace and quiet"*

Causes of Hyperprolactinemia

- Prolactinoma
- Uremic women on hemodialysis
- Drugs (Molitch 2005)

Antipsychotics (neuroleptics)
Phenothiazines, Thioxanthenes, Butyrophenones, Atypical antipsychotics
Antidepressants
Tricyclic and tetracyclic antidepressants, MAO inhibitors, SSRI's,other
Opiates and cocaine
Antihypertensive medications
Verapamil, Methyldopa, Reserpine
Gastrointestinal medications
Metoclopramide, Domperidone
Histamine2 receptor blockers?
Protease inhibitors?
Estrogens

5.Sexual aspects of hormonal contraception

Myths:

- OC's have no negative effects on sexual functioning
- All pills are equal

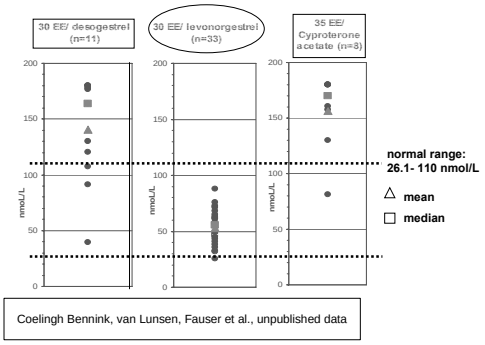
The effects of OC on sexuality

- In general positive effects on sexuality, but:
- 20-40% report changes in sexual desire
- More women (12.1%) report negative than positive (6.1%) on sexual desire (Oddens 1999)
- Disappearance of the androgen dependant midcycle increase and pre-menstrual decrease of sexual interest (Graham 1995, Mc Coy 1996)
- Sexual side effects of OC hidden but important cause of non-compliance (Bancroft 2000)

Effects of OC's on androgens

- Suppression ovarian androgens
- Decreased bio-availability (SHBG↑)
- Differential (anti)androgenic properties of progestogens because of differential effects on SHBG and differential intrinsic (anti)androgenic properties

SHBG levels of different OC's



Coelingh Bennink, van Lunsen, Fauser et al., unpublished data

- A substantial proportion of women who take OC's experience a marked decline in serum androgen levels without adverse sexual effects
- Women who experience sexual side effects on OC have lower bioavailable T levels than women who don't
- What distinguishes women who experience negative sexual side effects from those who do not ?

- Panzer C, Wise S, Fantini G, Kang D, Munarriz R, Guay A, Goldstein I, *J. Sex Med. 2006*
- Graham C, Bancroft J, Doll H, Grecod T, Tannere A *Psychoneuroendocrinology* 2007

ARC(androgen restored contraception) study

(van Lunsen, Laan, Coelingh Bennink, Termeer)

- Double-blind, placebo controlled, randomised, 2-way cross-over study over 10 treatment cycles with an oral contraceptive (OC) containing 150 mcg levonorgestrel and 30 mcg ethinylestradiol or 3 mg drospirenone and 30 mcg ethinylestradiol, with co-treatment of a low dose of an androgen or placebo during 5 cycles each.
- Primary objective:

  To determine the effect on:
  - Sexual arousability, levels of sexual desire, frequency of sexual fantasies assessed with a Sexual Function Diary (SFD)
  - Sexual function assessed with the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS)
  - The vascular component of the sexual arousal response (VPA) determined by vaginal photoplethysmography (VPP)
  - Number of satisfying sexual events assessed with the SFDExperience of sexual arousal during self-induced erotic fantasy (SEF) and visual sexual stimulation (VSS)

Study in progress; publication 2009

6. Sex, hormones, and the menopause

Myths:

- Vaginal dryness and dyspareunia are related to estrogen depletion
- Estrogen replacement restores sexual functions

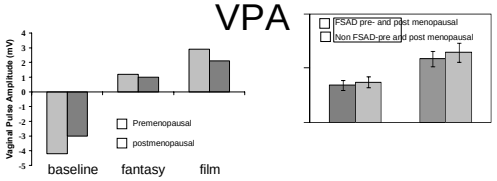
But,

The majority of studies show that there is a discrepancy between decrease of vaginal dryness with estrogen therapy, and a lack of changes in masturbation, orgasm, frequency of intercourse or coital satisfaction.

Sexuality and menopause

- Increase in the prevalence of women's sexual desire and arousal dysfunctions with the natural menopausal transition
- Vaginal dryness occurs in only 20% -30% of all postmenopausal women *(Oldenhave 1994)*
- Women using hormone therapy report more dyspareunia than women not using hormone therapy *(Dennerstein et al. 1994)*
- Several studies fail to find a correlation between vaginal dryness and dyspareunia on the one hand, and estrogen levels and objective measures of vaginal atrophy on the other *(Leiblum et al. 1983, Bachmann et al, 1984, Laan & van Lunsen 1997)*
- The majority of postmenopausal women report no decline of sexual desire *(Dennerstein et al. 1994)*

VPA



In the non-aroused state vaginal blood flow in postmenopausal women is decreased but there is no difference in sexual response (increase in vaginal blood flow measured as vaginal pulse amplitude) between pre-and postmenopausal women (Laan & van Lunsen 1997; Laan, van Driel, van Lunsen 2003)

Medically healthy women with sexual arousal disorder (FSAD criteria DSM IV) have similar genital arousal responses to sexual stimuli as women without sexual problems (Laan, van Driel, van Lunsen 2003)

- Premenopausal women, when not aroused, may not experience pain and/or discomfort because they are, to a certain extent, protected by the permanent non-sexual and estrogen dependent lubrication reflecting a higher vaginal blood flow in the non-aroused state
- Postmenopausal women may be more dependent on their arousal because of the lower blood flow in the non-aroused state compared to premenopausal women

van Lunsen RHW, Laan E. Genital vascular responsiveness and sexual feelings in midlife women: Psychophysiological, brain and genital imaging studies. Menopause 2004; 11(6):741-748, 2004

For clinical practice this implies that the reported relief of dyspareunia and vaginal dryness by the use of topical or systemic estrogens might represent a restored potential to have intercourse in an unaroused state, without serious difficulty

However, these women might benefit more from symptomatic treatment combined with a behavioral approach addressing the psychological, relational, and contextual factors that have resulted in ineffective sexual stimulation

The best predictors for both postmenopausal sexual satisfaction and vaginal health seem to be positive previous sexual experiences, current relationship status and continuation of sexual activity

Aging has some effect on both central and peripheral aspects of the sexual response

Decreased "arousability" (responsivity) caused by:

- decreased vascular elasticity
- physiological age-dependent neuro- endocrine changes

→ More, more direct (genital) and longer sexual stimulation is necessary for a complete sexual response

General conclusions

- Hormones play an important facilitating role in the sexual reponse system but have limited effects on sexual responses and sexual behaviour per se
- Large inter-individual differences in sensitivity to changes in T make it impossible to generalize findings in study populations to individual clinical situations
- Contextual factors largely predict sexual behaviour, not genital response or hormones (Dennerstein & Lehert, 2004).
- Contextual and relational variables resulting in a lack of adequate sexual stimulation and/or cognitive inhibitions are probably the underlying cause for most sexual problems of women
- Nevertheless, it is necessary to assess all possible physical, endocrinological, psychological, relational and social aspects to establish the best integrated multifaceted treatment options for each individual sexual problem

Literature

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- van Lunsen RHW,, Laan E. Genital vascular responsiveness and sexual feelings in midlife women: psychophysiologic, brain, and genital imaging studies. Menopause, 11 (6): 741-748, 2004
- Nappi R. Salonia A. Traish AM. van Lunsen RHW. Vardi Y. Kodiglu A. Goldstein I. Clinical biologic pathophysiologies of women's sexual dysfunction. Journal of Sexual Medicine. 2(1):4-25; 2005.
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- Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, Moufarege A, Rodenberg C, Buch A, Purdie DW.Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial.Menopause. 2006 May-Jun;13(3):387-96.
- Nijland EA, Weijmar Schultz WCM, Nathorst-Böös J, Helmond FA, van Lunsen RHW, Palacios S, Norman RJ, Mulder RJ, Davis SR for the LISA study investigators. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women; results of a randomized active-controlled trial. J Sex Med 2008;5:646–656
- Laan E, Van Driel E, van Lunsen RHW.Genital responsiveness in healthy women with and without sexual arousal disorder . J Sex Med 2008;5:in press

