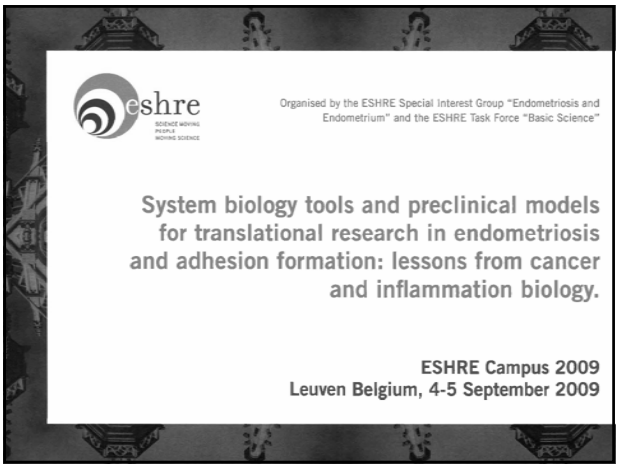

Nonhuman primate models for translational research in endometriosis

Thomas M.D'Hooghe, MD, PhD
-Coordinator Leuven Univ Fertil Ctr (B),
-Chair, Int'l Advisory Board, Institute of Primate Research (WHO Collab Ctr), Nairobi, Kenya

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Learning Objectives: NHPmodels for translational research in endometriosis

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6. **Endo research baboon model: 5 relevant observations**

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Gynaecology
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L Meeuwis
K Peeraer
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P De Loecker
L Segal
A Spaepen
I Thijs
Ph Albertyn
V. Vloeberghs

Gastro enterological surgery
A. D'Hoore

Psychology and Counselling
K Demyttenaere
P. Enzlin
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Center for Medical Genetics
JP Fryns
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L Rijkers
S Schildermans
H Verbiest
S Verschueren
A Verlinden
C Craenen
W Leus
G Roels
M Toetenel

Research coördinator
M Welckenhuysen

Fertility Lab
C Spiessens
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H Devroe
H Afschrift
O De Maeght
L Hollanders
A Velaers
F Vynckier
P Bols
E Vergison
K Bullens
B Quintens

European Board and College of Obstetrics and Gynaecology (EBCOG)

European Society of Human Reproduction and Embryology

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Leuven University Fertility Center / Department of Obstetrics and Gynaecology
"UZ Gasthuisberg", Leuven, Belgium

is recognised as an accredited

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Prof. W. Dunlop
President EBCOG & UEMS Section

Prof. J.W. Wladimiroff
Chair of the Subspeciality Recognition Committee

Prof. J. Geraedts
Chairman of ESHRE

B.C. Tarlatzis
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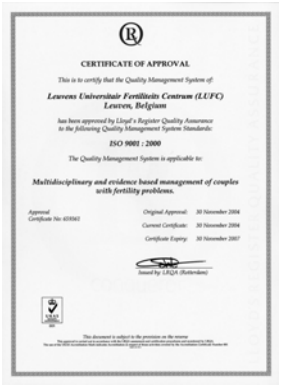

CERTIFICATE OF APPROVAL

This is to certify that the Quality Management System of:

Leuvens Universitair Fertiliteits Centrum (LUFC)
Leuven, Belgium

has been approved by Lloyd's Register Quality Assurance to the following Quality Management System Standards:

ISO 9001 : 2000

The Quality Management System is applicable to:

Multidisciplinary and evidence based management of couples with fertility problems.

Approval Certificate No: 659361

Original Approval: 30 November 2004
Current Certificate: 30 November 2004
Certificate Expiry: 30 November 2007

Issued by LRQA (Rotterdam)

Leuven Endometriosis Research Group/Network: 8 PhD students

Clinical Leuven

GYN

T D'Hooghe

C Meuleman

L Meeuwis

K Peeraer

C Tomassetti

S Pelckmans

P De Loecker

V Vloeberghs

URO

B. VCleynenbreugel

GE surgery

A D'Hoore

Clinical Nairobi

D Chai

Postdocs Leuven

A Mihalyi; S. Debrock

PhD Students Leuven-Nairobi

C Kyama

A Atunga

PhD Students Leuven

A Vodolazkaia

A Fassbender

C Meuleman

PhD Students Leuven – int'ntl

P Simsa (Budapest)

A Bokor (Budapest)

H Falconer (Karolinska)

