

Endometriosis Research: Barriers to Progress

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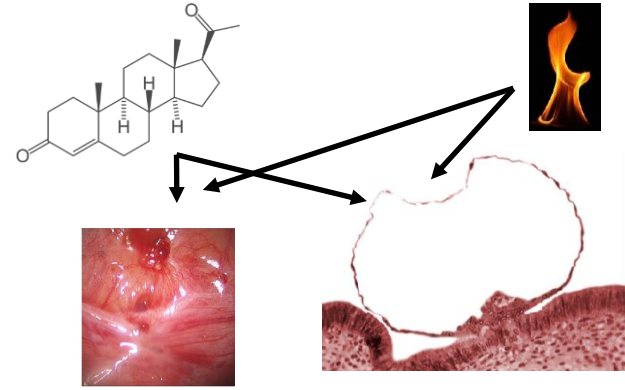
The Bleeding Roses, Salvador Dali, 1930



COI Disclosure and Acknowledgements

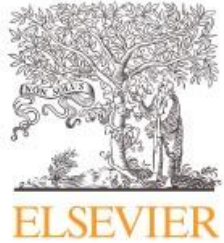
- I receive royalties from Cicero Diagnostics for the ReceptivaDX[®] test for screening/diagnosis of endometriosis in subfertile women.
- grateful recipient of the following grants from the Eunice Kennedy Shriver NICHD/NIH that currently support endometriosis research: P01HD106485, R01HD100329
- I will use gender binary terms for clarity and brevity but are not meant to exclude the spectrum of gender diversity.

What is Endometriosis?



Endometriosis is the chronic persistence of endometrial cells outside the uterine cavity ,

Symptoms
and/or
burden



In Press



pain
sion

Associated
complications
endometriosis

Invited Special Article

A Call for New Theories on the Pathogenesis and Pathophysiology of Endometriosis

The Endometriosis Initiative Group^{1*}

cy
disease,

Cause and risk factors remain obscure.

Scope of Endometriosis



Common, but true incidence is uncertain:

- $\approx 10\%$ of reproductive age women

Endometriosis is a common, highly impactful, sometimes debilitating disease of unclear etiology, which is difficult to diagnose or assess, lacks a cure, and lacks adequate treatment options.

Treatment

Clear opportunity for endometriosis research to make a powerful impact on the lives of many women.

- Surgical treatment sometime requires hysterectomy.
- Medical treatments incompatible with fertility and limited by side effects.

🌈 **Goal:** Readily diagnose and prevent, treat or cure endometriosis.

- Political, Regulatory, and Resource Issues
- Lack of Non-Surgical Diagnosis & Evaluation Methods
- Animal Model Differences

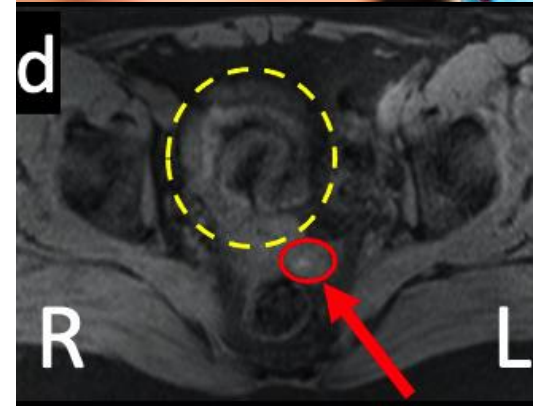


Endometriosis Diagnosis Difficult

PubMed Search “Endometriosis Diagnosis” (March 2, 2024):
18,817 articles!

Non-surgical Methods that have been proposed:

- Symptom Surveys
- Ultrasound and MRI – DIE, Endometrioma
- Blood and urine biomarkers
- 2016 Cochrane Reviews:
 - Systematic reviews of possible Urinary, Blood, Endometrial Tissue, and Combined biomarkers
 - Among the 792 relevant papers, reviewers could not recommend any biomarkers as screening or diagnostic test.