Estrogen, Cognition and the Aging Brain

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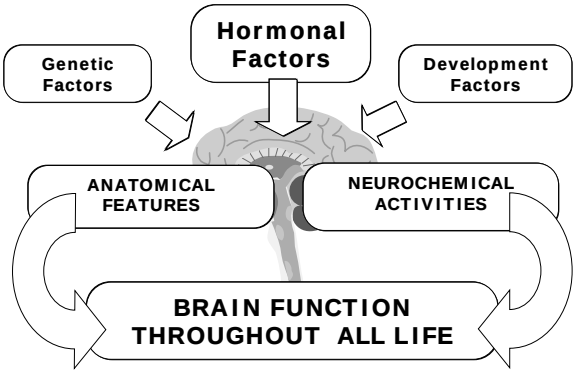
University of Pisa

Learning Objectives

- Basic principles of estrogen activity in the brain
- Cognitive Dismorphism and Steroids
- The role of Neuroactive steroids *vs* neurosteroids
- Cognitive function, Menopause and the Aging process: The role of ERT/HRT
  - Experimental Evidences
  - Clinical Evidences

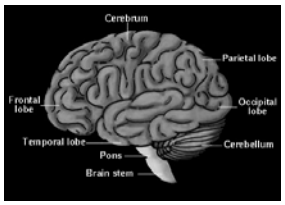
Brain Vulnerability



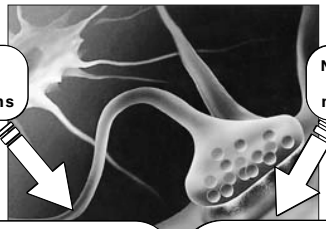
Hormonal Factors

Distribution of ER(α,β) PR(A,B) and AR in CNS

- Pituitary
- Hypothalamus
- Amygdala
- Hippocampus
- Cerebral cortex
- Olfactory bulbs
- Cerebellum



Mechanisms of Action of Steroids in the Brain



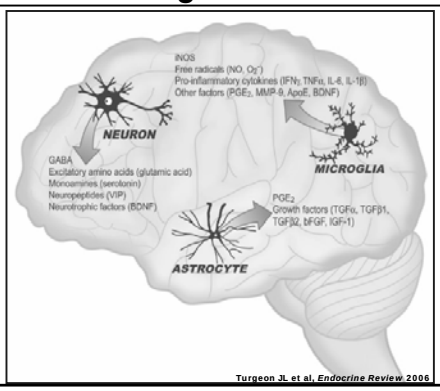
Genomic signaling mechanisms

Nongenomic signaling mechanisms

- Gene expression and new protein synthesis (GABA-A subunits)
- Relatively long latency of onset
- Medium- and long-term cell program
- Organization of cell networks for complex functions

- Activation / repression of pre-existing cell proteins
- Rapid onset of action
- Rapid adaptation to changes in the milieu
- Dynamic modifications of long-term cell program

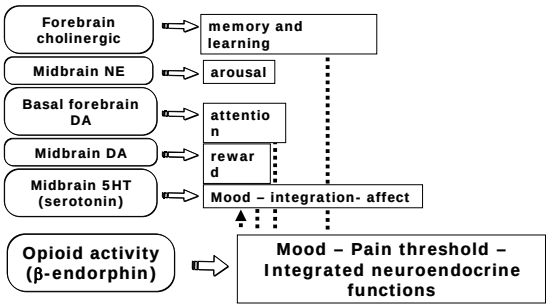
Cellular and Subcellular Estrogen Effects



Turgeon JL et al, *Endocrine Review* 2006

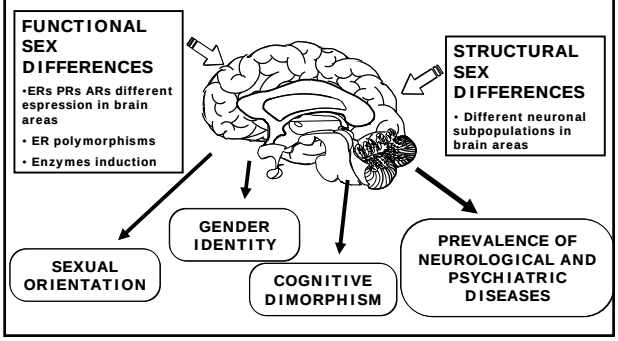
Neurotransmission and Brain Function

Role of Estrogen



The Brain and Sex Steroids

CNS Sexual Dimorphism



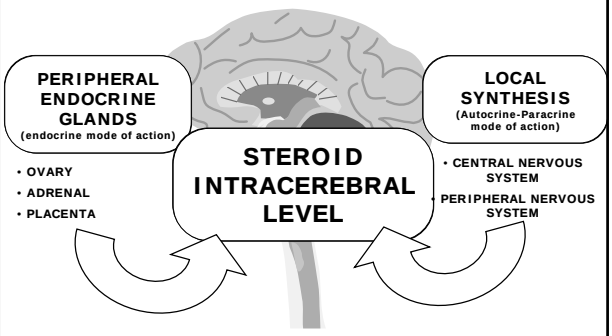
Cognitive Dimorphisms

- Compared to men, women tend to excel at
  - Verbal skills
  - Articulatory skills
  - Fine motor skills
- Compared to women, men tend to excel at
  - Visuospatial skills
  - Mathematical skills
  - Targeting skills
- Overall differences are small

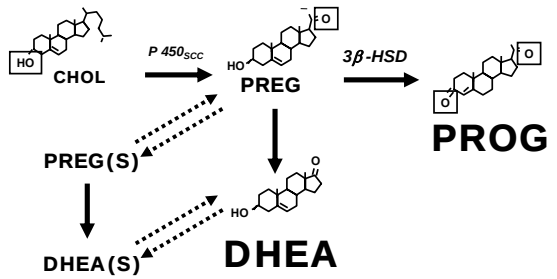
Putative Neuroprotective Effects of Estrogens (Basic Science)

- Modulation of neuronal growth and synaptic plasticity
- Reduced cell apoptosis
- Modulation of mithocondrial activity
- Antioxidant properties
- Modulation of brain immune system
- Reduced formation of β-amyloid
- Induction of tau protein
- Modulation of the ‘‘extrasynaptic volume transmission”

Steroids and Neurosteroids

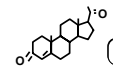


Biosynthesis of Progesterone and Androgens in CNS



Neurosteroids are steroids synthesized in the brain, de-novo from cholesterol or by metabolism of blood-born precursors

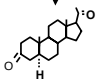
Metabolism of Progesterone in CNS



PROGESTERONE

Finasteride — *5α-reductase*

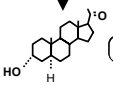
- Neurons
- Oligodendrocytes
- Astrocites type 1
- Astrocites type 2



