PRE-CONGRESS COURSE 4

SIG Endometriosis & Endometrium
"Abnormal uterine bleeding: strategies for management"

CONTENTS

PRE-CONGRESS COURSE 4 - PROGRAMME

SIG Endometriosis & Endometrium

Abnormal uterine bleeding: strategies for management

Course co-ordinators: H. Critchley (UK) & Th. D'Hooghe (B)

Course description: Problematic uterine bleeding impairs quality of life for many women and often involves invasive treatments and significant cost. Agreement is needed on terminology and defi nitions in order to facilitate the establishment of multi-centre clinical trials evaluating the strategies for management. Contemporary management also requires an understanding of the patient's perspective of her complaint and an understanding of acceptability to women of the available modes of investigation and treatment options. Optimal therapies will only be possible with a detailed understanding of the mechanisms involved in endometrial bleeding including unscheduled bleeding with exogenous hormone administration. Novel therapies need to be evaluated in the context of potential health benefits from therapies that reduce the number of menstrual cycles experienced by women. The course provides an opportunity for dialogue between clinicians, basic scientists and all professionals involved in the care of women with complaints of abnormal bleeding.

Target audience: The course content should appeal to clinicians, basic scientists and all professionals involved in the care and study of abnormal uterine bleeding from both the consumer and provider perspective.

Programme

09.00 - 09.30:	Abnormalities of menstrual bleeding: getting our terminologies right - ***I. Fraser (AUS)***
09.30 - 09.45:	*Discussion*
09.45 - 10.15:	Abnormal uterine bleeding: the patient perspective - ***P. Warner (UK)***
10.15 - 10.30:	*Discussion*
10.30 - 11.00:	***Coffee break***
11.00 - 11.30:	Optimising strategies for evaluation and management of abnormal uterine bleeding - ***A. Prentice (UK)***
11.30 - 11.45:	*Discussion*
11.45 - 12.15:	Unscheduled bleeding with exogenous hormone administration – ***P. Rogers (AUS)***
12.15 - 12.30:	*Discussion*
12.30 - 13.30:	***Lunch***
13.30 - 14.00:	Strategies to control; endometrial bleeding - ***D. Archer (USA)***
14.00 - 14.15:	*Discussion*
14.15 - 14.45:	Local mechanisms responsible for endometrial bleeding - ***H. Critchley (UK*)**

14.45 - 15.00: *Discussion*

15.00 - 15.30: ***Coffee break***

15.30 - 16.00: Is there a role for selective progesterone receptor modulators in management of uterine bleeding? - ***K. Chwalisz (USA)***

16.00 - 16.15: *Discussion*

16.15 - 16.45: Should menstruation be optional? – Health benefits of amenorrhoea - ***D. Baird (UK)***

16.45 - 17.00: *Discussion*

Abnormalities of menstrual bleeding: getting our terminologies right

Ian S. Fraser, MD

Professor in Reproductive Medicine,
University of Sydney

Occasional consultancy and lecture fees and expenses from Bayer Schering Pharma, Organon and Daiichi Pharmaceuticals

Learning objectives

- understanding of the current worldwide confusion with menstrual terminologies and definitions
- understanding of the need for consistency of terminologies for studying underlying mechanisms of abnormal uterine bleeding
- understanding the need for consistency for setting up multi-centre clinical trials
- a proposal for greater consistency and alternative terminologies in discussing symptoms, signs and causes of abnormal menstrual bleeding

Through the millenia, menstruation has been a taboo subject

- fraught with fears, misunderstandings, myths and discrimination against menstruating women
- heavily influenced by the male fear of this mysterious process
- highlighted by Pliny the Younger - and other writers over many centuries

Pliny on 'Menstruation'

PLINY (Second Century AD):

- Wine sours if they pass, vines wither, grass dies, and buds are blasted. Should a menstruating woman sit under a tree, the fruit will fall. A looking glass will discolour at her glance and a knife turn blunt. Bees will die and dogs tasting her blood will run mad.

Menstruation

"But to come again to women, hardly can there be found a thing more monstrous than is that bloody flux and course of theirs"

(Pliny, Second Century AD)

Terminologies have grown up reflecting this "secret women's business"

- professional male response was:
  - to formalise, sanitise and scientifically mysticise the process
  - use of terminologies with Greek & Latin origins:
    - menorrhagia; hypermenorrhoea
    - metrorrhagia
    - polymenorrhoea
    - polymenorrhagia (Latin-Greek hybrid)
    - oligomenorrhoea; amenorrhoea

Menorrhagia

- Greek: "to burst forth!"
  Latin equivalent: "hypermenorrhoea"
  - "excessively heavy"? or just "heavy"
  - regular intervals? irregular intervals?
  - prolonged bleeding?
  - normal or abnormal "pattern" of bleeding? -- the "shape" of the bleeding profile
  - **is this the woman's complaint or the physician's interpretation?**
  - first used by Professor William Cullen, University of Edinburgh, in the late 1700s

Woolcock et al 2008

The symptom of menorrhagia

"The physician's interpretation of the woman's description of her perception of her total menstrual flow"

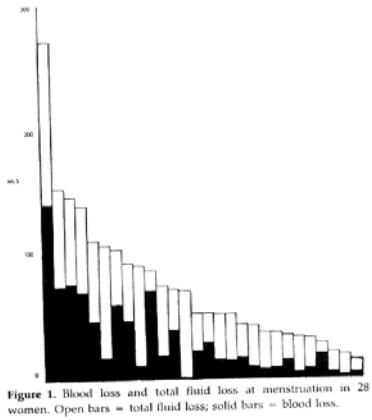

Figure 1. Blood loss and total fluid loss at menstruation in 28 women. Open bars = total fluid loss; solid bars = blood loss.

Blood and endometrial transudate as components of menstrual flow

(Fraser et al 1985)

Subjective assessment of DAILY menstrual blood loss (mL/24 hr)

	Mean (mL/24hr)	Range
❖ "spotting"	3	0.1 - 16
❖ light	9	0.1 - 63
❖ moderately heavy	18	0.5 - 109
❖ excessively heavy	25	1.4 - 216

❖ (Fraser et al 1984)

Clinical assessment of heavy bleeding

- ❖ how much does it matter to assess volume accurately?
- ❖ there is a spectrum of heavy bleeding from normal up to very heavy
- ❖ the condition associated with the heavy bleeding of "menorrhagia" is a complex of clinical symptoms
- ❖ issues of perception and tolerance are important in determining "complaint"
- ❖ decreasing tolerance of "normal" menstruation - desire for a "bleed-free" life

Dysfunctional uterine bleeding - a definition

❖ excessive bleeding (heavy, frequent or prolonged) of uterine origin, which is not due to complications of pregnancy, or to readily detectable pelvic pathology or systemic disease

- ❖ acute or chronic
- ❖ predominantly ovulatory or anovulatory
- ❖ a true endometrial or H-P-O dysfunction
- ❖ effectively a diagnosis of exclusion; but what do you exclude - and how?

Greatly differing definitions

	Menorrhagia	DUB
❖ USA	symptom, sign diagnosis (probably ≈ Ov. DUB)	anovulatory any abnormal bleed diagnosis or symptom
❖ Europe/ UK	symptom, sign	ovulatory or anovulatory diagnosis

Menstrual confusion

- ❖ inability to understand colleagues
- ❖ inability to critically interpret manuscripts
- ❖ inability to set up multinational clinical trials
- ❖ need for clarity and international agreement on standardization

Agreement process
Washington, DC; February 2005

- ❖ 35 invited "experts" from 16 countries
  - ❖ Co-chairs: Ian Fraser, Hilary Critchley, Malcolm Munro
- ❖ all have written extensively on relevant menstrual issues
- ❖ organized by The JL Company on behalf of the American Association of Health Centers
- ❖ concept supported by FIGO, WHO, ASRM, ESHRE, NIH, ACOG, RCOG, ECOG, RANZCOG
- ❖ Funded by a major unrestricted educational grant from Schering and TAP Pharmaceuticals

Intended outcomes

- ❖ internationally-based agreement on nomenclature for symptoms, signs and diagnoses
- ❖ should allow clinically and research-relevant classifications
- ❖ should allow robust structures for investigation - relevant to local technologies
- ❖ priorities for research should be identified
- ❖ should allow multi-national clinical trials
- ❖ should include quality of life considerations
- ❖ should be amenable to ongoing modification

Organization of the process

- ❖ modified Delphi process with specifically developed questionnaire
- ❖ discussion papers in advance
  - ❖ concept of the process
  - ❖ review of current confusion and practice
  - ❖ highlighting issues to be discussed
  - ❖ cultural issues
  - ❖ what is normal menstruation?
  - ❖ components of a clinical menstrual history

"Definition of menorrhagia"

- ❖ menorrhagia describes a symptom or sign and is NOT a diagnosis 64%
- ❖ menorrhagia is a diagnosis and NOT a descriptive term 14%
- ❖ menorrhagia can be a descriptive term OR a diagnosis 21%

Fraser, Critchley, Munro, Broder. Hum Reprod; Fertil Steril 2007

Plenary and subgroup discussions

- nomenclature, terminologies, definitions
- uterine structural anomalies classification
- endocrine and endometrial anomalies classification
- assessment of menstrual bleeding patterns
- approaches to investigation
- impact on quality of life and cultural issues
- electronic key pad responder system

Recommendations

- abolish confusing English language terminologies of Greek and Latin origin
- substitute simple, clear terms which women (and men) in the community can be expected to understand and which can be translated into any language

Fraser, Critchley, Munro, Broder. Hum Reprod; Fertil Steril 2007

Recommended terms - examples

- abnormal uterine bleeding (AUB)
- heavy menstrual bleeding (HMB)
- irregular menstrual bleeding
- prolonged menstrual bleeding

- (abnormal ovulatory bleeding)
- (ovulatory heavy bleeding)
- (anovulatory heavy bleeding)
- mechanisms currently unexplained
- idiopathic
- primary endometrial disorder

Defining menstrual bleeding

- regularity: absent, regular, irregular
- frequency: infrequent, normal, frequent
- duration: shortened, normal, prolonged
- volume: light, normal, heavy

- Limits to be defined by use of confidence intervals from population studies

Justification for abolishing use of the term "menorrhagia"

- a confusing term of Greek origin which most physicians use to describe some aspect of "heavy menstrual bleeding"
- used solely as a symptom or sign in most parts of the World
- used solely to describe regular heavy bleeding in USA
- used as a diagnosis in USA
- encompasses regular and irregular bleeding elsewhere
- encompasses prolonged bleeding for some (not always heavy)
- conveys sense of excessively heavy bleeding for physicians
- often encompasses just "heavy" bleeding for most women
- women in most countries do not understand "menorrhagia"

Justification for abolishing the term 'dysfunctional uterine bleeding'

- a diagnosis of exclusion and admission of ignorance
- terminology used very differently in different countries (symptoms, signs, diagnoses)
- research has defined two conditions
  - anovulatory DUB (a primary H-P-O dysfunction)
  - ovulatory DUB (a primary endometrial dysfunction)
- recommended that these disorders be simply called:
  - anovulatory heavy menstrual bleeding (AHMB)
  - ovulatory heavy menstrual bleeding (OHMB; or, once local and systemic pathologies have been excluded, "primary endometrial HMB", or perhaps "PEB")

Recommended outline of a simple classification of causes

- need for a robust and clinically relevant, but simple, classification of causes
- but, what is clinically important?
- and how does it vary from place to place?
- supplemented by a much more detailed research-relevant classification

Research

- it has become clear that there is much research to be done to clarify the identified gaps
- ongoing process
- flexible, "living" documents
- precedent of 'FIGO Oncology Staging process'
- need for "testing" these terminologies
- will need much specific continued funding
- FIGO Menstrual Disorders Study Group

DUB and menorrhagia - or whatever we call them - continuing challenges

- clinical assessment
  - including assessments of volume of flow and prognosis
- potential for precision in diagnosis
  - imaging, endoscopy and biopsy
- information and counselling
- evidence-basis for trials and treatment
  - new and older therapies; observation alone
  - new medical, procedural and surgical
- long duration of treatment needed
- treatment failures - 'risk' of hysterectomy

The future

- ❖ are you prepared to discard your use of familiar and favourite terms?
- ❖ and embrace something simpler - and clearer?
- ❖ and, will it help?

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Abnormal uterine bleeding: the patient perspective

Pre-conference Course
AUB: Strategies and management
ESHRE 2008, Barcelona

Pamela Warner, PhD

Centre for Public Health and Primary Care Research,
Division of Community Health Sciences,
University of Edinburgh

Objectives

This lecture will cover:

- Patient perspective on AUB (and HMB) - *illustrated with examples from recent research studies*:
  - Factors related to complaint and to seeking help
  - Experience of and satisfaction with healthcare
- Reflection on the need for systematic accumulation of clinical evidence base regarding patient perspective and outcome of health care

Structure

1. AUB and the patient perspective
2. Illustration of issues using recent research findings
3. Reflection on enabling systematic incorporation of patient perspective into management of AUB
4. Summary/discussion

1. AUB & the patient perspective

What does AUB encompass?

