

Clinical translation: IVF, Endometriosis and Pregnancy Outcomes

Bruce A. Lessey MD, PhD

Greenville Hospital System
University of South Carolina School of Medicine
Greenville, SC
USA



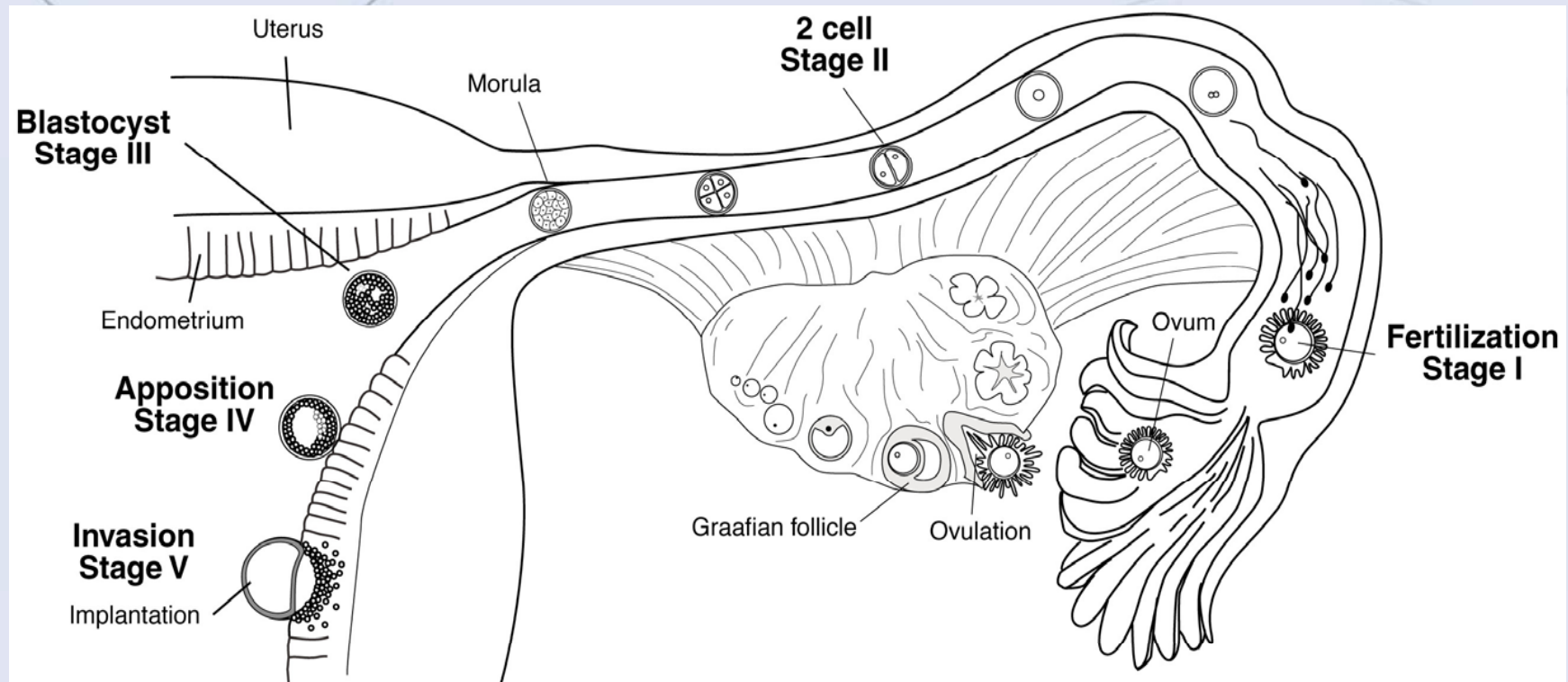
L SYSTEM
L CENTER



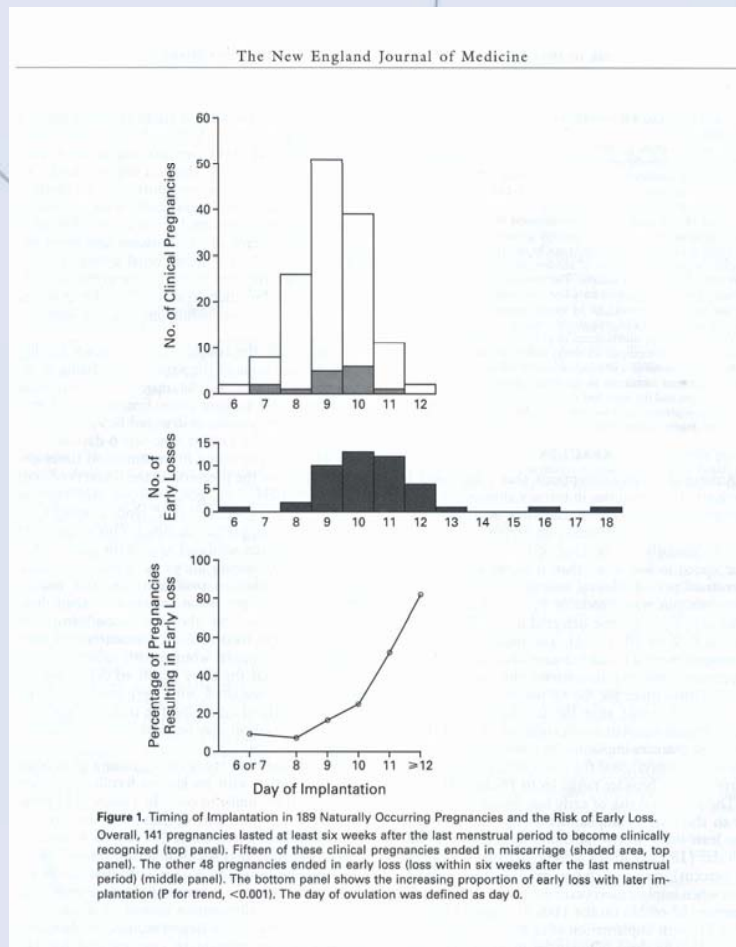
Overview

- Two recent studies
 - Endometriosis and unexplained infertility
 - Effect of surgical treatment
 - IVF and endometriosis
 - Unexplained IVF failure
 - Correctable defect?
 - Both studies give us insight into the role of minimal or mild disease on implantation
 - Real, profound and reversible