5α-dihydroPROG

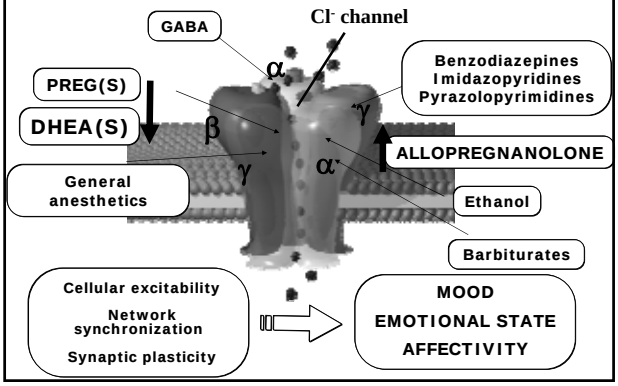
3α-HSD

Neuron-Glia CROSS TALK

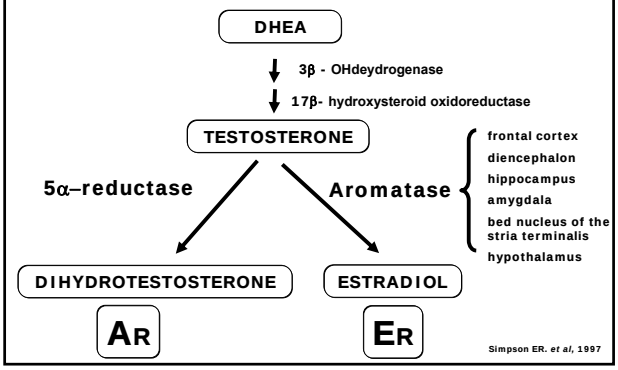


ALLOPREGNANOLONE

Neurosteroids and GABA-A

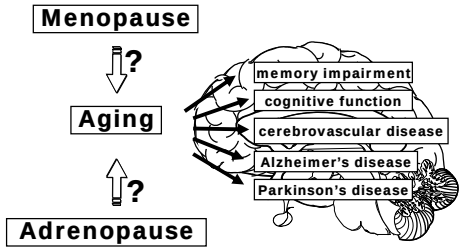


Androgens Metabolism in the Brain



Brain function and Menopause

Do sex steroids affect normal brain aging?

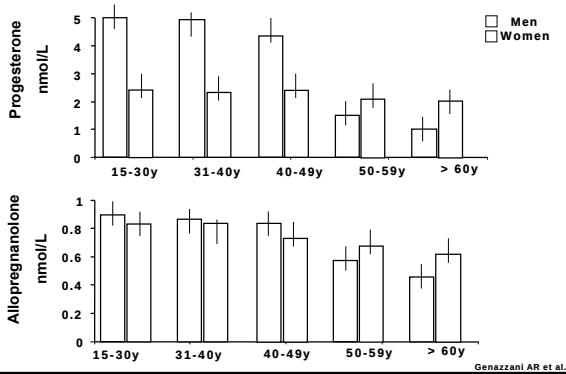


Estradiol, gender and age balances

Estradiol : **in > 60 y men : higher than in younger men**
in > 60 y men : higher than in untreated > 60 y women

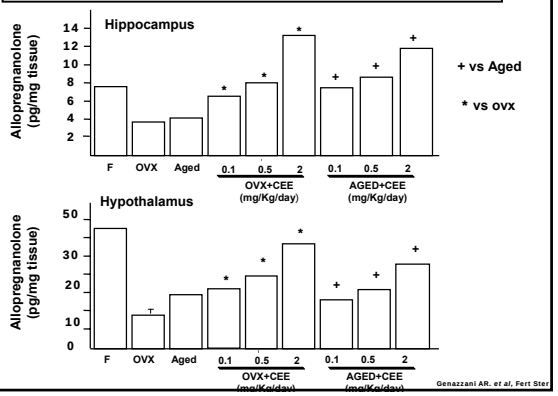
Vermeulen A, van Pottelberg I, 2002
Yaffe et al, 2002
Muller M, et al, 2003
M. Roger, N. Lahlou and E.E. Baulieu, 2003

Age-related changes in P and Allopregnanolone serum levels in human



Genazzani AR et al. 1999

Estrogens effects on Allopregnanolone in OVX and aged rats



Genazzani AR. *et al*, Fert Ster

Brain Vulnerability

SEX STEROIDS WITHDRAWAL

MECHANISMS ⇨ **SIGNS AND SYMPTOMS**

⇩ **CRH**

⇩ **POMC-related peptides**
⇩ **VASOPRESSIN**

⇩ **Central noradreneric system**
⇩ **Central dopaminergic system**
⇩ **Central serotoninergic system**

⇩ **GABA**

- **Irritability**
- **Anxiety**
- **Fear**
- **Depression**
- **Fatigue**
- **Psychosis**
- **Decreased Seizure Threshold**
- **Hot Flushes, Autonomic Hyperactivity**

Symptoms that Underline Brain Susceptibility to Estrogen-Androgen Deprivation

- Hot Flashes
- Sleep problems
- Climacteric Depression
- Decreased Sexual interest/activity

⇩

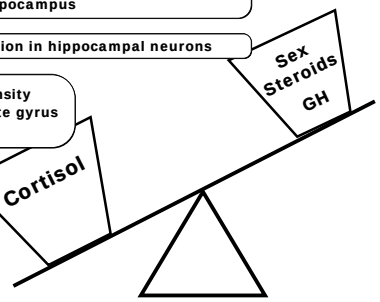
INCREASED RISK OF COGNITIVE IMPAIRMENT IN ELDERLY?

The age-dependent CNS imbalance

11βHSD type 1 increases conversion to cortisol in hippocampus

Long-Term potentiation in hippocampal neurons

- Hippocampal Spine Density
- Neurogenesis in Dentate gyrus
- Memory



Age-related reduced production of GH and sex steroids negatively affects the balance with cortisol in the brain.

Modified from Smith RG. et al. Endocrine Review 2005;

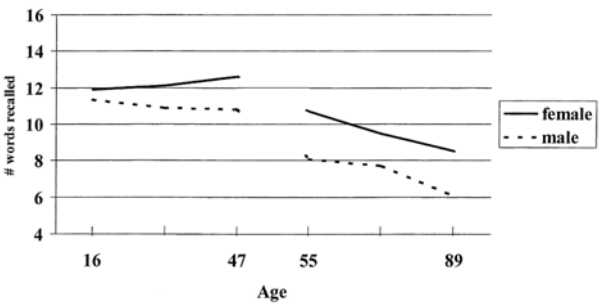
Negative relationship between cognition and age is only in postmenopause

Psychomotor Speed

Gestalt Completions

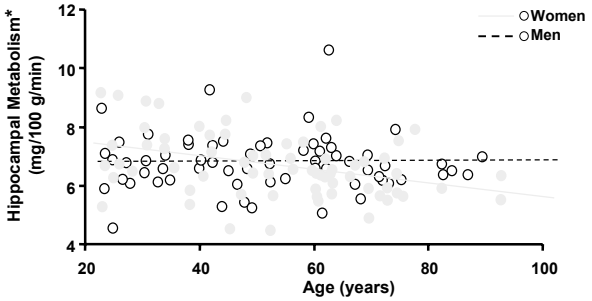
Halbreich et al. (1995). Possible acceleration of age effects on cognition following menopause. J Psychiatr Res. 29, 153-63

Verbal Memory Declines at Midlife



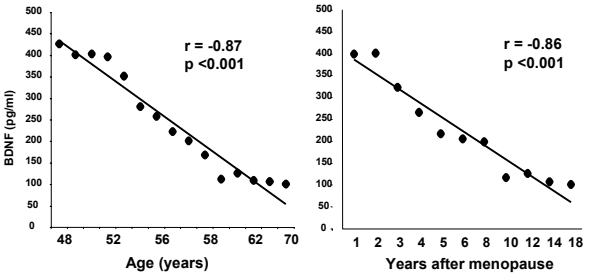
Kramer et al. (2003). Age and gender interactions on verbal memory performance. *J Int Neuropsychol Soc.* 9, 97-102.

Women Show a Decline in Hippocampal Glucose Metabolism With Age



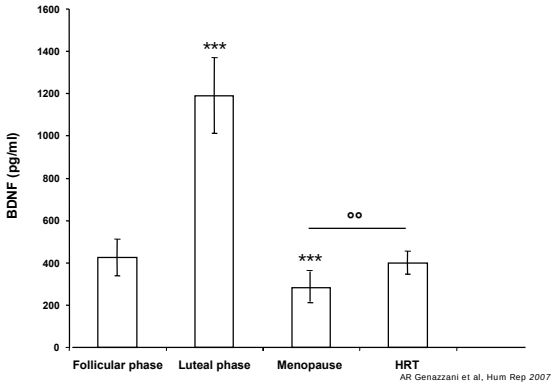
n = 65.
Adapted from Murphy DG, et al. *Arch Gen Psychiatry*. 1996;53:585-94. Used with permission.