Research Nairobi

J Mwenda

D Chai

N Kulia

E Omolo

Veterinary staff

Animal attendants

Leuven Research coördinator

M Welckenhuysen

International collaborators

D. Lebovic (Ann Arbor, USA)

G. Fried (Karolinska, Stockholm, SE)

G. Dunselman (Maastricht, NL)

A. Sharkey (Cambridge, UK)

F. Vilmos (Budapest, HUN)

K. Coleman (Oregon Primate Center, USA)

EU Network for Endometriosis (ENE)

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Disclosure

- Full Professor and Merck Serono Chair (2005-09) Reproductive Medicine (Leuven University)
- Clinical Head Leuven University Fertility Center
- Chair ESHRE Special Interest Group for Endometriosis
- PI ENDOCOST study

WORLD ENDOMETRIOSIS RESEARCH FOUNDATION

INSTITUTE OF PRIMATE RESEARCH NATIONAL MUSEUMS OF KENYA

WHO COLLABORATING CENTRE

Disclosure

- Board member, WERF WORLD ENDOMETRIOSIS RESEARCH FOUNDATION
- Editor-in Chief Gynecologic and Obstetric Investigation
- Research Associate and Chair International Advisory Board, Institute of Primate Research, Kenya
- Fundamental Clinical Investigator for endometriosis, Belgian Research Foundation FWO

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http://www.esnre.com

Learning Objectives: NHPmodels for translational research in endometriosis

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Endometriosis

- **EM (glands/stroma) outside the uterus + chronic inflammation**
- **Retrograde menstruation (Sampson 1927)**
- **Variable phenotype, localization and extent**
- **Subfertility, pelvic pain, reduced QOL**
- **Prevalence**
  7-15% of reproductive age women
  up to 50% patients with pelvic pain/infertility
- **Estrogen dependent**
  rare before menarche or after menopause
- **Progressive:**
  >50% women/baboons after 1-2 years




Endometriosis treatments

- Pain killers
- Oral contraceptives
- Progestins
- GnRH-agonists
- Surgery
- Assisted reproductive therapies
- Hysterectomy
- Yet little investment in causal research

- **Often more than one**
- **Hit and miss**
- **All have side effects**
- **No cure**



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The cost of endometriosis

DRUGS	DIAGNOSTICS	SURGERY	HEALTH CARE	OTHER
NSAIDs	Ultrasound scan	Laparoscopy	GP	ART
Progestagens	Internal scan	Laparotomy	Gynaecologist	A&E visits
c-OCP	MRI	Hysteroscopy	Nurse	Hospitalisation
Danazol	Blood tests	Hysterectomy	Urologist	Alternatives
Gestrinone	Swabs	Endometrial ablation	Gastro-enterologist	Transportation
GnRH-a	Barium enema		Anaesthetist	Child care
Add-back HRT	Sigmoidoscopy	Theatre costs	Radiologist	Work absence
Mirena coil	Endoscopy		Theatre staff	↓ productivity
Antibiotics	Bone scans		Haematologist	↓ education
Anti-depressants	X-rays		Counsellor	↓ activities
			Physiotherapist	
			Psychiatrist	

COMPARATIVE COST: ENDOMETRIOSIS versus OTHER CHRONIC DISEASES

- Review of endo-related cost estimates in USA (Simoens et al, 2007)

  1. annual (2002) healthcare costs + costs of productivity loss:
  = about $ 4000 per patient per year

  2. USA cost per year for endo (2002)
  $22 billion per year
  (at 10% prevalence of endo among women of reproductive age)

  3. **Endo cost considerably higher than cost related to Crohn's disease or to migraine in the USA for 2002**

COMPARATIVE COST:
ENDOMETRIOSIS versus OTHER CHRONIC DISEASES

- **Retrospective review of administrative data for commercial payers of a US insurance company (Mirkin et al, 2007):**

  Extrapolated cost per patient per month (PPPM):

  $ 791: endo
  $ 500: hypertension
  $ 916: diabetes
  $ 1.121: rheumatoid arthritis

  explained by high hospital admission rate/ surgical procedures.