- Change in menstrual pattern/ volume
- Heavy menstrual bleeding (HMB)
- Post-menopausal bleeding
- Post-coital bleeding
- Bleeding on Tamoxifen *(taken for prevention of recurrence of breast cancer)*

Patient perspective on AUB

Symptoms may be

a minor inconvenience	⟷	**intolerable burden**
untroubling to patient	⟷	**cause of concern**

Clinician perspective on AUB

Symptoms might be a sign of

No organic disease	Benign disease	**Serious disease**

Women presenting with HMB are not at high risk of serious disease, but….

- Their symptoms of HMB can nevertheless be *intolerable….*
- Each year 5% of a GP's female patients in the 30-49 age group will consult for heavy menstrual bleeding (HMB)
- HMB affects approximately 880,000 women in the England

Heavy menstrual bleeding

- Defined ***by NICE*** as excessive menstrual blood loss **affecting quality of life**:
  - physical
  - emotional
  - social
  - material
- Can occur alone or **in combination** with other symptoms
- Socio-cultural factors may be implicated in the woman's ***response*** to HMB

http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf

Therefore, NICE:

- Defines HMB:
  - in terms of impact on quality of life,
  - **not** in terms of *volume* of menstrual blood loss
- High-lights the importance of **individual factors** in the woman's reaction to her HMB…

Questions:

- Do we know how to ascertain the **patient perspective** on her HMB?
- Do we understand how **individual factors** are associated with experience of/response to HMB?
- Do we know how the patient's perspective can best be translated into optimum management of HMB?

2. ILLUSTRATION OF ISSUES FROM RECENT RESEARCH

presented in relation to

patient perspective/ individual factors

Menorrhagia study

Setting: Gynaecology outpatient clinics at 3 hospitals in Edinburgh & Glasgow

Participants: Women aged 25-49 years, newly referred for **menstrual problems** (n=952)

Design: **1**. Cross-sectional questionnaire survey
2. Embedded menstrual loss measurement study
3. Case note review follow-up

Funded by the Chief Scientist Office for Scotland

Recruitment

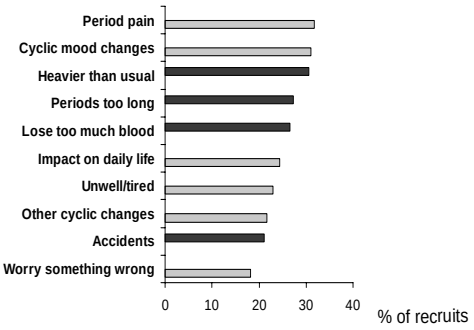
	n
Study discussed	1370
Consented to participate	1320 (96%)
Basic questionnaire at least	952 (72% of 1320)
Menstrual collection	226 (26% of 865)
Follow up after 8 months	665 (89% of 748)

- **The nature of the referral for HMB**

Among 342 women referred to GOPD clinic and rating their periods 'very heavy':

- Only 46% state that the volume of blood loss is a severe problem
- Only 35% state that volume of blood loss is cause of help-seeking

Menstrual aspects rated a 'severe problem' (n=947)



Further illustrations

Reflection

- Is the GOPD clinic patient's complaint solely HMB?
- Or even mainly HMB?!

- **Impact of HMB on quality of life (QoL)**

What is meant by quality of life?

'Quality of Life' Measure	Description
Generic QoL	Very broad ranging, encompassing satisfaction with life, opportunities, housing/environment etc
Health-related QoL *eg SF-36*	Addresses physical/ emotional/ social well-being, including ability to undertake daily activities and absence of discomfort/distress
Disease-specific QoL *eg UFS-QoL (Spies 1999)*	Severity of symptoms (typical *of the specific condition*) and impact on activities of daily life and emotional well-being
Symptoms/impact qu. *eg Ruta 1995, Shaw 1998, Warner 2001, 2004*	Severity of symptoms and possibly also impact on activities of daily life and emotional well-being

Illustration from research

Reflection

- HMB is defined ***by NICE*** as excessive menstrual blood loss **affecting quality of life…**

but perhaps this should be

- 'HMB' is considered to be *report* of heavy periods *in combination with* **poor quality of life**

- **Relevance of socio-cultural factors**

What is meant by 'socio-cultural factors'?

Socio-cultural factor	How can this be 'measured'?
Personality	Personality scale (eg NEO)
Material circumstances	? Deprivation code (post code)
Environment (home/ work)	? Direct questions
Attitudes to periods/ health…..	? Direct questions

➢ Home and work

Management of periods: home

- 81% have nowhere suitable to soak bloodstains
- 75% have no toilet separate from the bathroom
- 26% report that others in the home complain about her periods

Management of periods: work

- 59% have a job involving a lot of standing
- 57% say frequent trips to the toilet are noticed
- 50% say absence because of periods is disapproved of
- 35% say it is hard to get away from her post to change

Health 'style'

- Self-perceived general health
- Tendency to worry about health
- Sensitivity to pain
- Preferred way of interacting with doctor

Trial of Outpatient Methods of Endometrial Evaluation (OMEE)

Randomisation of women referred to GOPD for AUB, to various combinations of:

- Visualisation – by means of…
  - *hysteroscopy*
  - *transvaginal ultrasound*
- Biopsy – by means of…
  - *Pipelle*
  - *Tao brush*

Funded by the UK Health Technology Assessment programme

Randomisation within subgroups stratified by risk

- High Risk - post menopausal
- Moderate Risk – premenopausal, but…
  - *either* **aged 40 years and over**,
  - *or* younger but **with specific risk factors**
- Low Risk – premenopausal, age under 40 years and without specific risk factors

Measures completed by patients

Timing	Measure
Recruitment	**Health Questionnaire** **NEO personality inventory** **General Health Questionnaire (GHQ)**
Post-investigation	Clinic visit 'report' 'Report' for each investigation Review of clinic attendance (48 hrs)
Follow-up	Follow-up questionnaires (10 m & 2y)

Recruitment

Risk Grp	Recruitment Target	Participation (% of eligible)	Recruitment n (% of target)
High	200	67%	200 (100%)
Mod	400	69%	326 (81%)
Low	300	60%	157 (52%)
		TOTAL=	**683** patients

Study Patients

	RISK GROUP		
	High	Moderate	Low
	%	%	%
Presenting complaint :			
Post-menopausal bleeding	95	2	0
Postcoital bleeding	2	8	10
Heavy periods	**1**	**68**	**57**
Intermenstrual bleeding	**2**	**22**	**27**
Irregular periods	**5**	**47**	**46**
Previous bleeding complaints			
Postmenopausal bleeding	8	1	0
Heavy periods	**5**	**23**	**13**
Irregular periods	**4**	**12**	**14**

Illustrations from research

➢ Personality

NEO personality scales

Label	Description of high scorers
N neuroticism	experience negative feelings
E extraversion	sociable, assertive, outgoing
O openness	intellectually curious, experience emotions keenly
A agreeableness	co-operative, trusting
C conscientious	reliable, over-fastidious

What were the associations of health 'style' with personality?

Higher **Neuroticism** score ↔

- Sensitivity to pain
- Worry about health
- Think something seriously wrong
- Bleeding worrying

Higher **Extraversion** score ↔

- *Not* sensitive to pain
- *Don't* worry about health
- Likes to be told as much as possible

➢ Psychological well-being

GHQ (psychological well-being)

Scale	Description
A	Somatic symptoms
B	Anxiety
C	Social dysfunction
D	Depression

Associations of GHQ patient health 'style' with

- Severer **GHQ Total** & **Scale A** (Somatic) Score ↔
  - Judge own health worse than others
  - Sensitive to pain
  - Worry about health & Think something seriously wrong
  - Find bleeding symptoms worrying
  - Likes to be told as much as possible about condition
- Severer **Total GHQ** Score ↔
  - Likes to be given choice
- Severer **GHQ Scale A** ↔
  - Bleeding likely to be cancer

- **Deprivation**

Illustrations from research

- **What does all this mean for satisfaction with care?**

OMEE: outcome at follow-up
for <u>Moderate Risk</u> (*menstruating*) **women**

- Symptoms ***not*** *'much improved'* for:
  - over 50% of women, at 10 months &
  - over 33%, at 2 years
- Over 25% at both follow-ups reported their problem had ***not been cured***

Illustration from research

Rating clinic visit worthwhile was associated with:

- Symptom presentation –
  - Not worried about symptoms
  - Not intolerable
- Good GHQ Total and GHQ A scores (i.e. low)
- Low Neuroticism (personality) score
- Like to be told about condition & Understood what doctor said
- Did not wish for more investigation

Reflection

- We need to distinguish better between those seeking:
  - symptom relief
  - reassurance/ exclusion of serious disease
- We should try to improve explanations given
- Many individual factors are associated in different ways with response to care for HMB…. Do *all these* need to be measured?

3. Incorporating patient perspective into management of AUB

If we are to build up an evidence base regarding incorporation of patient perspective into management of HMB, then:

- We need standardised relevant assessment of:
  - HMB
  - Any key associated factors
- Clarity as to how key factors are to be integrated into definition/management of HMB, and evaluation of outcome

Comment

- It is unlikely that any QoL measure could be used as a tool to assess *need for care* in a patient, since a QoL score is too confounded by
  - patient's general quality of life and broader health
  - patient's socio-cultural factors.
- Nevertheless QoL scores can be very useful if applied as within-patient 'before and after measures' in treatment trials, and indeed have been used in this way with some success

Factor analysis of questionnaire responses, separately for:
(i) factual statements, &
(ii) feelings about symptoms

Symptom Factors	'Feelings' factors
Impact of volume	Containment Distress
Variable Flow	Periods a burden
Resource issues	Worry about change
Loss of well-being	Resent resources used
Unpredictable onset	Had enough of periods

For three of the factors: indication of the statements contributing to them

Symptom	Factors	'Feelings' factor
Variable Flow	**Impact of volume**	**Containment Distress**
Flow pattern unpredictable	Limit where I go	Accidents upset me
Heaviness varies period to period	Plan life to avoid outing during period	Worry all the time re changing
Period goes on too long	Limit what I do	Leaks are embarrassing
Never sure when finished	Cancel activities	Worry about leaks
Changed form normal	Rest during full flow	Annoyed re clothes
	Can't prevent accidents	Dread difficulty of containing flow

Illustrations from research

Reflection

- Descriptive sub-typing might form a useful basis for the consultation, and hence facilitate
  - discussion and decision-making with a patient about treatment options
  - well-focussed follow-up discussion of effect of any treatment tried
- If these sub-typing scores are recorded/ accumulated, then a body of data would build up that might in due course lead to insights as to mechanisms for specific patterns, and hence improve treatment and prognosis

4. Summary

- For patients attending GOPD, symptom relief seems be more important than reassurance
- Strong suggestion of effect on 'satisfaction' due to
  - Personality
  - Psychological 'well-being'
  - Self-rated health 'style'
- Pure QoL scale scores are non-specific to heaviness of menstrual bleeding, and to patterns
- There might be value in delineating descriptively the patient's perspective on AUB complaint

For discussion

- How can patient perspective on HMB be assessed?
- Would descriptive characterisation of HMB complaint have potential for:
  - Helping clinicians optimise clinic experience and 'satisfaction' of patients presenting with HMB? *(and if so, how far should this be taken?!)*
  - Improving design of research to increase power to evaluate interventions?

With thanks to all the women who have participated in the research studies, co-investigators and research staff, and to our funders:

- Contemporary menorrhagia complaint (1999)
  Warner P, Critchley HOD, Lumsden MA, Campbell-Brown M
  CSO
- Outpatient methods of endometrial evaluation (2003)
  Critchley HOD, Warner P, Williams A, Chambers S
  UK R&D HTA
- Heavy menstrual bleding in the community (2004)
  Santer M, Warner P, Wyke S
  MRC Fellowship to M Santer

Some references

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Dr. Andrew Prentice was unable to send in his presentation.

If you send an e-mail to ap128@mole.bio.cam.ac.uk, Dr. Prentice will be happy to send you a pdf file of his presentation.