Lack of a Non-Surgical Diagnosis Limits Human Research

Who has the disease in a study cohort?

- For non-DIE and non-Endometrioma cases, only those with reason for pelvic surgery can be detected and those who are detected often have had complete disease removal, further complicating case definition.

• Did disease recur in subjects?

An example of the difficulties posed by lack of a non-surgical test

• How does one test a new treatment?

- Can test pain symptoms...
- What is the natural history of untreated lesions?
 - Can only be inferred from those having multiple surgeries and age of patient.

Human Intervention Studies: Surgery for Stage 1 – 2 Endo



The New England Journal of Medicine

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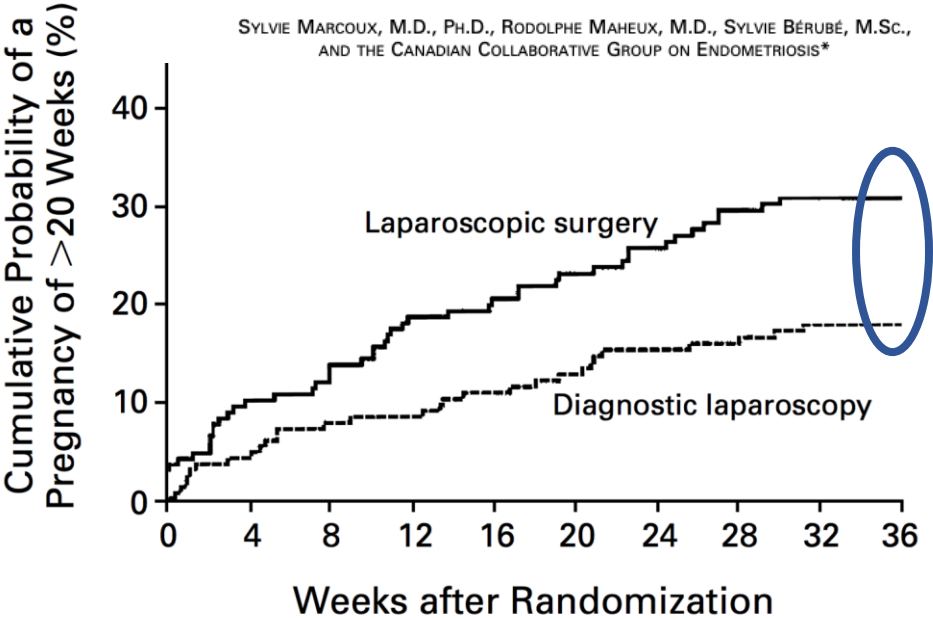
JULY 24, 1997

NUMBER 4



LAPAROSCOPIC SURGERY IN INFERTILE WOMEN WITH MINIMAL OR MILD ENDOMETRIOSIS

SYLVIE MARCOUX, M.D., PH.D., RODOLPHE MAHEUX, M.D., SYLVIE BÉRUBÉ, M.Sc.,
AND THE CANADIAN COLLABORATIVE GROUP ON ENDOMETRIOSIS*



After 9 months of follow-up, about twice the number of women were pregnant after surgical ablation of lesions!



Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Study or Subgroup	Ablation or excision Events	Total	Diagnostic laparoscopy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Ablation or excision vs diagnostic laparoscopy							
Gad 2012	7	20	5	21	9.6%	1.72 [0.44, 6.72]	
Marcoux 1997	63	172	37	169	71.8%	2.06 [1.28, 3.33]	
Moini 2012	9	73	7	73	18.6%	1.33 [0.47, 3.77]	
Subtotal (95% CI)		265		263	100.0%	1.89 [1.25, 2.86]	
Total events:	79		49				
Heterogeneity: Chi ² = 0.59, df = 2 (P = 0.75); I ² = 0%							
Test for overall effect: Z = 3.02 (P = 0.003)							