COMPARATIVE COST:
ENDOMETRIOSIS versus OTHER CHRONIC DISEASES

- **Retrospective review of administrative data for commercial payers of a US insurance company (Mirkin et al, 2007):**

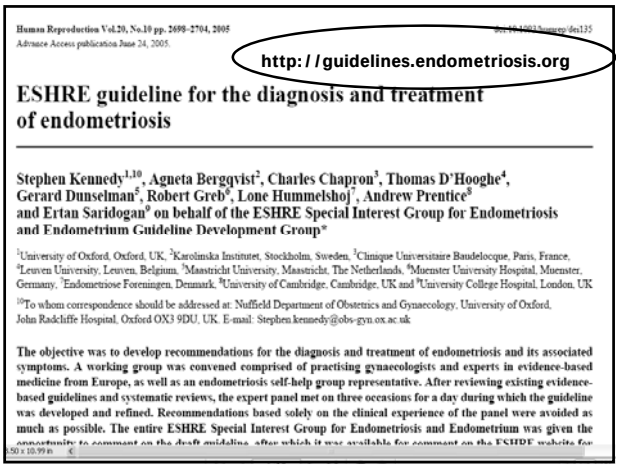
  Women with endometriosis: total direct medical costs: 63% higher than average women

  Explained by added cost due to comorbid conditions:
  interstitial cystitis,
  depression,
  migraine,
  irritable bowel syndrome,
  chronic fatigue syndrome,
  abdominal pain and infertility,...


CALCULATION OF
ENDOMETRIOSIS COST IN EU
IS NEEDED FOR

INCREASED AWARENESS OF
ENDOMETRIOSIS IN

POLITICS DETERMINING
HEALTH POLICY
+ RESEARCH FUNDING

Human Reproduction Vol.20, No.10 pp. 2698–2704, 2005
Advance Access publication June 24, 2005.

http: / /guidelines.endometriosis.org

ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Kennedy[1,10], Agneta Bergqvist[2], Charles Chapron[3], Thomas D'Hooghe[4], Gerard Dunselman[5], Robert Greb[6], Lone Hummelshoj[7], Andrew Prentice[8] and Ertan Saridogan[9] on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group*

[1]University of Oxford, Oxford, UK, [2]Karolinska Institutet, Stockholm, Sweden, [3]Clinique Universitaire Baudelocque, Paris, France, [4]Leuven University, Leuven, Belgium, [5]Maastricht University, Maastricht, The Netherlands, [6]Muenster University Hospital, Muenster, Germany, [7]Endometriose Foreningen, Denmark, [8]University of Cambridge, Cambridge, UK and [9]University College Hospital, London, UK

[10]To whom correspondence should be addressed at: Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK. E-mail: Stephen.kennedy@obs-gyn.ox.ac.uk

The objective was to develop recommendations for the diagnosis and treatment of endometriosis and its associated symptoms. A working group was convened comprised of practising gynaecologists and experts in evidence-based medicine from Europe, as well as an endometriosis self-help group representative. After reviewing existing evidence-based guidelines and systematic reviews, the expert panel met on three occasions for a day during which the guideline was developed and refined. Recommendations based solely on the clinical experience of the panel were avoided as much as possible. The entire ESHRE Special Interest Group for Endometriosis and Endometrium was given the

Role of ESHRE Special Interest Group for Endometriosis (SIGEE)

- Education and training
- ESHRE Guidelines for endometriois: Annual update via Working Group
- ESHRE endometriosis cost working group: 2007-10

ESHRE Endometriosis Cost Working Group

- Initiative for ENDOCOST study
- 8 countries, 10 centers:
  Germany, Hungary, UK, Italy, Denmark, France, Netherlands, Belgium, Switzerland, USA (2)
- Retrospective/Prospective study (2009)
- Team per center: 1 gynecologist + 1 health economist
- Travel/lodging supported by ESHRE
- Collaboration with ASRM SIG Endometriosis
- Sponsored by World Endometriosis Research Foundation

European Network on Endometriosis

First ever EU research grant for endometriosis

1. Pan European epidemiological study
2. Internet based endometriosis gateway
3. Consolidate and formalise the European Alliance

- 8 Associate partners and 4 Collaborating partners
  - Endometriosis UK lead partner
  - Belgium, Denmark, Italy, UK
- Application scored very highly – 87/100 and received funding 300.000 Euro (2007-9)

Learning Objectives: NHPmodels for translational research in endometriosis

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LACK OF PROGRESS IN ENDOMETRIOSIS RESEARCH

1.Unknown duration of endo at diagnosis

2.Inadequate study design: nl controls needed

- **pelvic condition (endo, nl pelvis, other)**
- **symptoms (none, infertility, pain, other)**

3.Endometriosis>surgical gynecological disease. Need for multidisciplinary clinical and research teams.