MONASH INSTITUTE OF MEDICAL RESEARCH

Unscheduled bleeding with exogenous hormone administration

PETER A. W. ROGERS, PhD

Centre for Women's Health Research

Department of Obstetrics and Gynaecology
Monash University
Melbourne, Australia

Commercial relationships and potential conflicts of interest: Nil

MONASH INSTITUTE OF MEDICAL RESEARCH

Learning Objectives

Unscheduled bleeding with exogenous hormone administration

Definition of unscheduled bleeding
The extent of the problem
The effects of progestin exposure on endometrium
Local endometrial mechanisms that may be involved
The effects of progesterone on endometrial blood vessels:
- **endothelial cells**
- **smooth muscle cells**

MONASH INSTITUTE OF MEDICAL RESEARCH

ABNORMAL UTERINE BLEEDING WITH EXOGENOUS HORMONE ADMINISTRATION

Progestin-only contraception
Combined-continuous HT
→ **Continuous progestin +/- estrogen**

Cyclical HT → **E plus 14 days P**

Cancer
Hyperplasia
Polyps
Fibroids
Endocrine disorders
→ **Varied endocrine background**

MONASH University

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World Health Organisation (WHO) definitions of abnormal menstrual bleeding patterns based on a daily record taken for 90 days:

Amenorrhea – no bleeding or spotting

Prolonged bleeding – at least 1 bleeding/spotting episode lasting 10 days or more

Frequent bleeding – more than 4 bleeding/spotting episodes

Infrequent bleeding – fewer than 2 bleeding/spotting episodes

Irregular bleeding – range of lengths of bleeding/spotting-free intervals >17 days

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PROGESTIN-ONLY CONTRACEPTION

Estimated 20+ million women users worldwide

Depot-medroxyprogesterone acetate (DMPA) – 13 million

Norethisterone enanthate (NET-EN) – 1 million

Norplant; levonorgestrel implant – 6 million

Mirena; levonorgestrel IUD – 1 million

Implanon; etonogestrel

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PROGESTIN-ONLY CONTRACEPTION

Highly effective
Easy to use
Cheap
Long acting
Safe

MAJOR SIDE EFFECT

Menstrual bleeding disturbances

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PROGESTIN-ONLY CONTRACEPTION AND BTB

BTB problems worst during first year
(10-30% women will discontinue use because of menstrual issues)

Norplant users in year 1:

Average 92.3 bleeding/spotting days

26% amenorrhea
25% regular monthly bleed
15% prolonged bleeding

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BTB MECHANISMS

No clinically useful correlation between:

Bleeding pattern – prolonged to amenorrhea

Endometrial appearance – atrophic, progestogenic, secretory…

Peripheral estrogen – undetectable to mid-proliferative

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BTB WITH PROGESTIN-ONLY CONTRACEPTION

Incidence of BTB highly variable but can be associated with:

↑ circulating estrogen	Hadisaputra et al, 1996
↑ endometrial macrophages	Clark et al, 1996
↑ hydroxyeicosatetraenoic acid	White et al, 1991
↑ von Willebrand factor	Au et al, 1994
↓ endometrial perivascular cells	Rogers et al, 2000
↑ vascular fragility	Hickey et al, 2000

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BTB:
FOCUS ON LOCAL ENDOMETRIAL MECHANISMS

- **Vascular density**
- **Epithelial integrity**
- **Blood clotting mechanisms**
- **Leukocytes**
- **Tissue breakdown/MMP's**
- **Vessel fragility**

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ABNORMAL UTERINE BLEEDING

Comparison of normal versus continuous progestin-exposed endometrium

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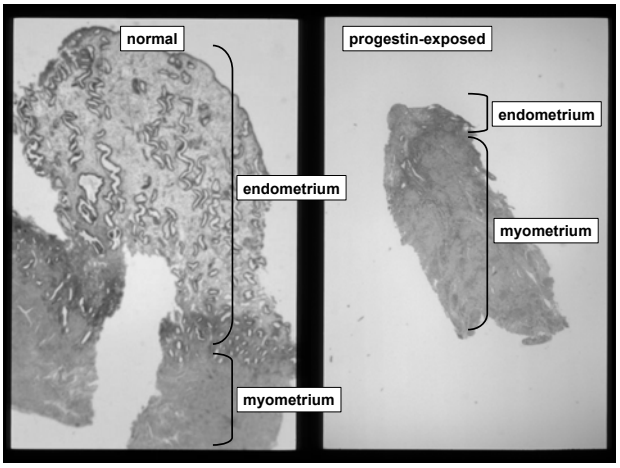
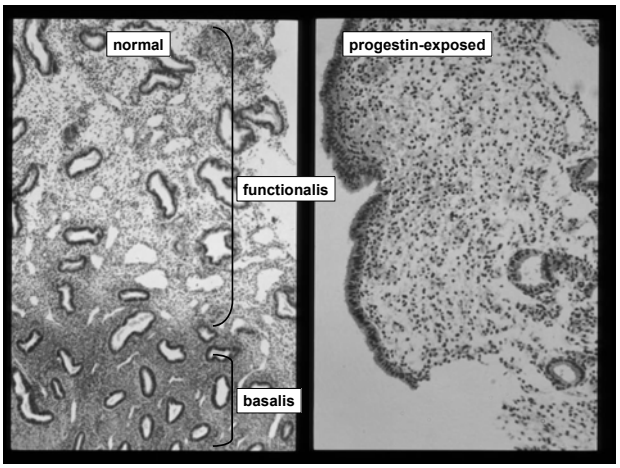
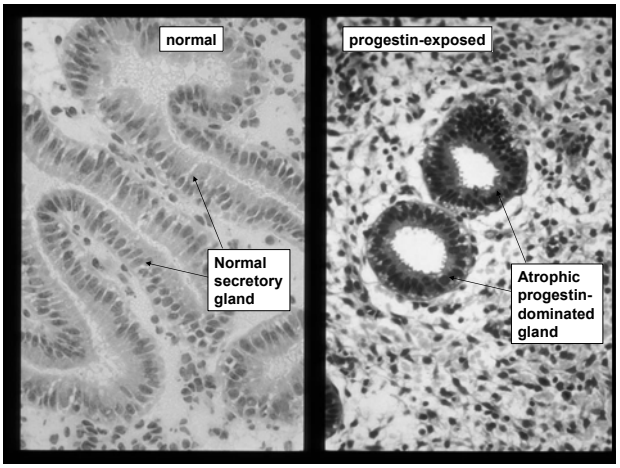
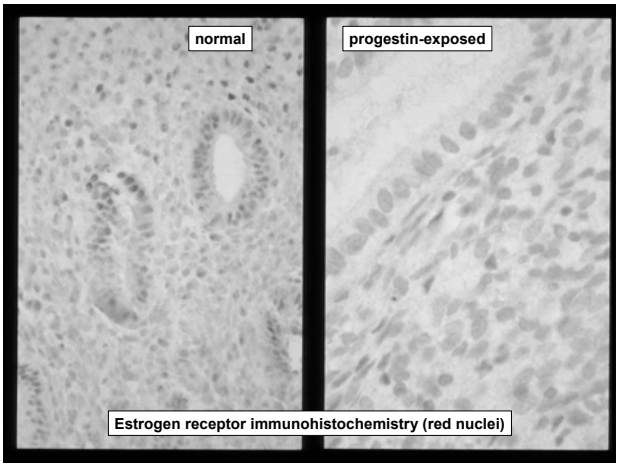
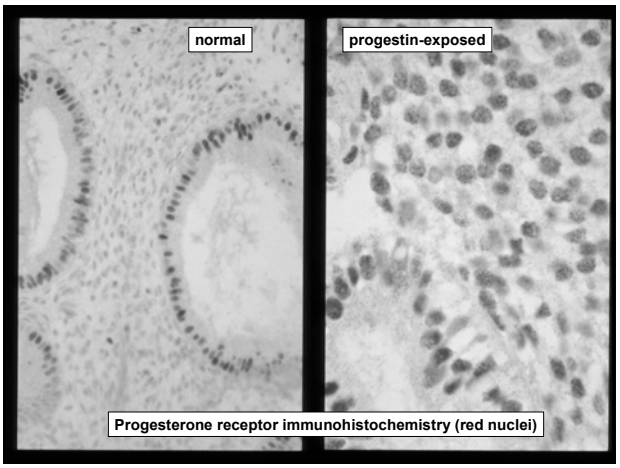
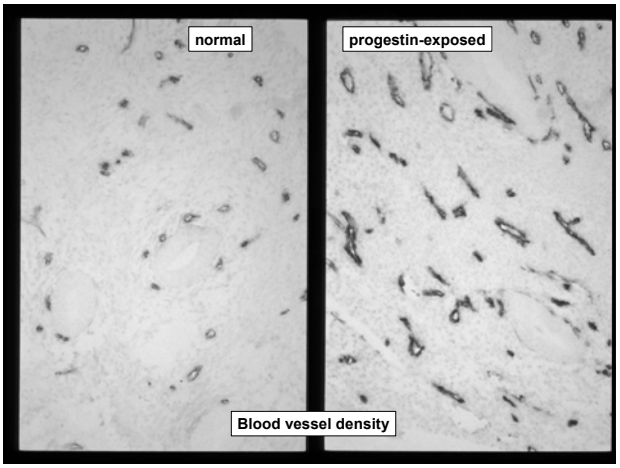


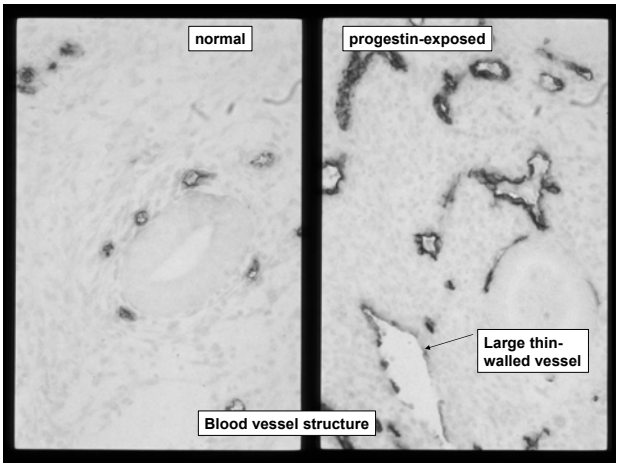

normal
progestin-exposed
functionalis
basalis

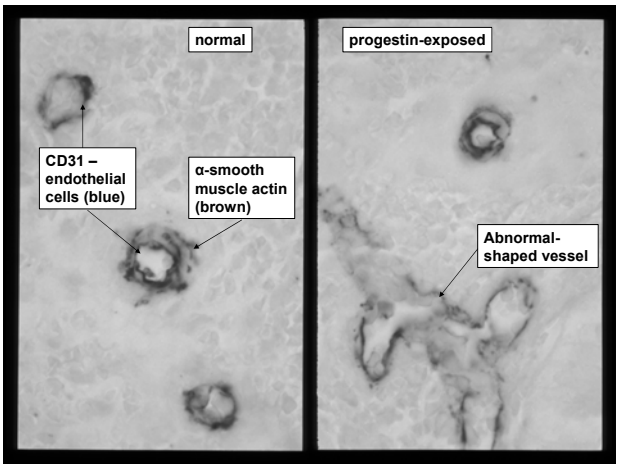

normal
progestin-exposed
Normal secretory gland
Atrophic progestin-dominated gland


normal
progestin-exposed
Estrogen receptor immunohistochemistry (red nuclei)

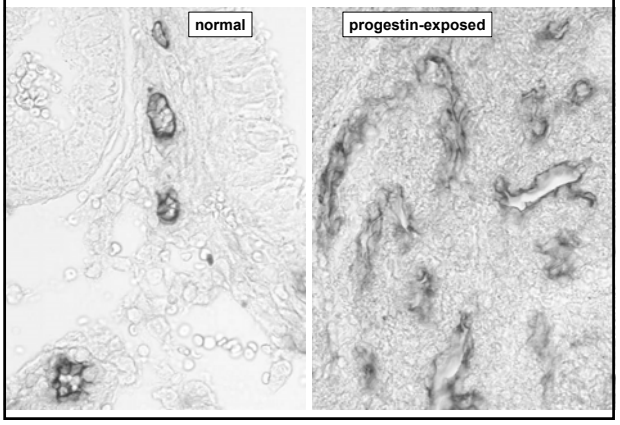

normal
progestin-exposed
Progesterone receptor immunohistochemistry (red nuclei)

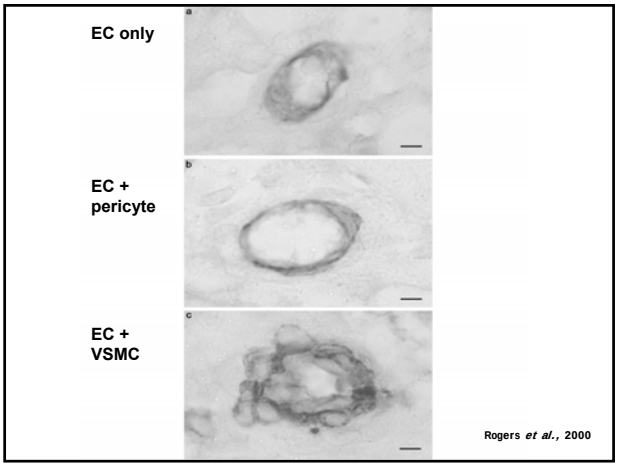

normal
progestin-exposed
Blood vessel density

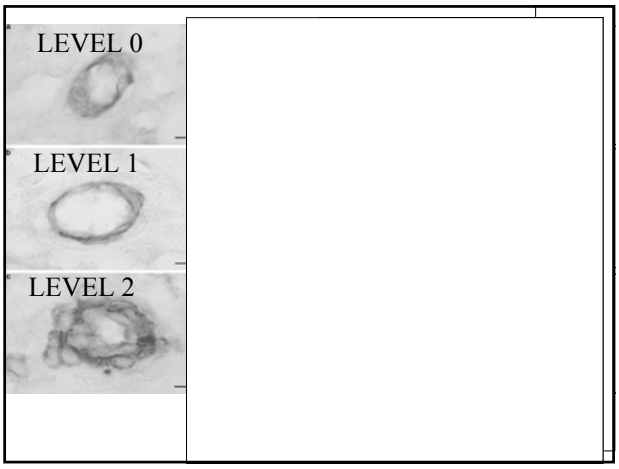

normal
progestin-exposed
Large thin-walled vessel
Blood vessel structure



Combined-continuous post-menopausal HRT







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WHAT ARE THE DIRECT EFFECTS OF PROGESTERONE ON ENDOMETRIAL BLOOD VESSELS?