BDNF in Postmenopausal Healthy Women



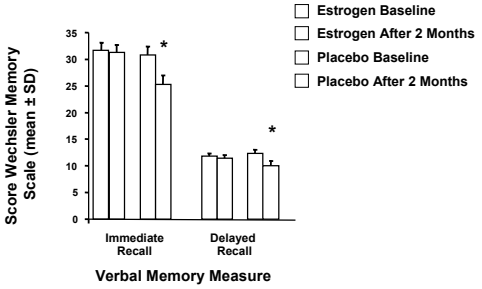
AR Genazzani et al, Hum Rep *in press*;

BDNF, menopause and HRT



AR Genazzani et al, Hum Rep *2007*

Surgical Symptomatic Menopause is associated with a significant decrease in verbal memory



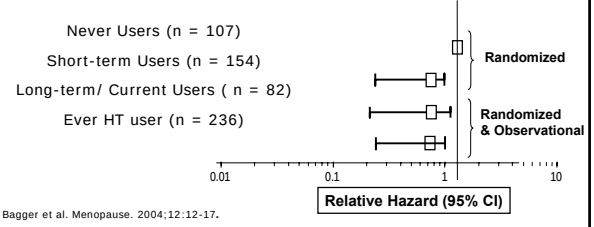
n = 19; mean age = 48
*Significant within-group difference at $P < .05$.
Phillips SM, Sherwin BB. *Psychoneuroendocrinology*. 1992;17:485-95.

Verbal memory is enhanced among younger women (< 65y) randomized to HT: Evidence from 6/6 RCTs

Author	N (All) Final ET/PI	Mean Age (SD or span)	Prior HT Use (%)	Menopausal Status/ Menopausal Symptoms/ Years since menopause[a]	Design	Dur
Hackman & Galbraith (1976)	(?) 18 (9/9)	29-68	?	8 surgically menopausal patients/ 10 patients with symptoms (4 mild and 1 moderate in ET group)/ Unknown yrs since menopause	Parallel (2 groups)	6 m
Sherwin (1988)	(53) 50[b]	45.4	Likely none	All surgical menopausal (BSO/TAH)/ Likely symptomatic from hysterectomy following baseline assessment/ No delay in intervention after surgical menopause	Crossover (4 groups)	3 m
Phillips & Sherwin (1992)	(31) 19 (10/9)	48 (5)	Likely none	All surgical menopausal (BSO/TAH)/ Likely symptomatic from hysterectomy following baseline assessment/ No time delay in intervention after surgical menopause	Parallel (2 groups)	2 m
Shaywitz (2003)	(60) 60 29/31	51.2 (32-64)	27% Used Postmenopausal HT	Postmenopausal/ 80% had menopausal symptoms/ Est. 3 yrs postmenopausal	Crossover	21 days
Krug (2003)	12 (12)[a]	58.6 (51-65)	42%	Postmenopausal/ Asymptomatic for at least 1 yr/ 9.1 yr since last menstrual bleed	Crossover	3 days
Linzmayer (2001)	(?) 49 16/17/ 16[b]	57 (46-67)	?	Postmenopausal at least 1 year/ Insomnia sleep disorder and moderate to severe menopausal symptoms on Kupperman Index (>15)/ Est. 6 yrs	Parallel (3 groups)	2 m

Risk of Cognitive Impairment: The Effect of Early Hormone Therapy Use

- 343 women received HT for 2-3 yrs in randomized, placebo-controlled trials
- Re-examined 5, 11, or 15 yrs after trial on Short Blessed Test



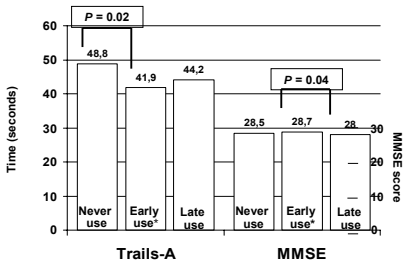
Bagger et al. Menopause. 2004;12:12-17.

Early HT: the REMEMBER pilot

Research into Memory, Brain function and Estrogen Replacement

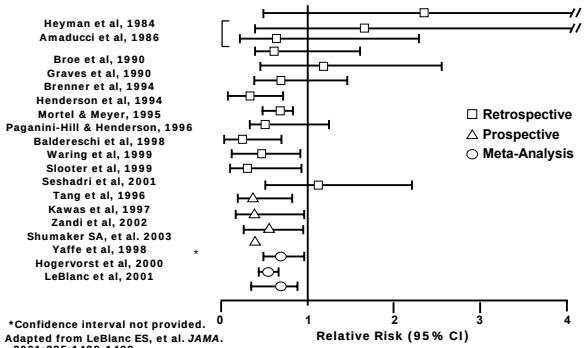
after: MacLennan AH et al, *Menopause* 2006;13:28-36

- Adelaide, Australia
- Random households; woman 60+ years; 428 agreed to interview and cognitive testing
- Compared to never-users of HT, tendency for early initiation to be associated with better cognitive scores and late initiation with worse scores; most differences NS



*Early use defined as before age 56 years (women with a uterus) or within five years of hysterectomy and oophorectomy

Observational Studies Show a Decreased Risk of AD in Hormone Therapy Users



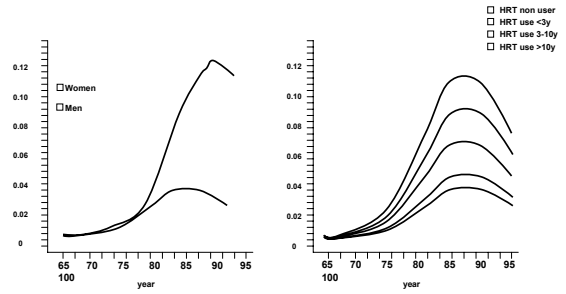
*Confidence interval not provided.

Adapted from LeBlanc ES, et al. *JAMA*. 2001;285:1489-1499.

Alzheimer's disease: differences between observational studies and WHIMS

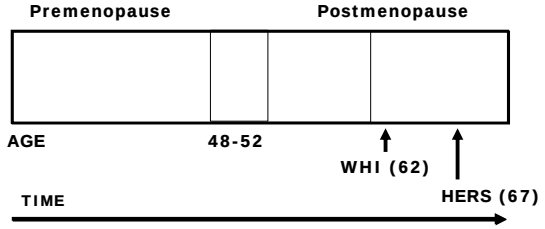
Factor	*WHIMS trial*	*Observational studies*
Susceptibility to bias	Small	Large
Primary outcome	All-cause dementia	Alzheimer's disease
Menopause symptoms	Uncommon	Common
HT formulation	CEE; continuous progestin	Often CEE; sequential progestin
Age at time of study	Older (65+ years)	Usually older
Timing of HT	Remote	Close to menopause
Age at HT exposure	Older (65+ years)	Usually younger

Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women The Cache County Study



Zandi PP et al, JAMA. 2002;288:2123-2129

Estrogen and cognitive function: A TIME-DEPENDENT FACTOR "The Critical Period Hypothesis"



Window of Opportunity for Neuroprotection

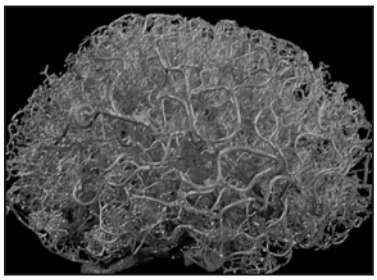
AR Genazzani *et al*, Hum Rep Update *2007*