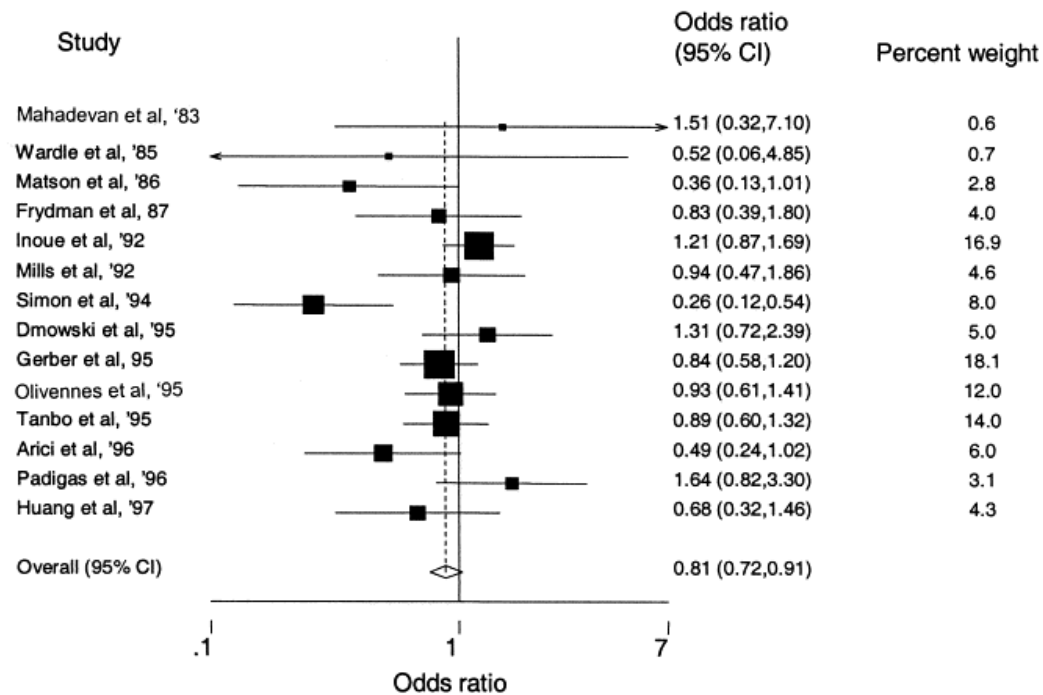
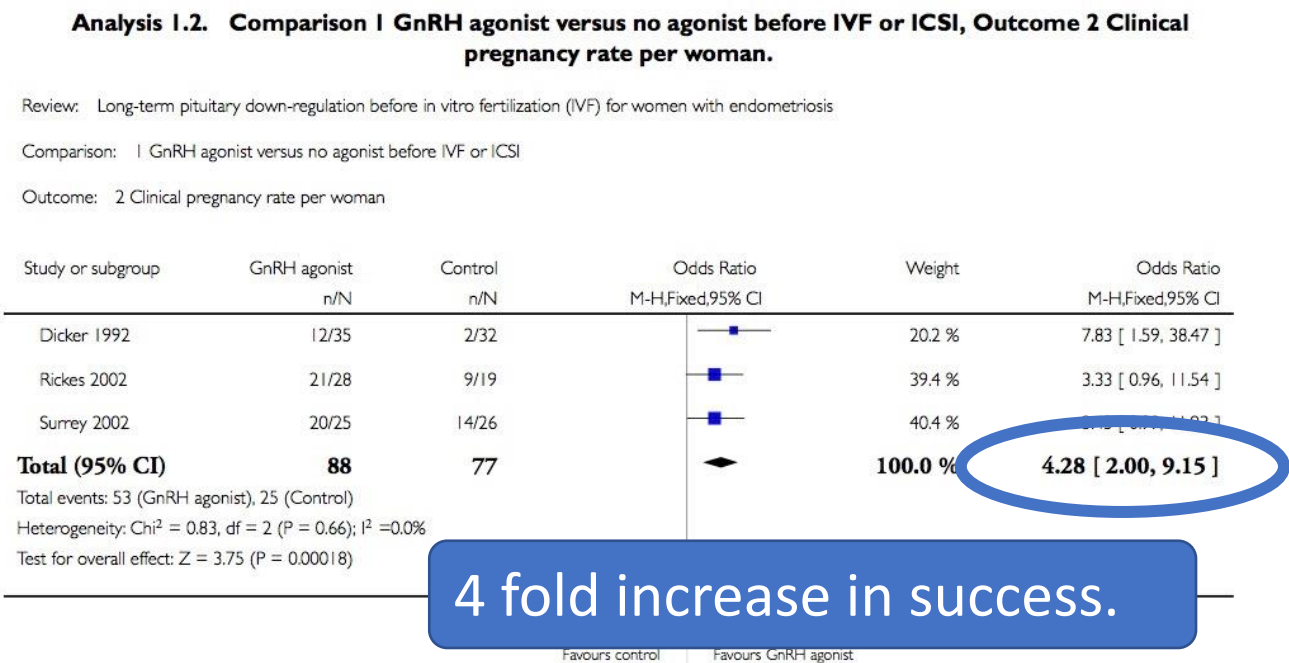
Risk of bias legend