Work with a mouse model

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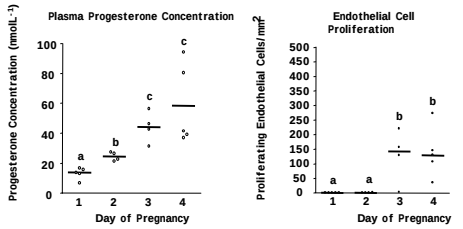
Background

Early pregnancy progesterone rise correlates with an increase in endometrial EC proliferation in the mouse



Walter *et al.*, 2005

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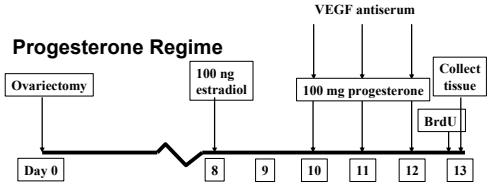
- How does progesterone induce endothelial cell proliferation in ovariectomised mice?
  - Estrogen priming?
  - VEGF?



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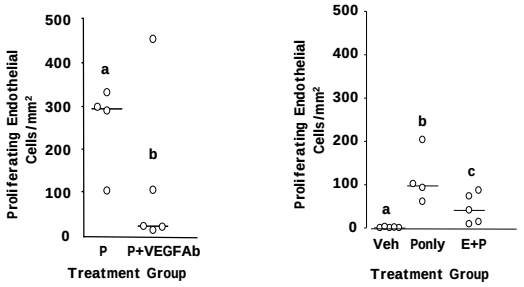
Endometrial Endothelial Cell Proliferation



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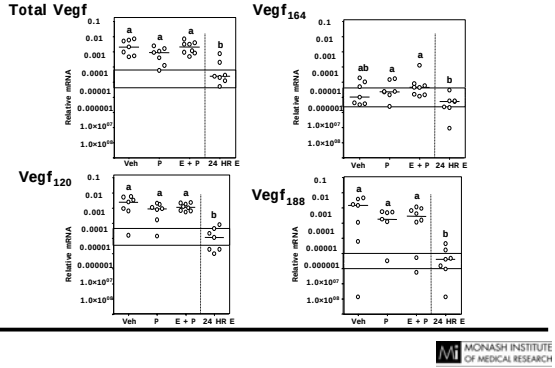
Walter et al. (2005) Reprod. 129: 765-77

Vegf isoform expression in ovariectomized mice



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Conclusions part 1

- **Progesterone alone stimulates endometrial EC proliferation**
- **VEGF plays a role in progesterone-induced endometrial angiogenesis in the mouse**
- **Estrogen has an anti-angiogenic effect in conjunction with progesterone**

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Centre for Women's Health Research

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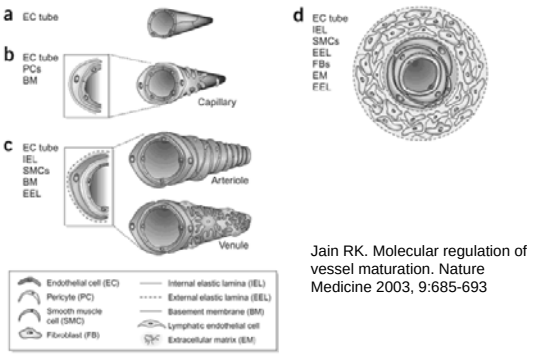
Vascular Maturation



Jain RK. Molecular regulation of vessel maturation. Nature Medicine 2003, 9:685-693

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To investigate whether progesterone stimulates **vascular maturation** in the mouse endometrium

•To quantify **proliferating** mural cells

•To quantify changes in the proportion of vessels covered by **α-smooth muscle actin**

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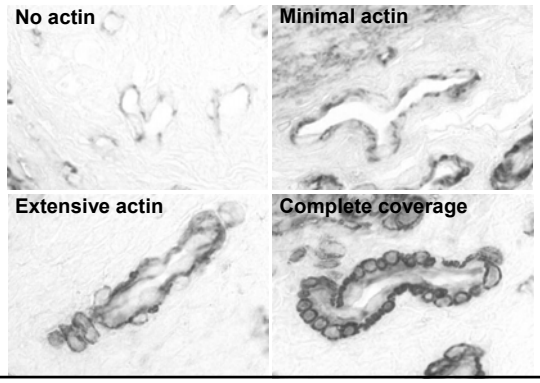
α-Smooth Muscle Actin vessel coverage in mouse endometrium



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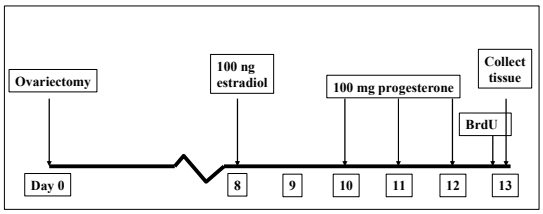
Progesterone Regime



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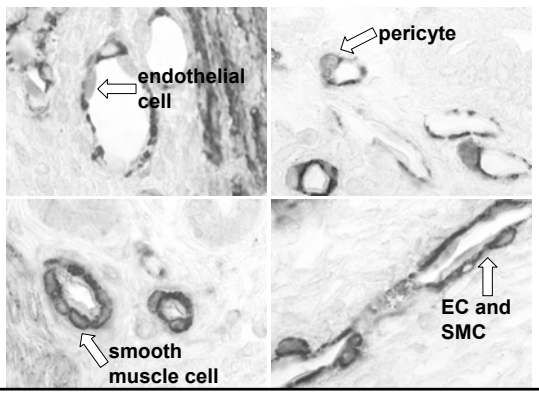
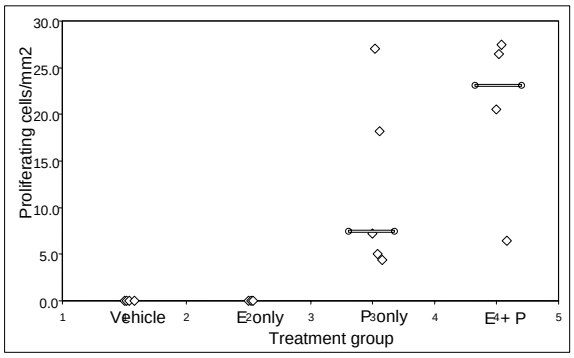
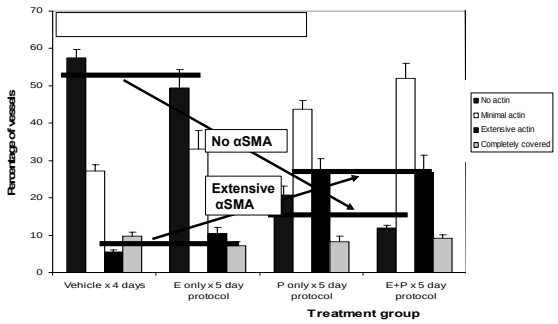
α-Smooth Muscle Actin/BrdU staining in mouse endometrium



α-Smooth Muscle Actin/BrdU positive cells in mouse endometrium



Percentage of mouse endometrial vessels covered by α-smooth muscle actin



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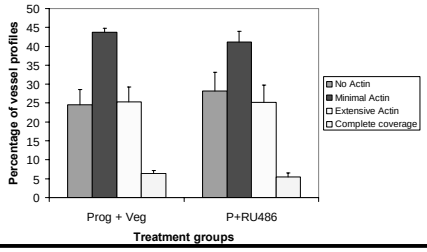
RU486 Experiment – Percentage of mouse endometrial vessel profiles covered by mural cells



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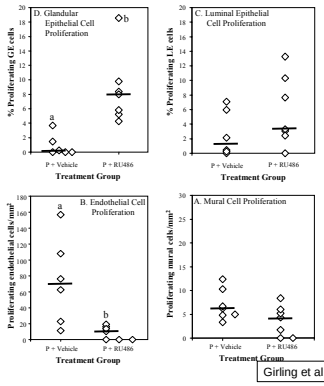
Effects of RU486 (progesterone receptor antagonist) on progesterone-induced endometrial angiogenesis and vascular maturation



Girling et al. (2007) Endocrinology

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Progesterone and Endometrial Arteriogenesis

- Progesterone increases vascular mural cell proliferation and vessel coverage
- Mural cell recruitment and proliferation are <u>not affected</u> by **oestrogen priming** or by **VEGF antiserum**
- Progesterone receptor antagonist RU486 blocks progesterone effects on epithelial and endothelial but not mural cells

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Clark DA, Wang S, Rogers PAW, Vince G, Affandi B. Endometrial lymphomyeloid cells in abnormal uterine bleeding due to levonorgestrel (Norplant). Hum Reprod 1996; 11:1438-1444.

Critchley HOD, Bailey DA, Au CL et al. Immunohistochemical sex steroid receptor distribution in endometrium from long-term subdermal levonorgestrel users and during the normal menstrual cycle. Hum Reprod 1993; 8:1632-1639.

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Girling JE, Lederman FL, Walter LM & Rogers PAW (2007) Progesterone, but not estrogen, stimulates vessel maturation in the mouse endometrium. Endocrinology 148:5433-5441.

Hadisaputra W, Affandi B, Witjaksono J, Rogers PAW. Endometrial biopsy collection from women receiving Norplant®. Hum Reprod 1996; 11(suppl 2):31-34.

Hickey M, Dwarte D and Fraser IS (2000) Superficial endometrial vascular fragility in Norplant users and in women with ovulatory dysfunctional uterine bleeding. Hum Reprod 15,1509–1514.

Jain RK. Molecular regulation of vessel maturation. Nature Medicine 2003, 9:685-693

Rogers PAW, Au CL and Affandi B (1993) Endometrial microvascular density during the normal menstrual cycle and following exposure to long-term levonorgestrel. Hum Reprod 8,1396–1404.

Rogers PAW, Plunkett D and Affandi B (2000) Perivascular smooth muscle α-actin is reduced in the endometrium of women with progestin-only contraceptive breakthrough bleeding. Hum Reprod 15,78–84.

Walter LM, Rogers PAW & Girling JE (2005) The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice. Reproduction 129:765-777.

White JO, Sullivan MHF, Patel L, et al. Prostaglandin production in human endometrium following continuous exposure to low-dose levonorgestrel released from a vaginal ring. Contraception 1991; 43:401-412.

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Strategies to Control; Endometrial Bleeding

David F. Archer, MD
Professor of Obstetrics and Gynecology
Eastern Virginia Medical School
Norfolk, Virginia
U.S.A.

Endometrial Bleeding

- **Altered Ovarian Funcion**
- **Hormonal Contraceptives**
- **Menopausal Hormone Therapy**

Hormonal Contraceptives Bleeding and Spotting

- **Ethinyl Estradiol**
  - **Short Term <30 days**
  - **Repetitive over One Year**

Conjugated Equine Estrogens

Hormonal Contraceptives Bleeding and Spotting

CombinationOral Contraceptives

Ethinyl Estradiol and Levonorgestrel

Used for Acute Episode

Hormonal Contraceptives Bleeding and Spotting

- **Non Steroidal Anti-inflammatory Agents**
  - **Acute use for an episode**
  - **Repetitive for persistent Bleeding and Spotting**

Hormonal Contraceptives Bleeding and Spotting

- **Antioxidents**
  - **Role of Nitric Oxide**
  - **Vitamin E**

Hormonal Contraceptives Bleeding and Spotting

Anti Progestins

- **RU-486**
- **Acute Effects**
- **Long Term Outcome**

Hormonal Contraceptives Bleeding and Spotting

Metalloproteinase Inhibitor

- **Doxycycline**
  - **Acute**
  - **Chronic**

Hormonal Contraceptives Bleeding and Spotting

Conclusions

- **No single Treatment Effective**
- **Etiology of Endometrial Bleeding Multi Factorial**
- **New Apporach to Management is Essential**

Abnormal uterine bleeding: strategies for management.