Neuroprotective Effects of Estrogen Depend on the Age of the Animal

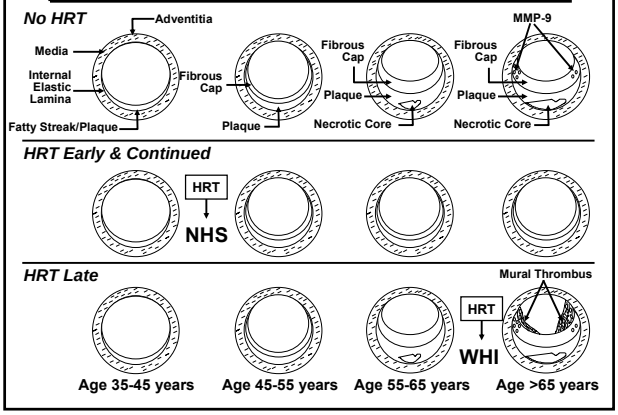
- Estrogen increases synapse density in young animals but not in older animals[1]
- In an animal model of amnesia, estrogen enhances memory in young-adult rats[2] and middle-aged rats[2,3] but not in older rats[3]
- These data indicate that aging processes may substantially modulate the mechanisms of estrogen action on the hippocampus and memory
- The data suggest that estrogen may be more effective in younger compared with older animals

[1]Adams et al. *Proc Natl Acad Sci U S A.* 2001;98:8071-8076.
[2]Markowska et al. *J Neurosci.* 2002;22(24):10985-10995.
[3]Savonenko et al. *Neuroscience.* 2003;119:821-830.

1/3 OF THE VOLUME OF THE BRAIN IS COMPOSED OF VESSELS



Hypothetical Pathogenetic Sequence



Timing of HT: Current trials

KEEPS (Kronos Early Estrogen Prevention Study)

Harman M, et al., http://www.clinicaltrials.gov/ct/show/NCT00154180

- **RCT, 720 women, ages 42-58, within 3 years of natural menopause, treated through June 2010**
- **Conjugated estrogens (0.45 mg/d) or transdermal oestradiol (50 mcg/wk) + vaginal progesterone gel**
- **Carotid IMT primary outcome; cognition secondary outcome**

***ELITE** (Early vs. Late Intervention Trial with Estrogen)*

Hodis H, et al., http://www.clinicaltrials.gov/ct/show/NCT00114517

- **RCT, 504 women, early group within ≤ 6 years of menopause, late group ≥ 10 years after menopause, mean treatment duration 3 years**
- **Oral estradiol (1 mg/d) + vaginal progesterone gel**
- **Carotid IMT primary outcome; cognition secondary outcome**

Estrogen and cognitive function: ADDITIONAL CLUES AND NEW DIRECTIONS

- **TYPE OF ESTROGEN** (mostly investigated CEE but not other molecules!)
- **DOSE** (low dose HRT and neuroprotection)
- **ROUTE OF ADMINISTATION** (oral vs transdermal: liver effects?)
- **THE PROGESTIN "STORY"**
- **THE ANDROGENS ROLE** in neuroprotection
- **GENETIC VARIANTS** (estrogen receptors and subcellural signals)

AR Genazzani *et al.* Hum Rep Update *2007*

Conclusions

- Short-term and long-term estrogen deprivation affect cognitive function
  - Effect of age on cognition accelerates after menopause
  - Early age of menopause is associated with poorer cognitive function
- Early estrogen therapy affect cognitive function
  - Positive evidence of effects on verbal memory from randomized trials in young women, follow-up RCT study
  - Biological plausibility from imaging studies and animal studies

ESHRE Pre-Congress Course 3
„Gender-specific medicine: redefining reproductive medicine“
Barcelona, July 6, 2008

„ Reproductive functions in the aging male“

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Institute of Reproductive Medicine
University of Münster
WHO Collaboration Centre for Research in Male Reproduction

The author has no conflict of interest to declare.

„Reproductive functions in the aging male“ -Learning objectives -

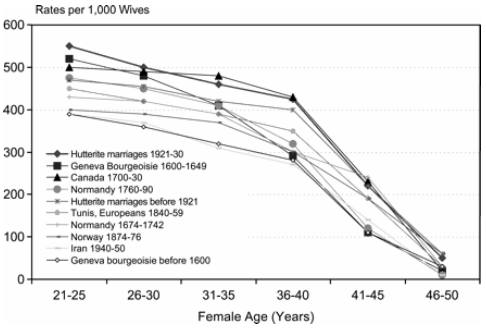
Human fertility and fecundity decline with age.
The female role in this process is well documented.
Does the male contribute to this phenomenon and if so to which extent ?

This lecture will explore the following issues
as possible contributors to declining male fertility:

- Spermatogenesis and sperm -
- Endocrine testicular function -
- Male mediated chances for pregnacy -
- Male mediated risks for abortion and miscarriage -
- Male mediated birth defects and inheritance of diseases -

Historic data on marital fertility rates (1600 – 1950).

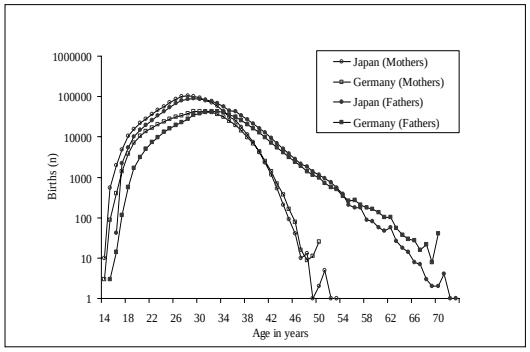
(Menken et al. Science, 233; 1389-1394, 1986)



F 1982

Age distribution of parents in Germany (n=550 659) and in Japan (n=1 135 222)

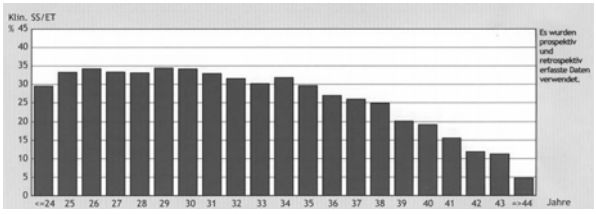
(Kühnert & Nieschlag Hum Reprod Update *10*, 327 – 339; 2004)



E1593E

Clinical pregnancy rate / embryo transfer following ICSI in relation to the women‘s age

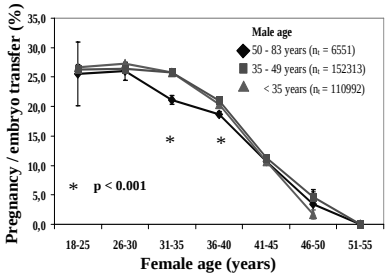
German IVF-Register DIR) 2005



I 362 E

Pregnancy / embryo transfer (%) in relation to the couples‘ age undergoing IVF or ICSI (German IVF Register 1998 - 2002)

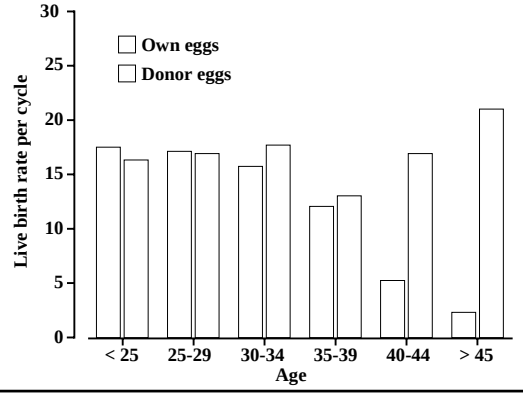
(Kühnert & Nieschlag, Hum Reprod Update 10; 327-339, 2004)



n_t =	43	380	149	2858	1626	143	11
n_t =	1168	13289	63413	62067	12019	349	8
n_t =	9871	42766	46586	10203	1508	58	0