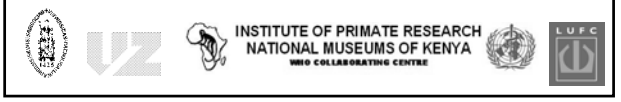
4. Need for good animal models.

NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

Rodents:

- **Advantages:**

1.Low cost
2.Easy handling
3.Genetic manipulation possible (cost!):
KO mice, K-ras transgenic mice (Dinulescu et al, 2006)



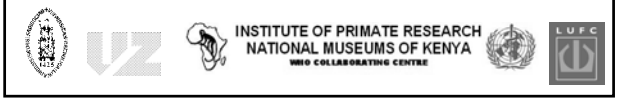
	Rodents	NHP's	Humans
Genetic ally close to humans	-	+	+
Repro anatomy close to humans	-	+	+
Estrus behavior	+	-	-
Repro cycle	5 days	28-33 days	28-30 days
Embryonic aneuploidy	-	?	+
Optional diapause	+	-	-
Multiple implantations	+	-	-
Embryonic control of endometrium	+	-	-
Invasive implantation	-	+	+
Menstruation	-	+	+
Spont Endo	-	+	+
Spt+Ind Endo similar to humans	-	+	+
Spont PF	-	+	+

NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

Rodents:

- **Disadvantages:**

1. wide phylogenetic gap with humans
2. different reproductive endocrinology and anatomy,
3. no menstruation
4. no peritoneal fluid
5. no spontaneous endometriosis,



NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

Rodents:

6. Induced endo: unphysiological induction by uterine square autotransplantation (→ adhesion formation)

7. Induced endo: unphysiological "endometriotic lesions" with limited phenotypes

8. ?human EM-murine peritoneal interaction in nude/SCID: extrapolation possible to human endometriosis?

9. ? Preclinical model for studies testing new drugs: extrapolation not always possible to human endometriosis (Interferon alpha 2b: + in mice, - in women)

NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

NHPs:

- **Disadvantage:**

1. High cost (affordable outside EU and US)
2. Handling requires special expertise/infrastructure
3. Ethically sensitive research

NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

NHPs:

- **Advantages when compared to humans:**

1. Very narrow phylogenetic gap
2. Comparable reproductive endocrinology/anatomy,
3. Menstruation (baboon, rhesus, not all other NHPs)
4. Spontaneous endometriosis,
5. Induced endometriosis by autologous seeding or injection of eutopic EM in pelvis (baboons, rhesus, cynomolgus)
6. Both spontaneous and induced endometriosis: similar phenotype as human endometriosis

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Baboon model endo

Institute of Primate Research
Nairobi, Kenya

WHO Collaborating Center

Research areas:
Reproduction
Infectious Diseases
Ecology and Conservation

20 yrs research collaboration Leuven-Nairobi

- **1990-1993 Baboon model for Endometriosis, Institute Primate Research, Nairobi, Kenya**
- **1993-1995 Fellowship Reproductive Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, (JA Hill/ DJ Anderson) Endometriosis in baboons and women**
- **PhD Leuven 1994 (Promotors: PR Koninckx, CS Bambra) Baboon as model for endometriosis**
- **1996-present: coordinator Center Reproductive Medicine, Leuven University Hospital, Belgium (ISO 9001-2000 certified 11/04)**

20 yrs research collaboration Leuven-Nairobi

1998-2008: 50% fundamental clinical investigator (Flemish fund scientific research)

Clinical Leuven: biobank frozen tissue and DNA + clinical database since 1998

Preclinical IPR Nairobi:

Baboon model: pathogenesis and testing of new drugs (prevention/treatment of endometriosis)

IPR International Advisory Board

- **Established 2007**
- **Initiative by NMK/IPR + supported by WHO (P. Van Look)**
- **Aim:**
- **advise Kenyan leaders about long term development of IPR into African Center of Excellence**
- **increase international research collaboration**

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x1

IPR International Advisory Board

- 12 experts in areas of reproduction, infectious diseases ecology and conservation
- Chair T. D'Hooghe
- Annual meetings, (August + December 07, February 09)

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Slide 36

x1 x292720; 9/11/2007

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UNICITY OF BABOON MODEL

1. Cost affordable outside EU or USA
2. Ethical issues

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***Institute of Primate Research*, Nairobi, Kenya**