Local mechanisms responsible for endometrial bleeding

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

ESHRE Pre-congress Course
Barcelona, July 2008

Research Grant support from Medical Research Council

Overview

"Local mechanisms responsible for endometrial bleeding"

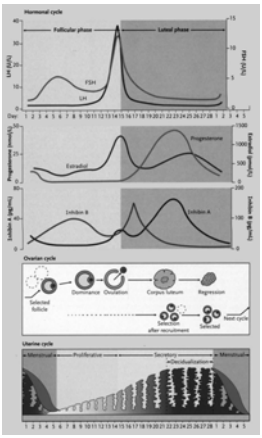
- **Magnitude of clinical problem: causes of problematic endometrial bleeding**
- **Normal endometrial cycle**
- **Endometrial steroid receptor expression patterns**
- **Progesterone (ligand) withdrawal-physiological**
- **Menstruation as an inflammatory event**
- **Candidates for Control of Menstrual Bleeding**
- **Progesterone receptor modulators: progesterone withdrawal-pharmacological**

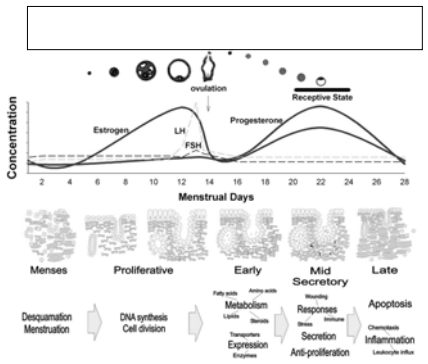
Clinical Problem

- Menstrual disorders impose considerable impact on physical, economic and psychological wellbeing of women.
- HMB affects approximately 880,000 women in England; *Nice Guidance, 2007*
- 1 in 20 women (aged 30 - 49) consult GP each year (1.5m women in E and W).
- 1 in 5 women can expect to have a hysterectomy by age of 60.
- Costs to NHS £65m p.a.; 3.5 million work-days lost annually.
- Large unmet need: Novel therapeutic medical options, with minimal side effects to reduce the number of surgical interventions.
- Essential to understand mechanisms involved in uterine bleeding if improved medical treatment strategies are to be developed.

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





Simmen & Simmen 2006; Endocrinology 147: 1094-1096
Talbi et al 2006; Endocrinology 147: 1097-1121.

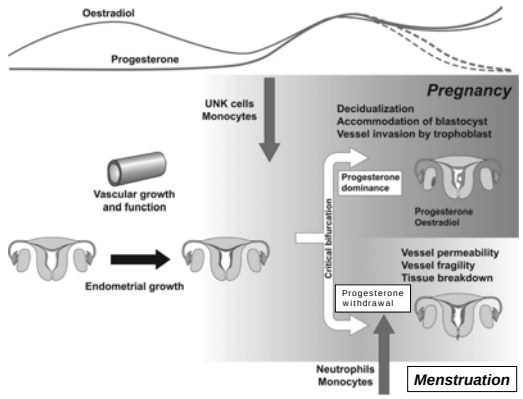
Normal endometrial cycle

- Unopposed **E** exposure promotes regeneration & proliferation post-menses
- **E** induces expression of ER & PR
- Period of **unopposed E** exposure essential for up-regulation of PR [endometrium responds to **P** in luteal phase - differentiation]
- **P** essential for establishment of pregnancy **following** a period of **unopposed oestrogen** (E) exposure

Steroid receptor expression in endometrium

Protein expression	Proliferative		Secretory		Decidua		uNK cells
	Glands	Stroma	Glands	Stroma	Glands	Stroma	
PR	+	+	–	+	–	+	–
ERα	+	+	+/–	+/–	–	+/–	–
ERβ1	+	+	+	+	+	+	+
ERβcx/β2	+	+	+/–	+	+	+	–
GR	–	+	–	+	+	+	+

Henderson et al 2003; JCEM 88:440-9



Jabbour, Kelly, Fraser, Critchley 2006 *Endocrine Reviews* 27:17- 46

Menstruation: an inflammatory event

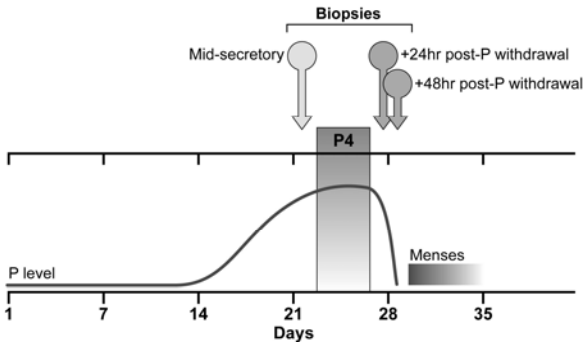
- ☐ Many lines of evidence underpin menstruation as an inflammatory event with tight temporal and spatial regulation at molecular and cellular levels.
- ☐ The functional layer of the human endometrium undergoes serial degeneration and renewal each menstrual cycle.
- ☐ Withdrawal of progesterone (P) due to luteal regression initiates the breakdown of the upper functional zone at menses.
- ☐ Novel injury-repair mechanisms:
- ☐ Progesterone - withdrawal and modulation of local steroid signalling
  - up-regulation of local inflammatory mediators
  -up-regulation of factors orchestrating ECM remodelling and vasculogenesis

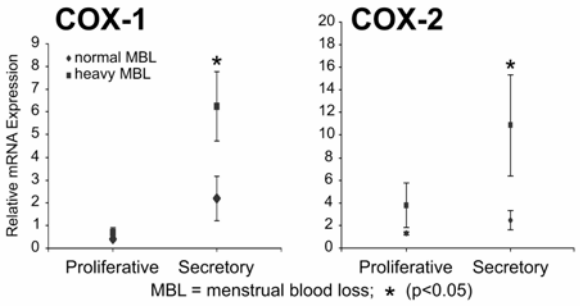
Critchley et al 1999; Milne et al 1999; J Clin Endocrinol Metab. 84: 240 & 2563
Nayak et al 2000; J Clin Endocrinol Metab 85: 3442-52
Brenner et al 2002; Ann NY Acad Sci 955: 60-74;
Hapangama et al 2002; J Clin Endocrinol Metab 87: 5229-34

Candidates for Control of Menstrual Bleeding

- Prostaglandins
- Endothelins
- PAF
- Cytokines : Interleukins
- Transforming growth factors
- VEGF
- EGF
- IGFs and IGFBP
- Impaired platelet aggregation: fibrinloysis
- Glucocorticoids

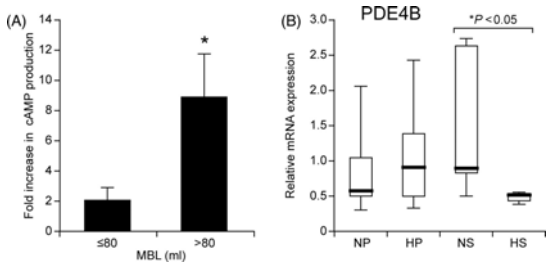
Model of Menses





Relative COX-1 and COX-2 expression in endometrium of women with heavy and normal menstrual blood loss.

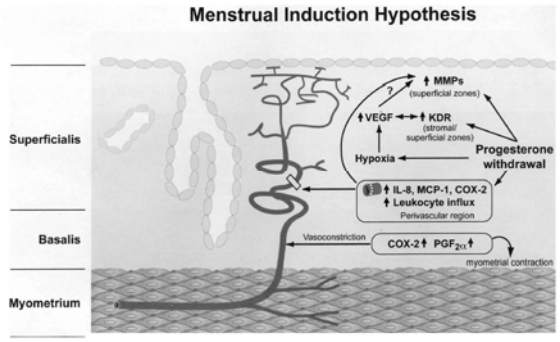
Milling Smith et al 2007; Hum Rep 22:1450-6



A: cAMP production by endometrium in response to PGE2.

B: PDE4B mRNA expression in endometrium of women with heavy and normal blood loss.

Milling Smith et al 2007; Hum Rep 22:1450-6



Critchley, Kelly, Brenner, Baird. 2001 Clin. Endocrinol. 55: 701-10

Vascular Endothelial Growth Factor- VEGF

- Potent angiogenic and mitogenic factor present in endometrium (*Smith 1998*)
- Stimulates MMP synthesis *(Ahmed et al 1997)*
- Binds to its receptors VEGFR-1(ftl-1) and VEGFR-2 (KDR)predominantly expressed in endothelial cells (*Skobe et al 1997*)
- VEGF and KDR present in decidualized stroma cells of endometrium just prior to menses *(Nayak et al 2000)*

American Journal of Obstetrics and Gynecology (2006) 195, 406.e1–406.e16

ELSEVIER

American Journal of Obstetrics & Gynecology

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Gene expression profiling of mid to late secretory phase endometrial biopsies from women with menstrual complaint

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Centre for Reproductive Biology,[a] Queens Medical Research Institute; Scottish Centre for Genomic Technology and Informatics,[b] The Chancellor's Building, The University of Edinburgh; Department of Pathology,[c] Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK

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Gene expression profiling of Mid secretory and Late secretory phases of Menstrual cycle

10 women

5 mid secretory phase pipelle/ hysterectomy samples

5 Late secretory phase pipelle / hysterectomy samples

Expression in each independent sample analysed using HG-U133A arrays

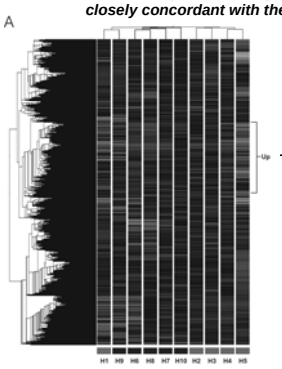
↓

Allow analysis of around 22,000 transcripts

Explorative analysis

Hierarchical clustering of variable genes (CV>0.2) results in a segregation closely concordant with the histological classification

A



Several well-known local mediators of endometrial function are up-regulated in the premenstrual tissue Including:

-Decidualisation (IGFBP-1, prolactin, prolactin receptor)

- Matrix metalloproteinase family (MMP-10, MMP-7, TIMP-2,-3)

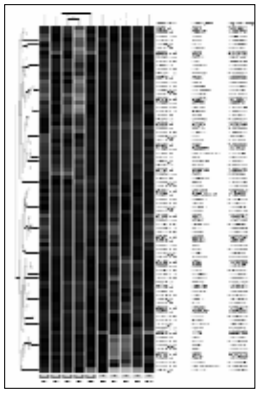
-Endometrial bleeding associated factor (ebaf)

-Endothelin (ET-1) and

- ETB receptor 2,3,4

Hypothesis Driven Analysis

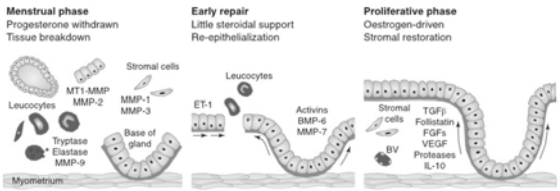
83 genes:
CV >0.1
p<0.01
FC>2



Despite patient and sample variability:

Known local mediators of endometrial function:
- **Endothelin Receptor B**
- **Matrix Metalloproteinases (MMP10)**

Novel genes:
Protease activated receptor 1
Lysyl Oxidase



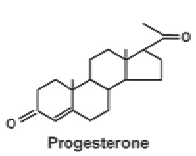
Salamonsen, 2003, Reproduction, Tissue injury and repair in the female human reproductive tract, 125:301-311. ©Society for Reproduction and Fertility 2003. Reproduced by permission.

Acute administration of a progesterone receptor antagonist in the luteal phase.