(A) Random sequence generation (selection bias)

0.1 0.2 0.5 1 2 5 10
Increased by diagnostic Increased by surgeon

Human Intervention Studies: Prolonged Lupron

3-6 Months of Lupron before IVF



Not all data show an effect of endometriosis on IVF success

ORIGINAL ARTICLE: ENDOMETRIOSIS



Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database

Suneeta Senapati, M.D., M.S.C.E.,^a Mary D. Sammel, Sc.D.,^b Christopher Morse, M.D.,^c and Kurt T. Barnhart, M.D., M.S.C.E.^{a,b}

- Careful Analysis
- Excellent statistical methodology
- USA SART data.

No effect of endometriosis on Pregnancy or Live birth.

Why does this study show no effect?

Who has Endometriosis in the Fertility Clinic?

SART Cohort:

- Surgery is no longer routine for infertility patients, so endometriosis ascertainment is extremely low.
- National data for 2019 shows **2.5% of first IVF cycles include a diagnosis of endometriosis.**
- **Previously estimated prevalence in infertile women, when surgery was common = is 25% to 75% .**

The lack of a non-surgical method of disease diagnosis and assessment is an enormous barrier to research progress.

2.5/75 (3 %) and 2.5/25 (10%) and the vast majority of women with endometriosis (90% – 97%) in the cohort are labeled as not having the disease!

Furthermore, many of those with surgically-detected disease, will have had lesion removal or destruction – further biasing away from an effect!

Diagnostic ideas being developed

Development is slow, restricted to those planning surgery or inferred from symptoms of pain and/or infertility.

Clear opportunity for diagnostic test research to have a large clinical and research impact! Probably needs a major funding push and ability to pursue novel ideas.

🌈 **Goal:** Readily diagnose and cure or optimally treat endometriosis.