Cost per baboon
Purchase: $ 450
Per diem: $ 3
Surgery: $ 60/hour

Proof of concept RCT
15-20 baboons, 6/12:
$ 100.000 USD

2. Ethics of endometriosis research in baboons at IPR

2.1. Baboons are not an endangered species but represent a threat to agriculture in Africa

2.2 Baboons live in their natural habitat at IPR

2.3. Lack of other clinically relevant preclinical animal models to study cause-effect relationships:

Only NHPs do have spontaneous/induced endo similar to the disease in women

2.4. Ethical need to show safety + efficiency of new drugs before application in women

Ethics of endometriosis research in baboons at IPR

2.5. For each project: double approval by ethical committees from both IPR and from Leuven University

2.6. Global level: capacity building of Primate Research Center in poor resource country could/should be seen as relevant effort in the context of North-South collaboration

UNICITY OF BABOON MODEL

3. Noninvasive monitoring of menstrual cycle:

- Perineal inflation= Foll. Phase
- Perineal deflation=Luteal phase
- Ovulation = perineal deflation minus 2 days

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4. Continuous breeding in captivity
(>< rhesus)

5. Size (12-15kg) and Strength
(>rhesus>cynomolgus)
-repetitive blood sampling
(hourly during 24 hr in chair; daily)
-repetitive surgery
(every 2-3 days; D'Hooghe et al, 1996)

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6. Spontaneous peritoneal fluid (PF)
about 2 mL after ovulation (>< rhesus)
(D'Hooghe et al, 1991)

7. Vaginal transcervical uterine access.
-endometrial biopsy (D'Hooghe et al, 1991)
-embryo transfer
-preimplantation embryo flushing
-hysteroscopy
(D'Hooghe et al, 1991; 1995; 1996; 2004; Nyachieo et al. 2007, Chai et al., 2007).

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BABOON MODEL for non-endometriosis
REPRODUCTIVE RESEARCH

- **HCG exposure –EM implantation model (oviductal minipump HCG)- Fazleabas**
- **Embryo- EM implantation model (hysteroscopic interventions) –Leuven/IPR**
- **Reproducible IVF system in baboons (Embryonic stem cell development)- Leuven/IPR**
- **Prevention heterosexual transmission SHIV (vaginal immunology) –Leuven/IPR/BU**

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8. **Spontaneous endo similar to human endo:**

   laparoscopic appearance,
   pelvic localization,
   microscopic aspects

   [D'Hooghe, 1997]

UNICITY OF BABOON MODEL

9. **AFS/ASRM endo classification system adapted for baboon** (D'Hooghe et al, 1995)

10. **Full spectrum of spontaneous endo:**
    minimal endo (prev 25%, D'Hooghe et al, 1991**)**
    to severe endo →
    bowel obstruction/death

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11. **Induced endo similar to human endo:**

    laparoscopic appearances,
    pelvic localization,
    microscopic aspects

    [D'Hooghe et al, 1995]

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12. In vivo culture model for study of early endometrial-peritoneal interaction (after induction)

- EM pellet versus EM supernatant
- Early establishment of endo: D1-3-6-10-15-25

UNICITY OF BABOON MODEL

13. Preclinical model for study of cause-effect relationships in endometriosis (after induction)

Design:
- longitudinal observation in same baboon
- before, during and after induction

- interventions at well defined times of the cycle

- assess local effects: EM, PF, nl peritoneum, endo lesions
- assess systemic effects: PB

IDEAL ANTI-ENDOMETRIOSIS DRUG

1. Prevent the development of endometriosis
2. Cures existing endometriosis, also after cessation of treatment
3. No interference with menstrual cycle
4. No side effects
5. Safe for women who wish to become pregnant

UNICITY OF BABOON MODEL

14. Evaluate new drugs for prevention of endometriosis

Aim: prevent endometrial-peritoneal attachment after IP injection of menstrual EM

3 groups, n=5 each,
test drug, - control, + control

a. Pretreatment of baboons N days→induction
b. Pretreatment of EM at time of induction
c. Combination of a+b

(TNF-alpha inhibitors, D'Hooghe et al, 2006)

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15. Evaluate new drugs for treatment of endometriosis

Aim: reduction of existing endometriotic lesions (after induction using IP injection of menstrual EM)

3 groups, n=5 each,
test drug, - control, + control

1. **Induction laparoscopy (D1-2)**
2. **Staging laparoscopy pre-treatment (D25)**
3. **RCT 3 groups and treat during 1-3 months**
4. **Staging laparoscopy post-treatment**