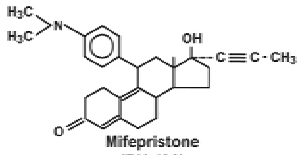
Progesterone Receptor Modulators (PRMs)

- 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

Progesterone receptor antagonist used in clinical studies



Progesterone



Mifepristone
(RU 486)

Mifepristone induced P-withdrawal reveals novel regulatory pathways in human endometrium

(Catalano et al 2007; *Mol Hum Rep* 13:641; Hapangama et al 2002 *J Clin Endocrinol Metab* 87:5229)

- **Single dose of PA - mifepristone – in secretory phase renders endometrium unreceptive**
- **Model for P-regulated genes at time of endometrial receptivity and induction of menstruation**
- **cDNA microarray study to monitor endometrial response 24h following PA in mid-secretory phase**

Mifepristone induced P-withdrawal reveals novel regulatory pathways in human endometrium

(Catalano et al 2007; *Mol Hum Rep* 13:641-54)

- 571 transcripts significantly altered
- New P-regulated members of: Wnt; MMP; prostaglandin and chemokine regulatory pathways - adding to existing knowledge of the role of these pathways in endometrial receptivity
- **Transcripts involved in local thyroid hormone metabolism and signalling (type II iodothyronine deiodinase and THR) regulated by PA**
- ***In vivo* evidence for direct/ indirect regulation of novel transcripts by P**

CONTRIBUTIONS TO EMBRYOLOGY, NO. 177

MENSTRUATION IN INTRAOCULAR ENDOMETRIAL TRANSPLANTS IN THE RHESUS MONKEY

BY J. ELDRIDGE MARKEE

Department of Anatomy, Stamford University, and Department of Embryology, Carnegie Institution of Washington

With seven plates and one text figure

[Issued August 15 1940]

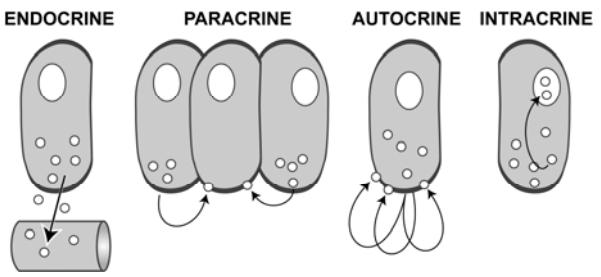
Mechanism of Menstrual Bleeding

1. **Shrinkage of Stroma : increased coilage of arterioles: vascular stasis**
2. **Vasodilation and perivascular bleeding**
3. **Vasoconstriction**
4. **Tissue necrosis and menstruation**

Changes are not sychronized across endometrium but occur in local foci

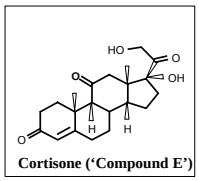
Markee 1940

Schematic representation of *endocrine*, paracrine, autocrine and *intracrine* action



After Labrie *et al*, J Mol Endocrinol (2000) 25:1-16

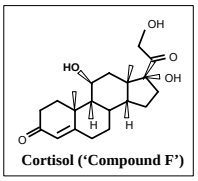
The Cortisone-Cortisol Shuttle



Cortisone ('Compound E')

11βHSD1 ⇌

11βHSD2 ←



Cortisol ('Compound F')

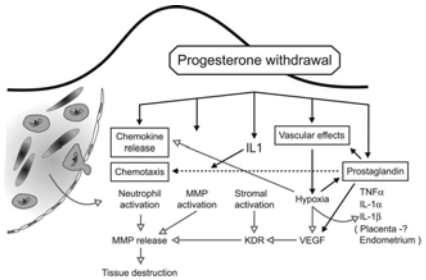
'INACTIVE' 'ACTIVE'

Agarwal/Albiston/Edwards/Frey/Funder/Krowzowski/Mason/ Monder/Mullins/Odermatt/Seckl/Stewart/White/et al

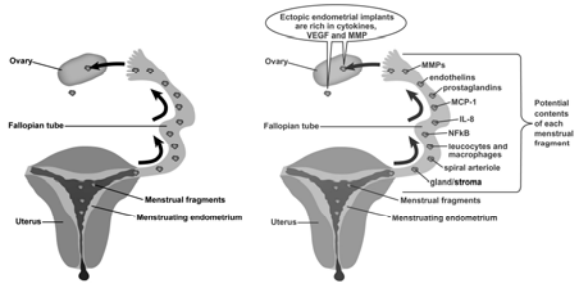
---

Glucocorticoids and endometrial angio/ vasculogenesis

- Glucocorticoids inhibit angiogenesis both *in vitro* and *in vivo*, and 11βHSD1 knockout mice display increased angiogenesis in wounds
  Small et al 2005; *Proc Natl Acad Sc USA* 102: 12165
- Glucocorticoid metabolising enzymes, the 11βHSDs, expressed in the endometrium
  McDonald et al 2006; *Mol Cell Endocrinol* 248:72-8



Jabbour, Kelly, Fraser, Critchley *Endocrine Reviews* 2006; 27:17-46



Brenner, Nayak, Slayden, Critchley & Kelly. Premenstrual and Menstrual Changes in the Macaque and Human Endometrium. Ann NY Acad Sci. 2002; 955:60-74. Copyright 2002 Blackwell Publishing.

Summary

- **Pivotal reproductive events in which the endometrium plays a major role are implantation, and in the absence of pregnancy, menstruation.**
- **These processes are regulated by sex steroids and their interactions with cognate receptors. The subsequent cascade of downstream events involving the endocrine, vascular and immune systems is complex.**

  Many lines of evidence underpin menstruation as an inflammatory event with tight temporal and spatial regulation at molecular and cellular levels.
- **In the presence of ovulatory cycles, withdrawal of progesterone (P) triggers a cascade of molecular and cellular events within the endometrium, leading to menstruation.**
- **A detailed knowledge of steroid regulation of endometrial function is essential for understanding how disturbances of endometrial structure and function may play a role in menstrual bleeding complaints.**
- **'Injury' and 'repair' in the endometrium may serve as a paradigm for these processes elsewhere in the body. Physiological angiogenesis in the endometrium may provide insights into the mechanism of aberrant angiogenesis in disease (tumour formation and chronic inflammation).**

ESHRE 2008

Abnormal uterine bleeding: strategies for management

Is There a Role for PR Ligands in the Management of Uterine Bleeding?

Kristof Chwalisz, MD, PhD

Financial Disclosure

- Employee of TAP Pharmaceutical Products Inc., and owner of Abbott stock and stock options
- Co-inventor of multiple patent applications covering several SPRM compounds and their clinical applications.

Learning Objectives

- At the conclusion of this presentation, the participant will be able to:
  - Provide a comprehensive overview of the pharmacology of progesterone receptor modulators and their effects on the primate endometrium
  - Understand the mechanism of action of different PR ligands in the endometrium
  - Understand the potential of selective progesterone modulators and progesterone receptor antagonists in the management of heavy uterine bleeding

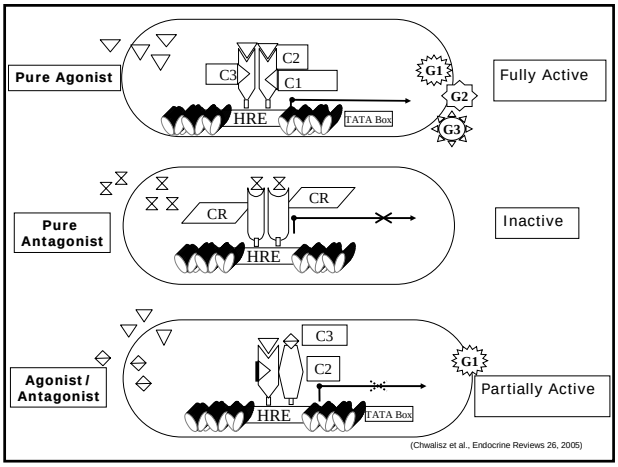
Definitions of PR Ligands

- Steroidal or non-steroidal compounds that bind with high affinity to PR and exert specific effects in target cells or tissues
  - PR agonists (progestins)
  - PR antagonists (PAs; antiprogestins)
  - Selective Progesterone Receptor Modulators (SPRMs; mixed or partial agonist/antagonists)

Selective Progesterone Receptor Modulators (SPRMs)

- SPRMs can be defined based on both functional (*in vivo)* and molecular (cell free) studies
  - Functional (*in vivo*) definition
    - Tissue selective effects
    - Partial agonist, antagonist, or mixed activities
  - Molecular definition
    - Presence of partial agonist or antagonist effects *in vitro*
    - Partial Interaction with coactivators
    - Partial interaction with corepressors

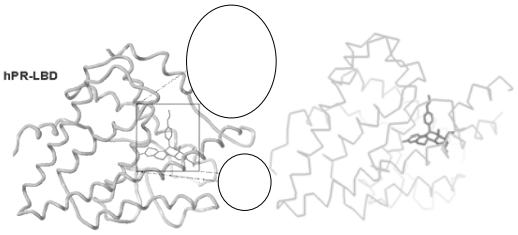
(Chwalisz et al, Endocrine Reviews 26, 2005)



(Chwalisz et al., Endocrine Reviews 26, 2005)

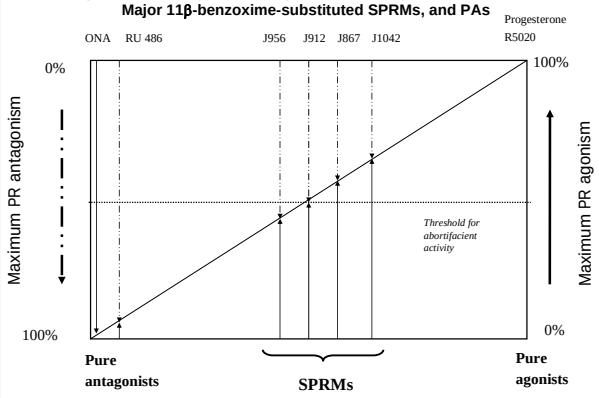
Predicted complex of PR with asoprisnil based on PR-agonistic conformation
(A. Hilishcsh, in Chwalisz et al. Reprod. Biol. Endo. 4, 2006)

X-ray structure complex of PR with asoprisnil
(Madauss et al, Mol. Endo. 21, 1066-81, 2007)

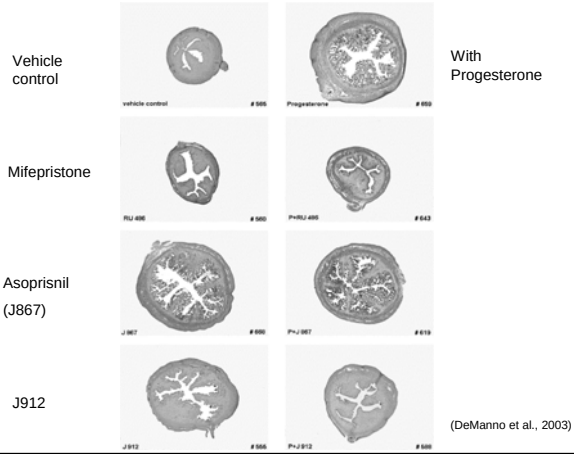


- **Precise prediction of asoprisnil binding mode**
- **Correct prediction of helix 12 displacement by 11ß-side chain of asoprisnil (antagonistic conformation)**
- **Conformation of displaced helix 12 not correctly predicted**

Spectrum of Progesterone Agonist and Antagonist Activities of Major 11β-benzoxime-substituted SPRMs, and PAs



(Schubert et al., 2005, Semin Reprod Med 23:58 – 73)



(DeManno et al., 2003)

Pharmacological Profile of SPRMs *in vivo*

Model	Agonists	SPRMs	Antagonists
McPhail Test*	Agonist	Partial and mixed agonists/antagonists	Antagonists
Abortifacient activity**	Absent	Marginal or absent	High
Cervical ripening**	Absent	Low or absent	High
Antiovulatory activity***	High	Inconsistent effects, dose-independent	High
Endometrial effect***	Secretory transformation	SPRM effect (non-physiologic secretory patterns)	Proliferative patterns
Uterine bleeding***	Breakthrough bleeding and spotting	Amenorrhea via an endometrial effect	Amenorrhea due to anovulation

* rabbits, ** guinea pigs, *** humans

(Chwalisz et al., Endocrine Reviews 26, 2005)

New Data from Molecular Studies Confirm Partial Agonist/Antagonist Activity of J867 (Asoprisnil)

- In T47D cells with endogenous *sgk-1* and a stably integrated MMTV promoter*, J867, but not RU486, induces:
  - Partial transactivation of a MMTV reporter gene
  - Partial recruitment of the co-activator SRC1

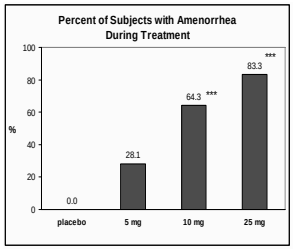
(Melvin et al., 2005, Endocrine Society)

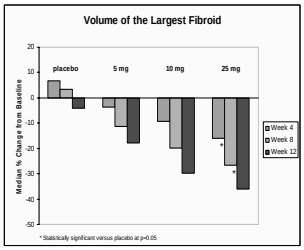
- J867, but not RU486:
  - Partially recruits Steroid Receptor Coactivator (SRC-1) and Amplified in Breast Cancer 1 (AIB1) Coactivator via the PR-LBD in COS-7 cells**
  - Partially activates Serum Glucocorticoid Kinase-1 (Sgk-1) and Periplakin (PPL) gene expression in T47D breast cancer cell lines
  - Exhibits progesterone-like activity on COX enzyme activity in rat leiomyoma ELT3 cells

(Madauss et al., 2007. Molec Endocrinol 21:1066-81)

Effects of SPRMs on Uterine Bleeding in Subjects with Uterine Leiomyomata

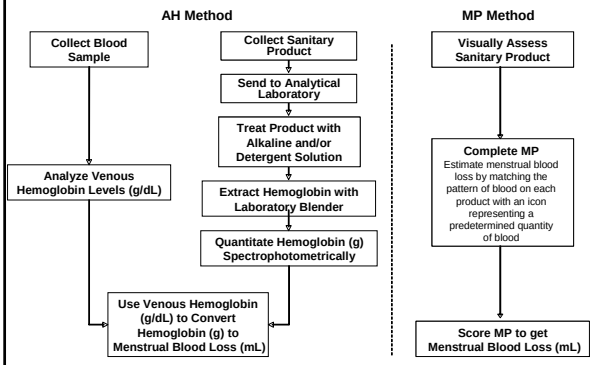
Clinical Effects of Asoprisnil in Subjects with Uterine Leiomyomta





(Chwalisz at al., 2007, Fertil Steril. 87:1399-1412)

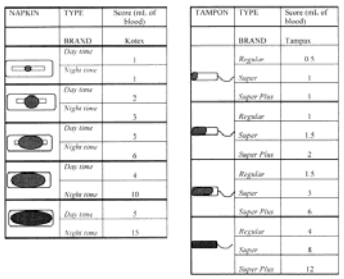
Menstrual Blood Loss Assessment Methods



(Soper et al., 2007)

Menstrual Pictogram

Subjects tally the number of used items of protection that resemble each icon daily. They DON'T have the scores.