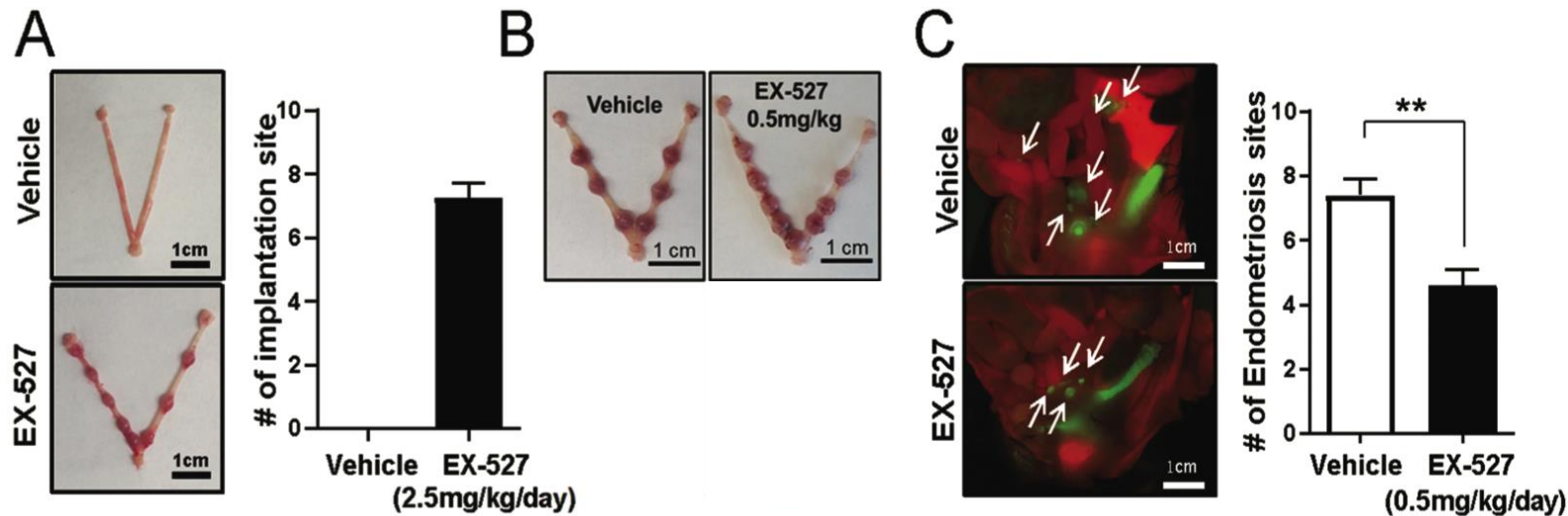
- Political, Regulatory, and Resource Issues
- Lack of Non-Surgical Diagnosis & Evaluation Methods
- Animal Models



Rodent Models



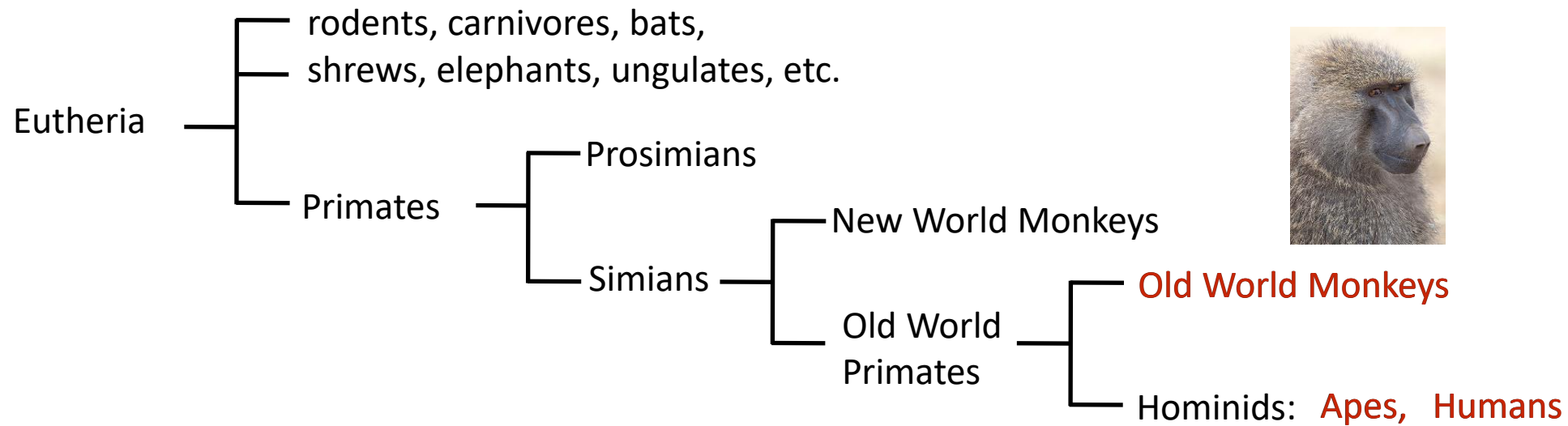
Murine models are genetically tractable, cost-efficient, and reproduce aspects of human disease, including pain and infertility as well as defective decidualization as well as endometrial overexpression of BCL6 and SIRT1.