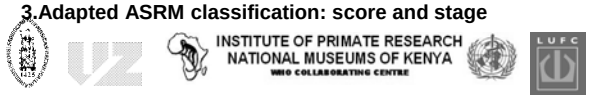
(TNF-alpha inhibitors, Falconer et al, 2006; ROSI, Lebovic et al, 2007)

UNICITY OF BABOON MODEL

16. Endometriosis outcome variables in prevention or treatment trials
(D'Hooghe et al, 2006; Falconer et al, 2006; Lebovic et al, 2007)

1.Endometriosis Lesions: N, surface area, depth, volume
2. Phenotype of endo lesions: black, red, white,….
2. Adhesions: N and surface area
- **endo-related versus non endo-related**
- **Integrated in >< independent from ASRM staging**

3.Adapted ASRM classification: score and stage



UNICITY OF BABOON MODEL

17. General and reproductive safety in prevention or treatment trials

(D'Hooghe et al, 2006; Falconer et al, 2006; Lebovic et al, 2007)

1. General: side effects
2. Cyclicity
   - -cycle length, length follicular phase/luteal phase
   - -E2/P assays
3. Fertility and miscarriage
4. Offspring: congenital abnormalities

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18. Model Endometriosis-associated infertility

(D'Hooghe et al, 1994 and 1996)

1. Normal MFR in baboons with minimal endo
2. Reduced MFR in baboons with
   mild, moderate or severe endo (spontaneous and induced),
   - related to an increased incidence and recurrence
   of the Luteinized Ruptured Follicle Syndrome
   - also in the absence of ovarian endometriotic cysts
   (D'Hooghe, 1997; D'Hooghe et al, 1996 several studies).

   - ? Causal role of EM changes (Fazleabas)
   - ? Temporal relationship between
   time of induction and onset of subfertility




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19. Model for Treatment of endometriosis-associated subfertility

(Falconer et al, 2007)

with standardization for:

1. Degree of endometriosis (amount EM for Ipseeding)
2. Ovulation (perineal cycle),
3. Male factors (proven fertility, nl sperm)
4. Sexual intercourse
   - timing
   - behavioral observation
   - postcoital test




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UNICITY OF BABOON MODEL

20.? Endometriosis -associated pain

- **Under investigation at IPR**
- **Pilot study in 5 baboons with 24 hour camera surveillance before-after induction**
- **Collaboration Dr Coleman (Oregon Primate Center, USA)**

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VALIDATION OF BABOON ENDOMETRIOSIS MODEL

- **Pub Med (updated 28th Jan 2009):**
- **Baboon AND Endometriosis N=62**
  - **34 Leuven-IPR Nairobi group (T. D'Hooghe)**
  - **14 Chicago group (A. Fazleabas)**
  - **6 San Antonio Group (B. Barrier)**
  - **8 others**

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Learning Objectives: NHPmodels for translational research in endometriosis

1. **Introduction**
2. **Endometriosis cost**
3. **NHPrimate >< rodent models**
4. **Development baboon model endo**
5. **Unicity/validation baboon model endo: 20 relevant points**
6. **Endo research baboon model: 5 relevant observations**

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5 observations
BABOON ENDOMETRIOSIS MODEL

- **Uninterrupted retrograde menstruation causes endometriosis**
- **Endometriosis causes pelvic inflammation + systemic immunomodulation**
- **Endometriosis causes secondary endometrial changes**
- **General immunosuppression does not cause or cure endometriosis**
- **Specific immunomodulation may prevent and/or cure endometriosis**

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UNINTERRUPTED RETROGRADE MENSTRUATION CAUSES ENDOMETRIOSIS

1. **Prevalence of spontaneous endometriosis increases with duration of captivity (D'Hooghe et al, 1996a).**
2. **Spontaneous endometriosis is progressive when followed during 2 years (D'Hooghe et al, 1996b)**
3. **Baboons with an initially normal pelvis develop in 64% histologically proven minimal endometriosis after 32 months (D'Hooghe et al, 1996c)**
4. **Positive correlation between weight of EM tissue used for intrapelvic seeding and extent of endometriosis in baboons (D'Hooghe et al, 1995)**