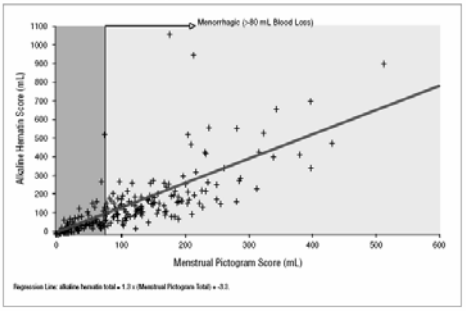


NAPKIN	TYPE	Score (mL of blood)
	BRAND	Kotex
	Day time	1
	Night time	1
	Day time	2
	Night time	3
	Day time	5
	Night time	6
	Day time	4
	Night time	10
	Day time	5
	Night time	15

TAMPON	TYPE	Score (mL of blood)
	BRAND	Tampax
	Regular	0.5
	Super	1
	Super Plus	1
	Regular	1
	Super	1.5
	Super Plus	2
	Regular	1.5
	Super	3
	Super Plus	6
	Regular	4
	Super	8
	Super Plus	12

(Soper et al., 2007)

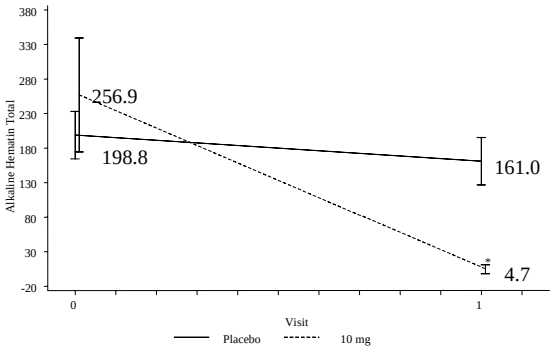
Alkaline Hematin Total Against Menstrual Pictogram Total for Non-Amenorrheic Visits



- AH totals from baseline and treatment collections are compared with the corresponding MP totals
- Using Intraclass and Pearson correlation coefficients, the association between the 2 methods was 0.64 (CI = [0.55, 0.71]) and 0.74 (CI = [0.68, 0.80]), respectively
- Overall, a 1 mL increase in blood loss according to the MP corresponded to a 1.3 mL increase in blood loss according to the AH method

(Soper et al., 2007)

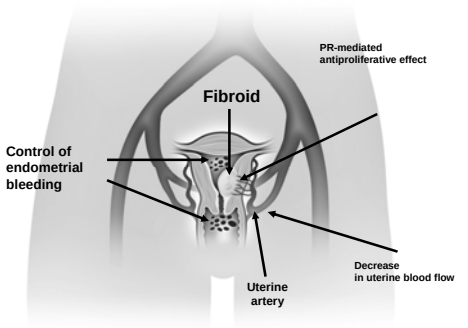
The Effects of Asoprisnil on Menstrual Blood Loss Measured with AH Method in Subjects with Heavy Uterine Bleeding



Note: Error bars are +/- 2 standard errors of the mean
Note: Visit 0 is Screening, Visit 1 is Treatment
* Statistically significant compared to placebo.

(Soper et al., 2007)

Mechanism of Action of SPRMs in Women with Uterine Leiomyomata



(Chwalisz K., Perez. M.C., Winkel C. 2005)

Effects of SPRMs and PAs on the Primate Endometrium

Assessment of Endometrial Safety of SPRMs in Animal Models

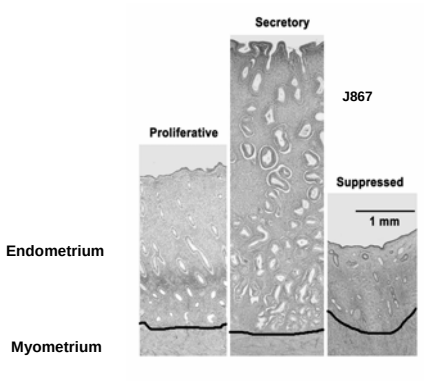
- Endometrial effects of SPRMs and PAs depend on
  - Compound (ratio of PR agonist:antagonist activities)
  - Animal species
  - Duration of treatment
  - Effects on the ovary
- Rodents (rats, mice) and rabbits are not suitable to assess endometrial safety of both SPRMs and PAs
- Critical role of nonhuman primate models

(Chwalisz et al., *Steroids*. 2000;65:741-751)

Endometrial Antiproliferative Effect of PAs and SPRMs

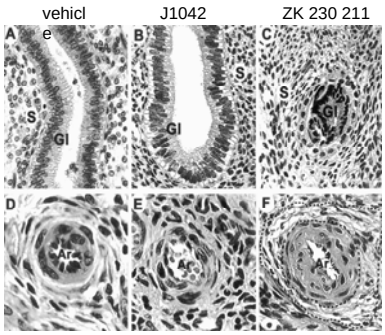
- "Noncompetitive antiestrogenic effect" of RU 486 in macaques
  (Hodgen, 1989)
- **"**Endometrial antiproliferative effect"
  - Novel mechanism
    (Brenner and Slayden,1990-2000)
- Both PAs and SPRMs exert endometrial antiproliferative effect
  (Brenner, Slayden and Chwalisz, 1990-2005)
- Reversible suppression of menstruation with PAs and SPRMs via an endometrial effect
  (Brenner, Slayden and Chwalisz, 1990-2005)
- Role of AR
  (Brenner, Slayden, Critchley et al, 2001-2002)

J867 has endometrial antiproliferative effects in cynomolgus macaques



(Brenner et al. 2005)

The effects of J1042 (SPRM) and ZK 230 211 (PA) on endometrial glands and spiral arterioles in intact cynomolgus monkeys (3 mg/kg i.m., cycle days 2-22, hysterectomy: day 23)



(Schubert et al., 2005)
(Schubert et al., 2005, Semin Reprod Med 23:58 – 73)

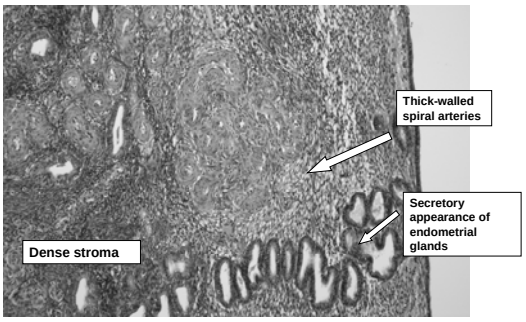
SPRM Effects on the Primate Endometrium

PR Antagonist Effect ⇩ **Endometrial Stroma**

PR Agonist Effect ⇩ **Endometrial Glands**

(Schubert et al.,2005, Semin Reprod Med 23:58 – 73)

Non-physiologic Secretory Pattern in Humans



(Chwalisz at al., 2005, Hum Reprod 20)

SPRM Endometrial Effect (SPRM-EE)

- Early SPRM-EE:
  - attenuation of mitotic activity in proliferative type glands
  - presence of weak secretory changes in underdeveloped glands
  - Thickening of the wall of spiral arteries
- Late SPRM-EE
  - gradual acquisition of the distinctive changes:
    - cystic dilatation of glands
    - increasing relative prominence of stroma
    - increasing prominence of thick-walled spiral artery clusters

- NIH Conference: "Endometrial Effects of PRMs - Changes and Consequences", April 6-7, 2006 in Bethesda, MD
  - Class effect of SPRMs and PRAs
  - Unique endometrial changes that do not fit with current diagnostic categories
  - New diagnostic categories need to be developed

(Chwalisz at al., 2007, in press)

(Horn & Blithe 2007, HR Update, 2007; Chwalisz at al., 2008)

Endometrial Effects of Asoprisnil in Monkeys and Humans: <u>Similarities</u>

- Amenorrhea
- Dose-dependent antiproliferative effects in the glandular epithelium
  - Inactive epithelium with no unopposed estrogen effects
  - Decrease in mitotic counts and proliferation markers (Ki-67, Phospho H3)
- Patterns of steroid receptor expression (PR, ER, GR)

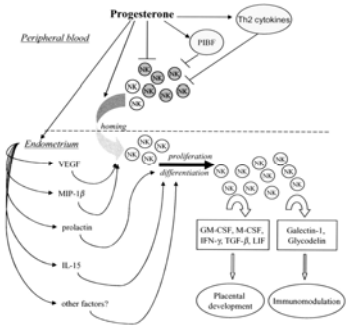
(Chwalisz et al., 2008)

Endometrial Effects of Asoprisnil in Monkeys and Humans:
Differences

Effect	Monkeys (cynomolgus macaques)	Humans
Onset	Rapid induction of endometrial atrophy (~1 month)	Slow transition from non-physiologic secretory effect towards quiescent patterns (>6 months)
Glands	Little secretory effect	Moderate secretory effect with gland dilatation
Stroma	Very dense	Tendency for decreased edema, increased compactness No decidual change
Stroma/vessels	No effect	Formation of muscularized thick-walled vessels

(Chwalisz et al. 2006)

A Model of Hormonal Regulation of Uterine Natural Killer Cells in Pregnancy



(Dosiou C, Giudice LC 2005, Endocr Rev 26:44–62)

Conclusions

- Both SPRMs and PAs are very effective agents in controlling heavy uterine bleeding
- Unlike progestins, SPRMs do not induce breakthrough bleeding and spotting
- SPRMs and PAs control uterine bleeding via different mechanisms
  - SPRMs predominantly target the endometrium
  - PAs control uterine bleeding via anovulation
- The local endometrial immune system may play an important role in mediating SPRM effects on the endometrial vasculature
- Endometrial safety remains the major concern of chronic use of both SPRMs and PAs
  - New therapeutic regimens addressing endometrial safety need to be developed
- The currently available animal models, including non-human primates, do not predict endometrial effects of SPRMs and PAs in humans

Acknowledgments

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(University of Edinburgh, Scotland, UK)

Asgi Fazleabas
(UIC. Chicago, USA)

Dean Edwards
(University of Colorado)
Takeshi Maruo
(Kobe University School of Medicine (Japan)

Henning Beier
(Rhine-Westphalia Technical University Aachen Germany)

Horacio Croxatto
(*ICMER, Santiago de Chile)*

Endometrial Pathology Panel
Michael Hendrickson
Richard Kempson
(Stanford University, CA, USA)
Alistair Williams
(University of Edinburgh, Scotland, UK)
Robert Young
(Boston, Massachusetts, USA)
Michael Glant
(DCL, Indianapolis, USA)

Key References

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Why Menstruate?

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University of Edinburgh
Edinburgh UK

Potential sources of conflict: none

Potential conflicts of interest

David T Baird
Centre for Reproductive Biology
University of Edinburgh

Over the last 30 years I have held grants and/or consulted for most pharmaceutical companies involved with reproductive health

Currently I have no direct contracts or shares in relevant commercial companies

Why Menstruate?
Learning Objectives

1. To understand the nature of the endometrial and menstrual cycle
2. To put in perspective the historical evolution of menstrual cycles and their social and cultural significance
3. To recognize the morbidity associated with repeated ovarian and menstrual cycles
4. To consider strategies which would result in prolonged amenorrhoea

Menstrual Cycles

- **Only occur in primates(mainly Old World) and a few others such as elephant shrew and bat**
- **Sign of ovarian cyclicity ;**
  "*Red flag at Auction Sale - sign of something going on"*
  *(***Matthews Duncan 1890)**
- **Social and biological significance**

Evolution of Menstrual Cycle

- Sign of femininity and youth
- Indicator of Health and Fertility
- Monthly chore("the curse")
- Unclean(menstrual toxin)
- Restriction on social and physical activities

Why do Primates Menstruate?