Limitations of Animal Models:

Only Menstrual Species Get Endometriosis

Rodent models are surgically-induced and cannot naturally have endometriosis: limits generalization of findings.



Studying primates and trying to monitor for endometriosis is, similar to humans, very difficult.



Serendipity: A New, Non-surgical, Monkey Endometriosis Model!

Rhesus Monkeys Treated with low
dose Testosterone

Endometriosis (n=10/group)
Previously published at year 5

A non-surgical, NHP model that both allows observation of early endometriosis AND suggests that altered energy metabolism is a potential cause of endometriosis!

An outstanding, but expensive opportunity to gain substantive knowledge about this disease.

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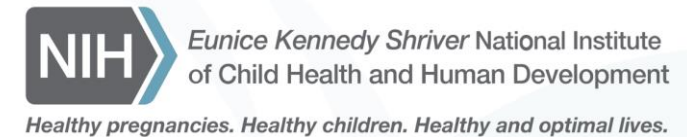


Systematic Limitations

Administrative burdens of NIH grants, health care systems, EHRs, educational and clinical administration, and EHR systems have increased exponentially. These result in a Sisyphean burden on physician-scientists, exacerbated in small academic REI divisions secondary to the demands of assisted reproduction.



There is not an Institute that is largely focused on gynecological or reproductive health.



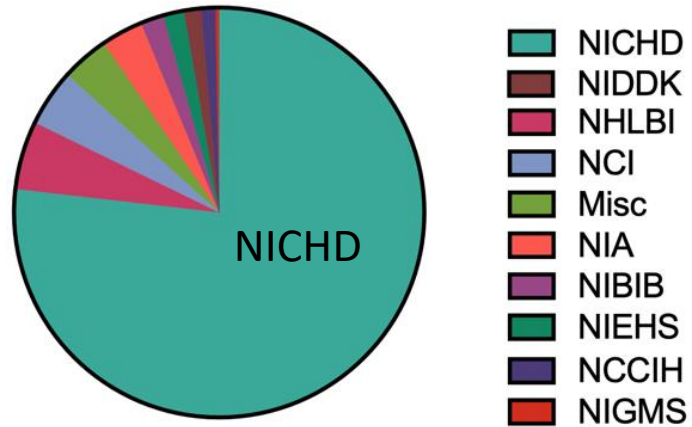
Dickey-Wicker and Hyde amendments prevent almost all research involving IVF, making it harder to study endometriosis and infertility.



NIH funding priorities for Endometriosis

Endometriosis

Prevalence = 10% Repro Age Women



Total NIH = \$34 Million

NICHD = \$26 Million

\$76.2 million NIH spent
on dermatitis

Diabetes

Prevalence = 11.6% Population

Total NIH = \$3.5 Billion <!>

**NICHD = \$71,447 million, ~3x
endometriosis**



Eunice Kennedy Shriver National Institute
of Child Health and Human Development

Healthy pregnancies. Healthy children. Healthy and optimal lives.

> 15x amount spent on endometriosis

NICHD = \$39.5 million/yr

Why are Endometriosis and Fibroids Low Priority



Dissolution of the Reproductive Medicine Network (RMN)



National Institute of Women's Health
Promoting Gender-Specific Health Throughout Life

*A wise man's question contains half
the answer.*

- Solomon Ibn Gabirol (aka Solomon ben Judah)
Andalusian Jewish Poet and Philosopher (1021 – 1070)