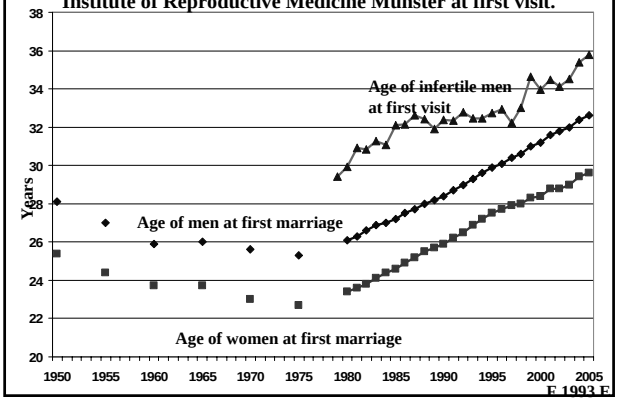
I 348

Live births per IVF cycle by age of the woman using own or donated eggs (HEFA data)

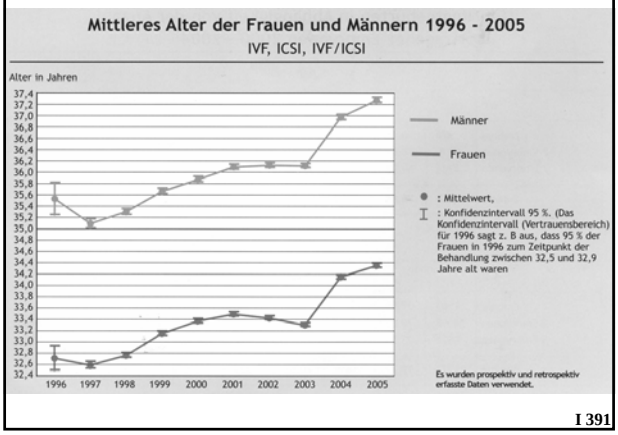


I 351

Mean age of men and women at first marriage in Germany and of infertile patients of the Institute of Reproductive Medicine Münster at first visit.



F 1993 E



I 391

„Reproductive functions in the aging male“

- **Spermatogenesis and sperm**
- **. Endocrine testicular function**
- **Chances for pregnancy**
- **Risk of abortions / miscarriages**
- **Birth defects and inheritance of diseases**

Testicular histology from 102 men over 90 years old

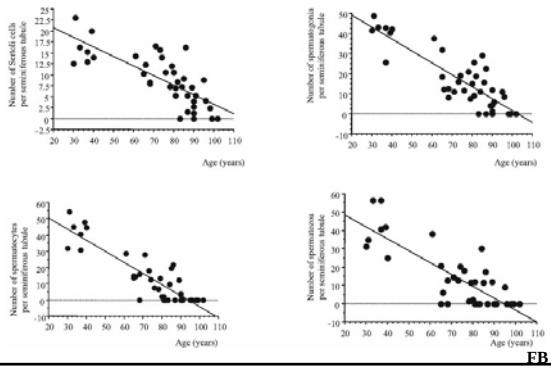
(Schlüter, Dissertation, University of Hamburg 1978)

	n
Normal histology	**27**
Reduced spermiogenesis, initial basal membrane thickening, reduced tubular diameter.	**35**
Severely reduced spermiogenesis, basal membrane thickening, tubular obliteration.	**40**

FB 67E

Number of Sertoli cells and germinal cells (spermatogonia, spermatocytes, spermatozoa) per tubule according to age

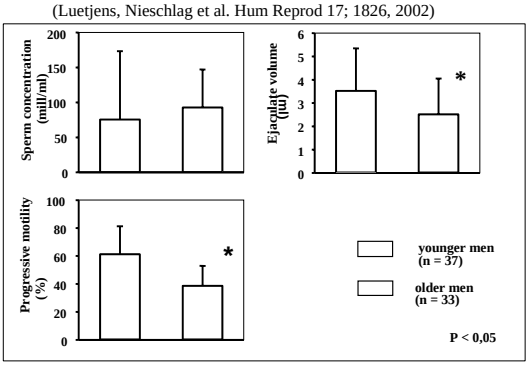
(Dakouane et al. Fertil Steril 83; 923-928, 2005)



FB 226

Semen parameters in younger (20-37 yrs) and older (60-88 yrs) healthy men

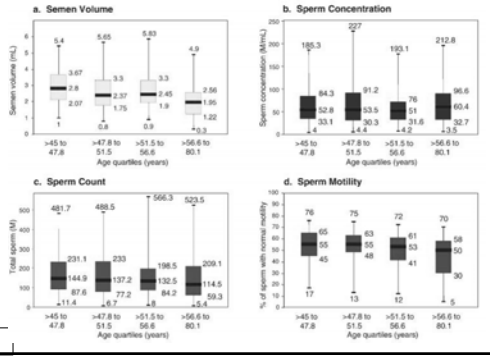
(Luetjens, Nieschlag et al. Hum Reprod 17; 1826, 2002)



FB173E

Semen parameters of 1177 men, on average 52.9 years old (range 45-80) recruited for a multicenter study on the effects of taladafil

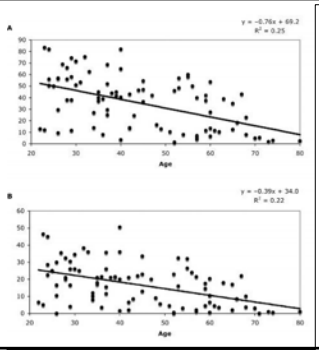
(Hellstrom et al. J Androl 27; 421-8, 2006)



FB 263

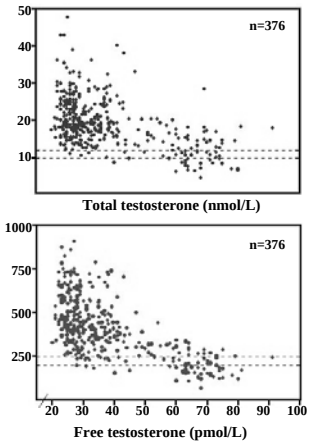
CASA determined sperm motility in 90 healthy men 22-80 yrs old

(Sloter et al. Hum Reprod 21; 2868-2875, 2006)



„Reproductive functions in the aging male“

- **Spermatogenesis and sperm**
- **. Endocrine testicular function**
- **Chances for pregnancy**
- **Risk of abortions / miscarriages**
- **Birth defects and inheritance of diseases**



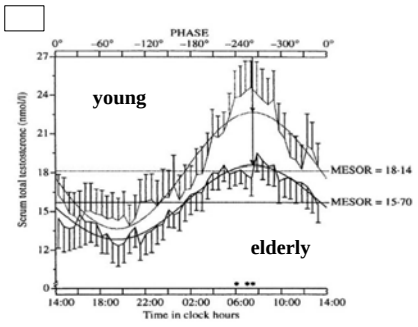
Total and free serum testosterone in 376 healthy men

(Zitzmann & Nieschlag Internist 44; 1313, 2003)

FB 197E

Circadian rhythm of serum total testosterone in 10 young (23-33 yrs) and 8 elderly men (55-64 yrs)

(Diver et al. Clin. Endocr. 58: 710, 2003)



FB 218

Late-onset hypogonadism (LOH)

Nieschlag et al. Int. J. Androl. 28:125-127, 2005: **Update 2008**

Definition A clinical ***and*** biochemical syndrome associated with advancing age and characterized by symptoms ***and*** a deficiency in serum testosterone levels (below the eugonadal young adult male reference range). This condition may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.

Diagnosis Clinical symptoms ***and*** total serum testosterone (T) (7.00 - 11.00 a.m.) ***plus*** free testosterone calculated from total T and SHBG.