- **Termination of Sterile Cycle**
- **Vascularisation and Decidualisation of endometrium complex and involves too much tissue for rapid and comprehensive reabsorption**
- **?Protective against infection**
- **Cyclical regression is more economic than maintaining decidua**

BJ Strassmann 1996 Rev Biol 71:181-220

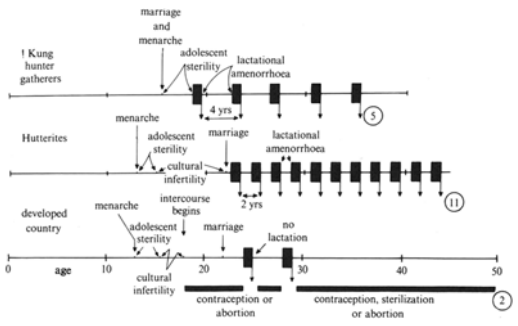
Why Menstruate: conservation of energy?

- **Metabolic rate 7% higher in luteal phase 13 MJ/cycle(1-2 days food)**
- **Secretory endometrium 7 fold increase in oxygen consumption**
- **One year of amenorrhoea saves 130MJ-- or half a months food**

Evolution of Menstrual Cycles

- **Repeated menstrual cycles a comparatively recent phenomenum**
- **Previously women had very few menstrual cycles because they were either pregnant or lactating**
- **Product of smaller families and methods of contraception which perpetuate menstrual cycles**
- **Decrease in age of menarche**

Patterns of Reproduction in Different Societies



Contraceptives of the Future, Short R.V. 1976, p16

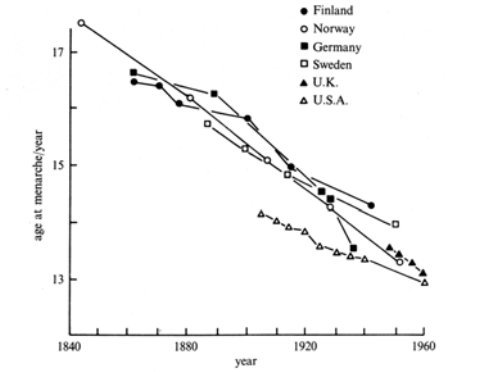


FIGURE 2. Secular decline in the age of menarche in developed countries. (Adapted from Tanner 1962.)

Natural History of Menstrual Cycles

Classic Longitudinal Study
Alan Treloar,Ruth Boyntion, Borghild Behn, Byron Brown
University of Minnesota and NIH Neurological Disease and Blindness Bethesda

Int Journal of Fertility 1967;12:77-113

Menstrual Cycles

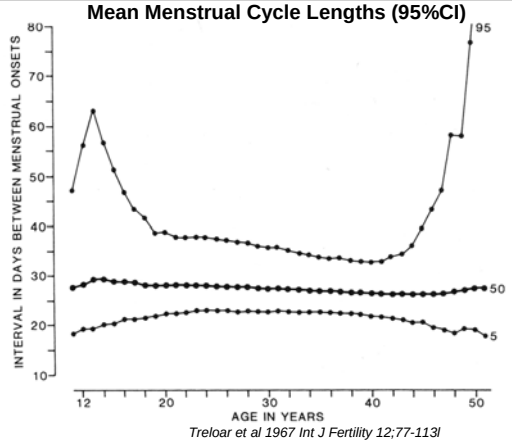
- 1934 Miss Esther Doerr(Graduate student) invited her friends and staff to record menses prospectively
- Only 50% agreed;50% returned menstrual card;big drop off at presumed menopause
- By 1961 25,825 person years of menstrual experience from 2700"colleagues"
- Data bank of 250,000 menstrual interval records

Treloar et al 1967 Inter J Fertility 12:77-113

Variation of the human menstrual cycle throughout reproductive life

- **" It is a major concern that the results of analysis of this unusually extensive array of data be presented in a form allowing rapid comprehension of the outcome without loss of significant detail. It is with this in view that we chose to rely chiefly on graphical presentations of changes observed through chosen spans of menstrual experience"**
- **"Complete regularity in menstruation through extended time is a myth"**
- **Main variable is age**

Mean Menstrual Cycle Lengths (95%CI)



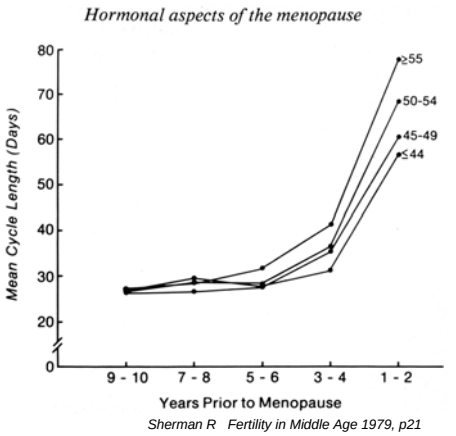
Treloar et al 1967 Int J Fertility 12;77-113l

Table 2. Changes in menstrual cycle length during reproductive life

Age (years)	*N*	Total cycle length	Follicular phase*	Luteal phase†
18–30	10	30·0 ± 3·6	16·9 ± 3·7	12·9 ± 1·8
40–45	7	25·4 ± 2·3	10·4 ± 2·9	15·0 ± 0·9
46–56	8	23·2 ± 2·9	8·16 ± 2·8	15·9 ± 1·3

* From the first day of menses to the LH peak.
† From the LH peak to onset of menses.

Sherman et al in Fertility in Middle Age 1979, p23



Morbidity and Menstruation

- Heavy,prolonged and /or painful periods very common
- Inconvenient and may lead to social isolation
- Anaemia
- Repeated menstruation associated with endometriosis and increased incidence of endometrial carcinoma and fibroids
- Cyclical morbidity eg PMS,epilepsy

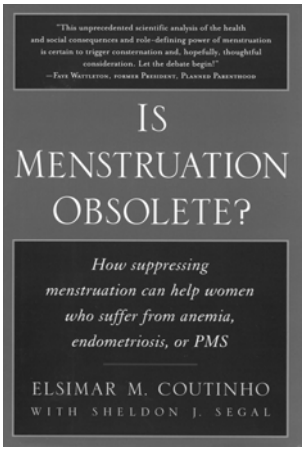
Attitudes of women towards menstruation

Do you Like Periods	**ED**	**CT-B**	**CT-W**	**CT-C**	**HK**	**SH**	**NG**
Yes	**26**	**75**	**35**	**42**	**50**	**33**	**81**
No	74	25	65	58	51	63	19
How Often?							
Monthly	**33**	**49**	**30**	**42**	**42**	**43**	**71**
3 monthly	**20**	**27**	**26**	**15**	**39**	**30**	**12**
Never	**37**	9	**29**	**36**	6	15	13

Glasier et al 2003

“Periodical uterine haemorrhage is, in fact, one of the sacrifices which women must offer at the alter of evolution and civilisation”

Beckwith Whitehouse 1914 Lancet Hunterian lecture



Health Benefits of Amenorrhoea

- Relief of menstrual symptoms
- Decrease in blood loss; less anaemia
- Decrease in inconvenience and social isolation
- Decrease in endometriosis,carcinoma of endometrium(and ovary)
- Cheaper

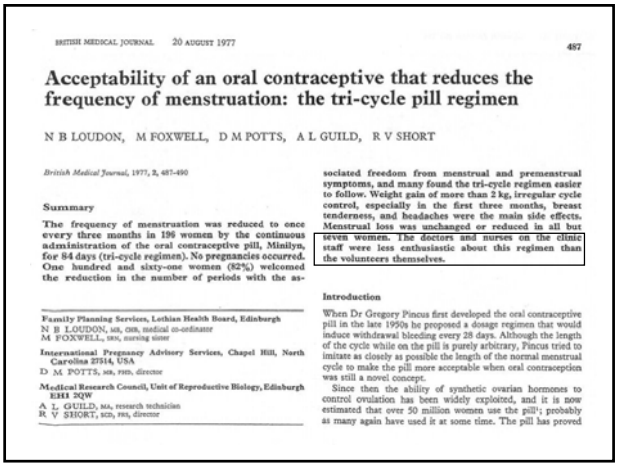
Strategies to induce amenorrhoea

- **Surgical : Hysterectomy,endometrial ablation**
- **Depo-Provera**
- **Mirena**
- **Continuous gestogen eg norethisterone**
- **Extended cycle combined OC**
- **Progesterone Receptor Modulators**

Extended use of Combined Oral Contraceptive Pills

- **Fewer periods but more spotting**
- **Many women preferred continuous regimen**

Loudon et al 1997, BMJ 2: 487-470
Cachvimanidou et al 1993,
Contraception 48: 205-216
Miller & Notter 2001,
Obstetrics & Gynecology 98: 771-778



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.

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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 pill[1]; probably as many again have used it at some time. The pill has proved

Attitudes to Amenorrhoea

- WHO sponsored in 14 cultural groups in 1973-1979 asked about attitudes to menses
- Preference for method of contraception which does not result in amenorrhoea or change blood loss; predictable bleeding
- But many would use or are using methods which alter pattern of menses

WHO (1981) Studies in Family Planning **12**:3-15

Amenorrhoea and Contraception

- **In 1990s re-investigation of preferred frequency and characteristics of menstrual bleeding in relation to reproductive status and contraception**
- **1300 women in Netherlands interviewed by telephone**
  - **80.5% of menstruating women preferred shorter, lighter and/or less frequent periods**
- **Wish for amenorrhoea increased with age**
  - **26% at 15-19 years**
  - **51% at 45-49 years**
  - **77% at 52-57 years**

Tonkelaar & Oddens 1999,
Contraception 59: 357-362

Amenorrhoea associated with contraception-- an international study on acceptability

Amenorrhoea highly acceptable to the majority of women in Edinburgh, Capetown,HongKong and Shanghai

Glasier et al (2003)Contraception ; 67. 1-8

Methods

Questionnaire Study of Providers and Users

5 Centres - Scotland
Nigeria
South Africa
PR of China
Hong Kong

200 Clients in each centre

50 Providers

Demographic characteristics of clients from all centres

	ED	CT	HK	SH	NG
Age (years)					
20 - 29	**53**	**56%**	**24%**	**49**	**13%**
> 40	**11%**	**7%**	**31%**	**16%**	**26%**
Married / Cohabit	**49%**	**33%**	**84%**	**81%**	**99***
Children					
None	**76%**	**46%**	**31%**	**42%**	**2%**
4 or more	**1%**	**4%**	**0.5%**	**0**	**59%***

Current Contraception (%)

Method	ED	CT	HK	SH	NG
COC	**40**	**35**	**28**	**6**	**17**
POP	**7**	**5**	**0**	**0**	**0.5**
Condoms	**21**	**2**	**38**	**39**	**23**
IUCD	**9**	**0**	**12**	**17**	**27**
Inject / Implant	**10**	**53**	**9**	**2**	**30**

Provided your periods and your fertility returned to normal immediately if you stopped using it, would you consider a method of contraception which stopped your periods?

	ED	CT - B	CT - W	CT - C	HK	SH	NG
	(percentage)						
Yes	65	52	64	61	37	58	73
No	25	41	26	33	32	35	24
Undecided	11	7	11	6	32	18	4

Attitudes of Providers to Amenorrhoea

- **% Providers who thought that their clients considered it important that they continued to menstruate whilst using contraception?**

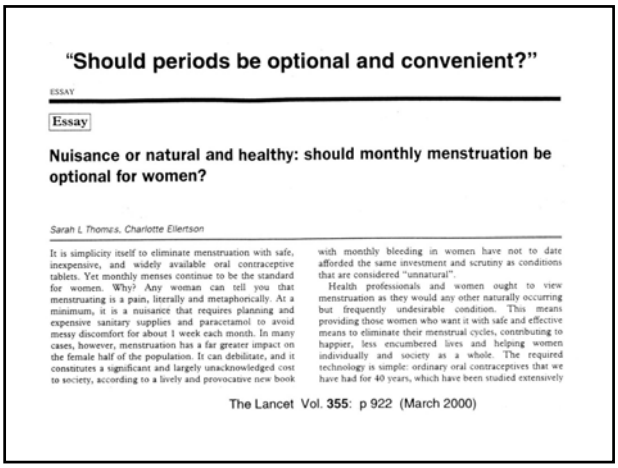
Edinburgh		**94%**
Capetown	Black	**93%**
	White	**81%**
Hongkong		**98%**
Shanghai		**90%**
Nigeria		**96%**

Message to marketing : always ask the customer

"It is the occurrence of menstruation,I say, which first renders the female an object of interest to an Obstetrical Society. Perhaps some would add,that were there no menstruation ,our occupation would be gone".

Professor Alexander Russell Simpson, President, from his inaugural address to the Edinburgh Obstetrical Society on 8th December 1875

"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)

Why Menstruate?
Evolution of the Menstrual Cycle

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