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UNINTERRUPTED RETROGRADE MENSTRUATION CAUSES ENDOMETRIOSIS

5. **Iatrogenic obstruction of the cervix (supracervical ligation) leads to diminished antegrade menstruation + pelvic endometriosis within 3 months**
   (D'Hooghe et al, 1994)
6. **Menstrual EM: higher capacity than secretory EM in endo induction**
   (D'Hooghe et al, 1995)

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ENDOMETRIOSIS CAUSES
PELVIC INFLAMMATION + SYSTEMIC IMMUNOMODULATION
(D'Hooghe et al., 2001, Kyama et al., 2003)

1. PF: Increased volume, WBC conc, inflamm cytokines:
- during spontaneous retrograde menstruation
- following intrapelvic injection of endometrium (within 1/12)
[D'Hooghe et al.,1999, D'Hooghe et al., 2001].

2. PF: Increased WBC concentration, increased % of macrophages and cytotoxic T cells:
- in PF of baboons with spontaneous endometriosis [D'Hooghe et al 1996a, D'Hooghe et al 1997a].




ENDOMETRIOSIS CAUSES
PELVIC INFLAMMATION + SYSTEMIC IMMUNOMODULATION
(D'Hooghe et al., 2001, Kyama et al., 2003)

3. PB:
increased % of CD4+ and IL2R+ cells in baboons with stage II-IV endo (both spontaneous long term endo and induced endo)
>< recent spontaneous endometriosis (Stage I) or nl pelvis.




Endometriosis causes secondary EM changes

- **Research Group A. Fazleabas (Chicago)**
- **? Clinical relevance to endometriosis-associated subfertility**



General immunosuppression does not cause or cure endometriosis

3/12 high dose immunosuppression with azathioprin and methylprednisolone

1. No effect on:
- **the incidence of spontaneous endometriosis**
- **the extent of induced endometriosis,**

2. Only marginal stimulatory effect on: progression of spontaneous endo

[D'Hooghe et al., 1995c]

Specific immunomodulation may prevent and/or cure endometriosis

- **PPAR-gamma activators reduce and prevent induced endometriosis (Lebovic et al, 2007; 2009)**
- **TNF alpha antagonists prevent and reduce spontaneous or induced endometriosis, mainly via an effect on active red peritoneal lesions (3 independent studies Barrier et al, 2004; D'Hooghe et al, 2006; Falconer et al, 2006)**
- **MAJOR CONCERN: GENERAL AND REPRODUCTIVE SAFETY**

Overall conclusions

- **NHPs = most relevant preclinical models for endo research**

- **Among NHPs, baboons represent**
- **the most relevant and**
- **the best validated model for endo research**

Overall conclusions

Most important areas of endometriosis research in baboons:

1. Early pathogenesis
2. Cause-effect relationship studies
   may lead to discovery of new biomarkers
   and therapeutic targets
3. Test new drugs in prevention or treatment of endometriosis and endometriosis-associated subfertility
4. Test new endometriosis drugs with respect to general and reproductive safety
5. Validation baboon model for pelvic pain

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Overall conclusions

Long term support for IPR, Nairobi, Kenya

1. Increasing international collaboration
2. Role of IPR International Advisory Board, Kenya Government and WHO

GLOBAL RESEARCH EFFORT TO STUDY CAUSE-EFFECT RELATIONSHIPS OF ENDOMETRIOSIS IN BABOON MODEL AT IPR

1. Sufficient N baboons with long term follow-up (+ pain)
2. Paired comparisons before+after induction (+ pain)
3. Building biobank for international collaborative research

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- Institute Primate Research, Nairobi, Kenya: CS Bambra, PhD
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K. Coleman (Oregon Primate Center, USA)
EU Network for Endometriosis (ENE)

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European Network on Endometriosis

First ever EU research grant for endometriosis

1. Pan European epidemiological study
2. Internet based endometriosis gateway
3. Consolidate and formalise the European Alliance

- 8 Associate partners and 4 Collaborating partners
  - Endometriosis UK lead partner
  - Belgium, Denmark, Italy, UK
- Application scored very highly – 87/100 and received funding 300.000 Euro (2007-9)

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B Quintens

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- WHO
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- Oxford and Cambridge Universities, UK
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- Karolinska University, Stockholm, Sweden (H. Falconer)
- Semmelweis University, Budapest, Hungary (A.Bokor)
- Endometriosis Association, Milwaukee, USA
- World Endometriosis Research Foundation, London, UK

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System biology tools and preclinical models for translational research in endometriosis and adhesion formation: lessons from cancer and inflammation biology.

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