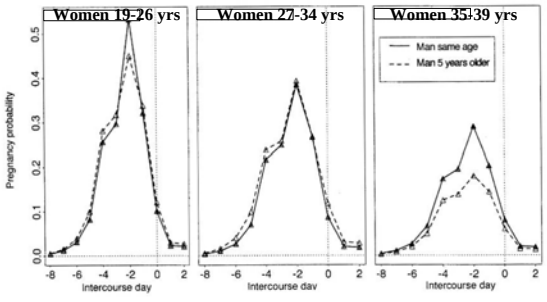
FE 666

„Reproductive functions in the aging male“

- **Spermatogenesis and sperm**
- **. Endocrine testicular function**
- **Chances for pregnancy**
- **Risk of abortions / miscarriages**
- **Birth defects and inheritance of diseases**

Probability of pregnancy for women with partners of same age or 5 years older

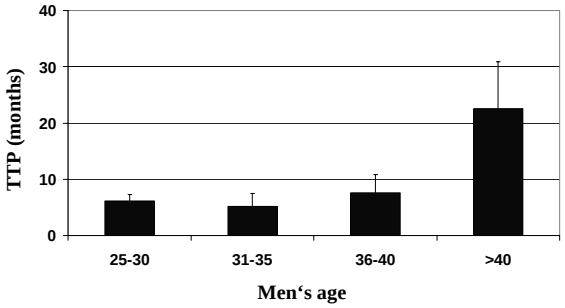
(Dunson et al. Hum Reprod 17; 1399, 2002)



F1807

Time-to-pregnancy (TTP) in women under < 25 years (n=638) in relation to the men‘s age.

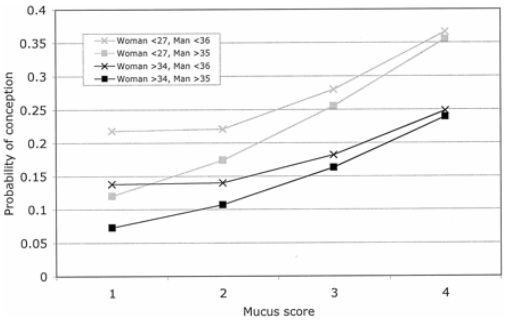
(Hassan & Killick, Fertil Steril 79, Suppl. 3; 1520, 2003)



FB 202

Probability of conception according to male age, mucus score, and female age assuming intercourse 3 days before ovulation on the most fertile day.

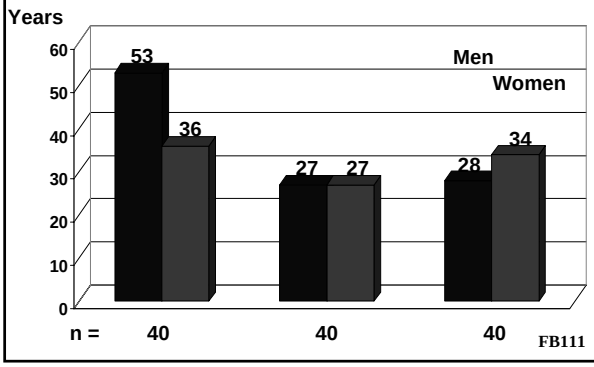
(Dunson et al. Obstet Gynecol, 105; 788-793, 2005)



FB 229

Comparison of older infertile couples with two groups of younger infertile couples: mean ages

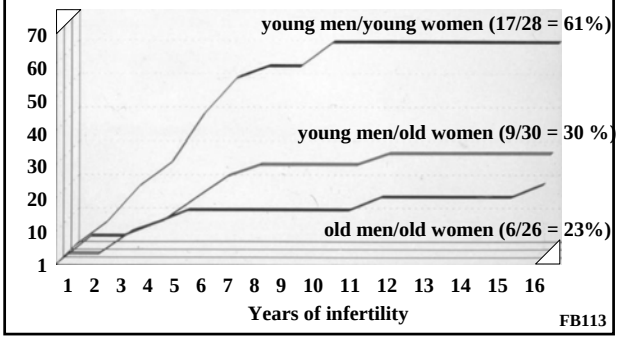
(Rolf et al. Int J Androl 19; 135-142,1996)



FB111

Cumulative pregnancy rates (%) in 3 groups of infertile patients attending the Institute of Reproductive Medicine in Münster

(Rolf et al. Int J Androl 19; 135-142, 1996)



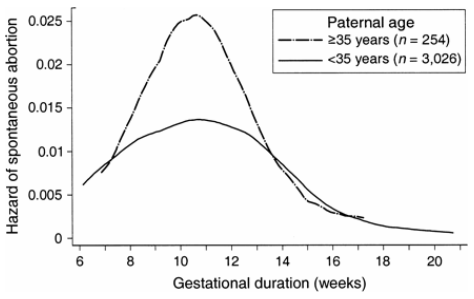
FB113

„Reproductive functions in the aging male“

- **Spermatogenesis and sperm**
- **. Endocrine testicular function**
- **Chances for pregnancy**
- **Risk of abortions / miscarriages**
- **Birth defects and inheritance of diseases**

Raw weekly hazard of spontaneous abortion according to gestational age, when the man was either under or over 35 years, among 3,280 Californian women under 30 years who were followed prospectively in 1990-1991.

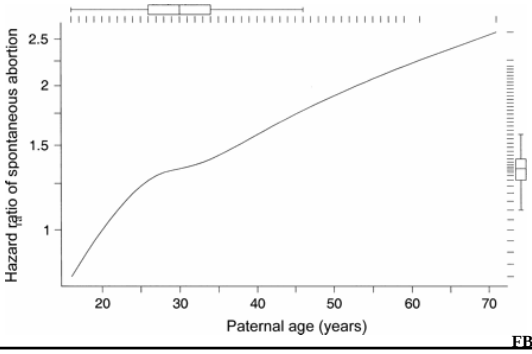
(Slama, R. et al. Am J Epidemiol 161; 816-823, 2005)



FB 231

Hazard ratios of spontaneous abortion according to paternal age, adjusted for maternal age, caffeine, alcohol consumption, and tobacco use, as well as paternal tobacco use, California 1990-1991 (5,121 women)

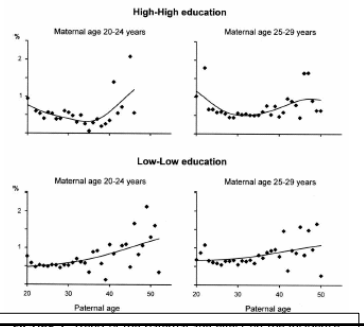
(Slama, R. et al. Am J Epidemiol 161; 816-823, 2005)



FB 230

Trend of paternal age effect on incidence of very preterm births (<32 weeks of gestation) by maternal age groups and couple education based on 1,510,823 births

(Astolfi et al. Epidemiology 17; 218-21, 2006)



Miscarriage risk for couples in different age groups.

Based on the European Infertility and Subfecundity Study (n = 3174)

(Rochebrochard & Thonneau, Hum Reprod **17;** 1649, 2002)

Maternal age

Paternal age	**20-29 years**	**30-34 years**	**35-44 years**
20-29 years			***high risk zone***
30-34 years	***standard risk zone***		**2.87 (1.86-4.45)**
35-39 years	**1.00 (reference)**		
40-64 years		***high risk zone***	***highest risk zone*** **5.65 (3.20-9.98)**

FB 205

„Reproductive functions in the aging male“

- **Spermatogenesis and sperm**
- **. Endocrine testicular function**
- **Chances for pregnancy**
- **Risk of abortions / miscarriages**
- **Birth defects and inheritance of diseases**

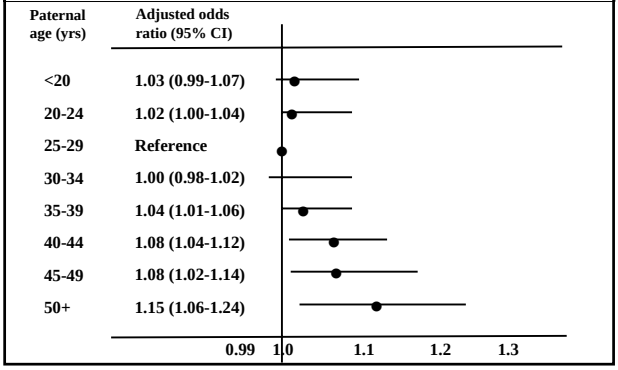
Cell divisions in gametogenesis

In the female:
From zygote to egg 24 divisions

In the male:
Until puberty about 36 divisions
Thereafter 23 divisions per year,
i.e. at 25 years ~ 310 divisions
at 50 years ~ 890 divisions
at 75 years ~ 1460 divisions

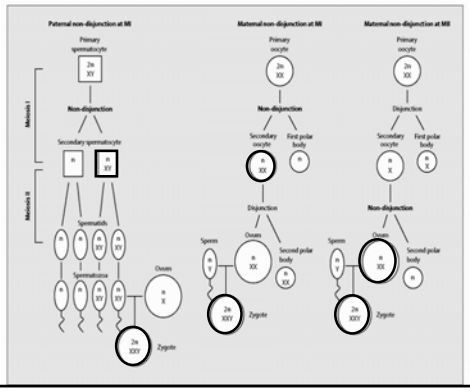
FB 128E

Relative risk of birth defects in 5,213,248 subjects depending on paternal age in USA (increased risk for cardiac, circulatory or respiratory defects, diaphragmatic hernia, tracheo-oesophageal fistulas, musculo-sceletal anomalies, Down's Syndrome)
(Yang et al. Hum Reprod 22; 696-701, 2007)



Etiology of the Klinefelter syndrome

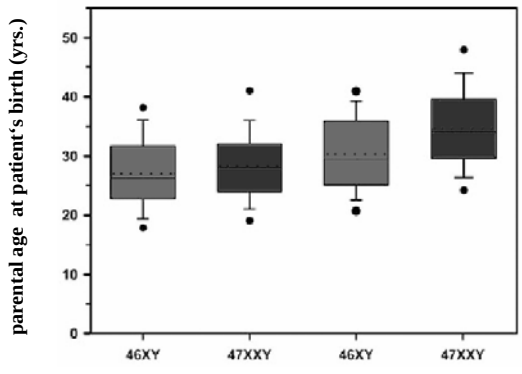
(Lanfranco, Zitzmann, Kamischke & Nieschlag, Lancet 364;273-283, 2004)



F 1950E

Parental age at patient‘s birth for 228 Klinefelter men (47,XXY) and 224 infertile men with normal karyotype □

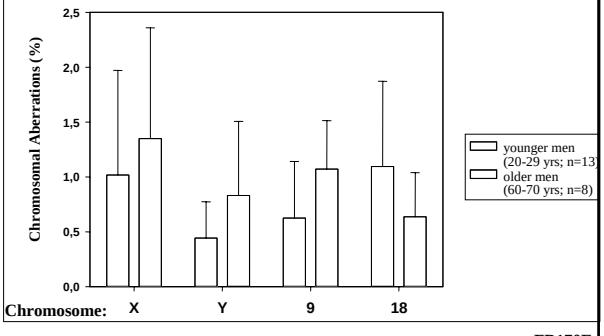
(Lanfranco et al. Lancet 364: 273-283, 2004)



F 1922 E

Frequency of chromosomal aberrations in sperm of 13 younger and 8 older men (mean +/-SD)

(Luetjens, Nieschlag et al. Hum Reprod 17; 1826, 2002)



FB170E

Frequencies of chromosomal abnormalities in postmeiotic cells of younger and older men with preserved spermatogenesis

	Chromosomal abnormalities	Younger men[a]	Older men[b]	Mann–Whitney statistical analysis
Subjects	—	10	14	—
Postmeiotic cells	—	4,882	4,738	NS
Nullisomy malsegregations	X0	20 (0.40%)	7 (0.15%)	NS
	Y0	1 (0.02%)	5 (0.11%)	NS
	O18	13 (0.27%)	8 (0.17%)	NS
Disomy malsegregations	XY18 (M I)	4 (0.08%)	7 (0.15%)	NS
	XX18 (M II)	2 (0.04%)	5 (0.11%)	NS
	YY18 (M II)	6 (0.12%)	6 (0.13%)	NS
	X1818 and Y1818	4 (0.08%)	11 (0.23%)	NS
	01818	1 (0.02%)	0 (0.00%)	NS
Diploidy meiotic arrest	XX1818 (M II)	2 (0.04%)	2 (0.04%)	NS
	YY1818 (M II)	1 (0.02%)	1 (0.02%)	NS
	XY1818 (M I)	0 (0.0%)	9 (0.19%)	NS
Total of aneuploidy	—	54 (1.1%)	61 (1.29%)	NS

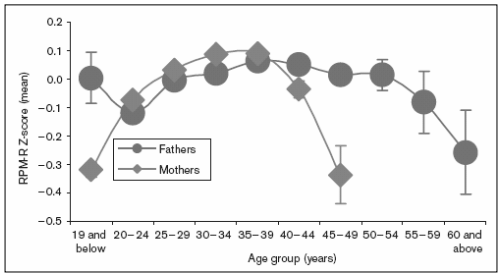
Note: M I = meiosis I; M II = meiosis II; NS = not significant.
[a] 29–40 years of age.
[b] 61–95 years of age.

Dokmanne. Study of testis from men 29–102 years old. Fertil Steril 2005.

FB 227

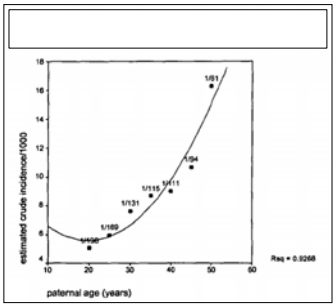
Influence of parents‘ age on childrens‘ intelligence (26.023 boys and 18.152 girls, 16-27 yrs old, tested by Raven‘s Progressive Matrices)

(Malaspina et al., Psychiatric Genetics 15; 117-125, 2005)



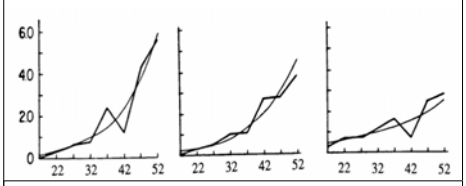
Relationship between paternal age and schizophrenia risk in 87,907 subjects born in Jerusalem between 1964 – 1976

(Malaspina et al. Arch Gen Psychiatry, 58; 361-7, 2001)



Relative frequency of affected children of normal parents as a function of paternal age

(Risch et al. Am J Hum Gen 41; 218, 1987)

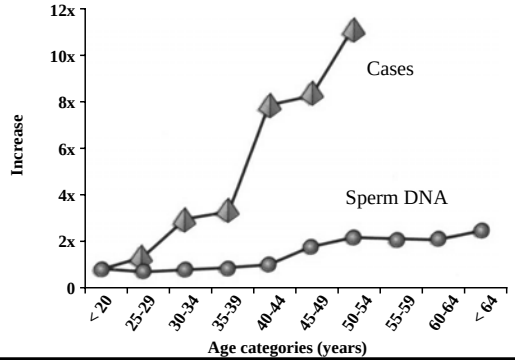


Apert syndrome	Achondroplasia	Neurofibromatosis
(n = 111)	(n = 152)	(n = 243)

FB129E

Increase of spontaneous cases of achondroplasia with paternal age and frequency of FGFR3 mutations in sperm

(Tiemann-Boege et al. PNAS 99; 14952, 2002)



FB204

Genetic abnormalities and advanced paternal age

Numerical chromosomal abnormalities:

- Aneuploidies not increased.
  (Trisomie 13 or 18, 45X0, 47XXY)

Structural chromosomal abnormalities:

- Slight increase in sperm,
  but not in fetuses or neonates.

Genetic mutations:

- Incidence of autosomal dominant diseases increases (e.g. Apert syndrome, achondroplasia, polyposis coli, hemophilia, neurofibromatosis).
- Abortions and very preterm births increase.

FB 125E

German social legislation: SGB V (2004)
(binding for mandatory, not for private insurances)

§ 27a Artificial Fertilization *(„Künstliche Befruchtung“)*

- **only for married couples**
- **only homologous gametes**
- **only for men and women > 25 years**
- **only for women < 40 years**
- **only for men < 50 years**
- **50 % of costs to be covered**

I 409 E

“Advanced paternal age is no indication for intensified prenatal diagnosis”.

Recommendations on Prenatal Diagnosis of the German Federal Medical Board, 2003.

FB 126 E

The End

E. Nieschlag - Literatur-Liste ESHRE Barcelona 2008

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