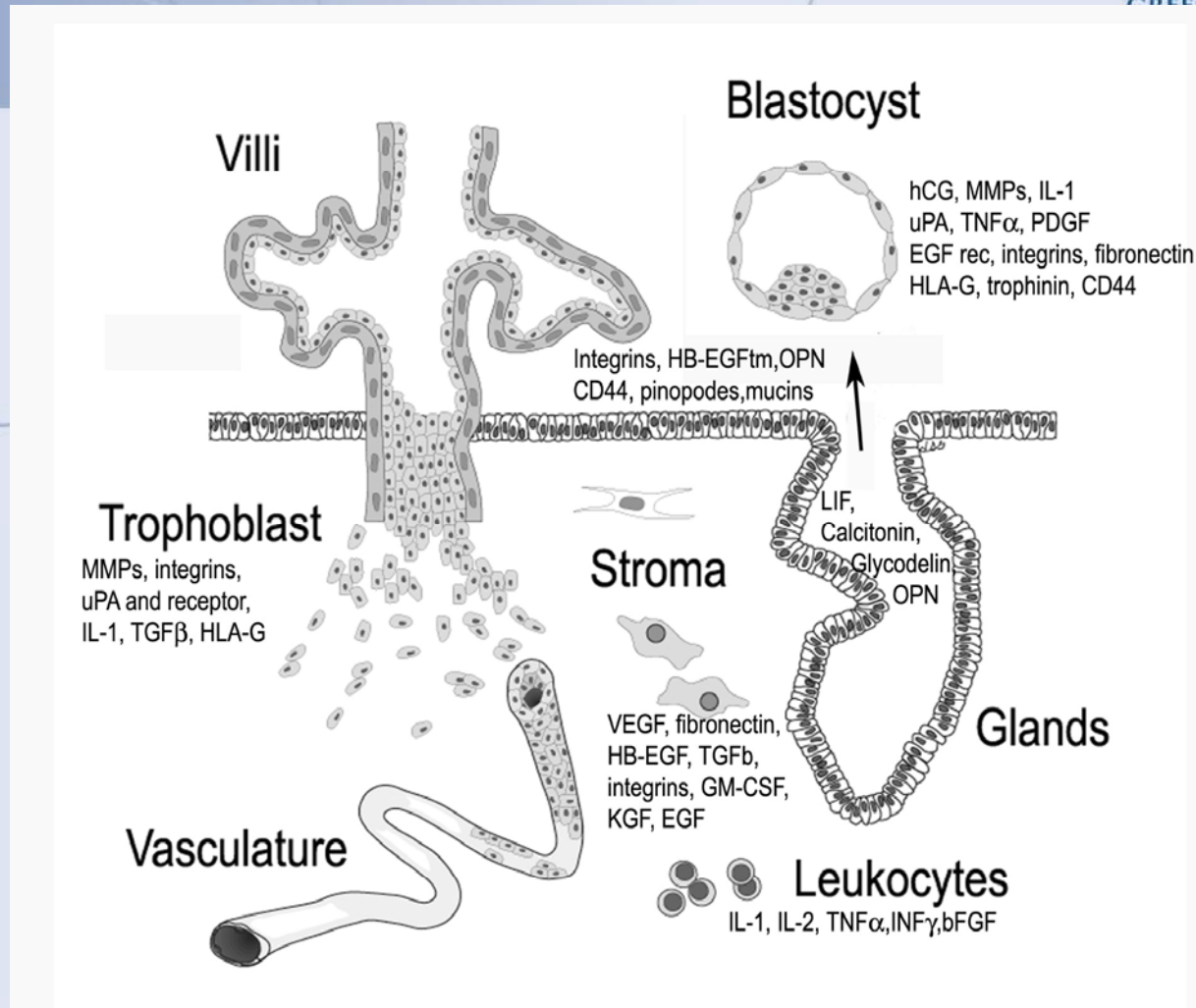
Implantation



Implantation Requires Synchrony

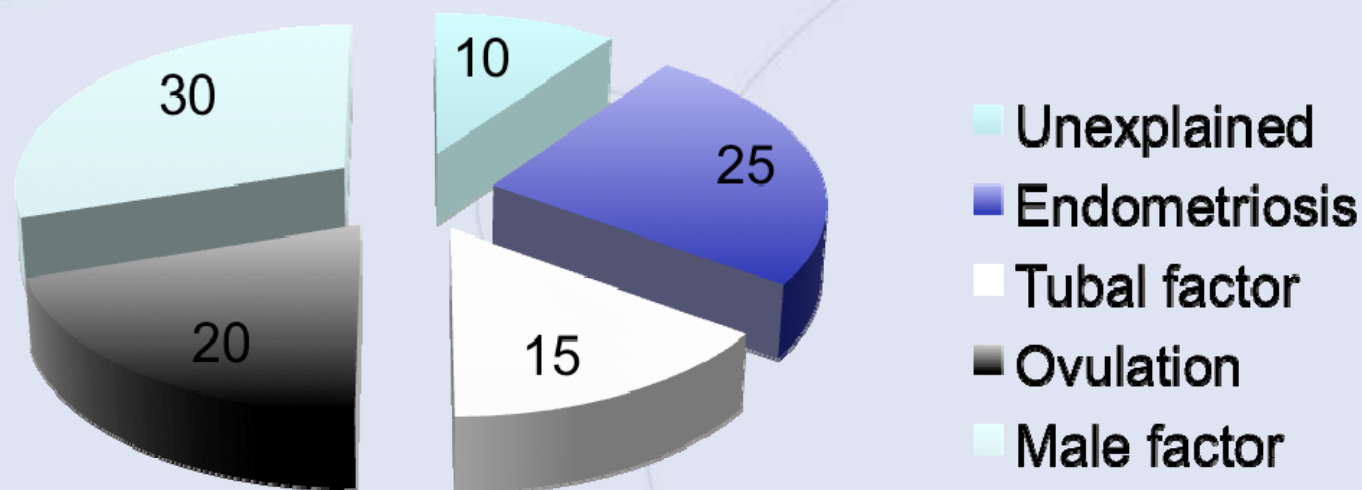


- Wilcox et al.
NEJM 340:1796,
1999
 - Delayed implantation leads to miscarriage
 - Miscarriage goes up with each day of delay
 - Clinical evidence for the window of implantation



Causes of Infertility

Diagnosis



Unexplained Infertility



- 10-20% of infertile couples are given this “diagnosis”
- Reflects an incomplete infertility evaluation
- Most cases represent undiagnosed endometriosis
- Can lead to empiric and costly therapies that may be effective

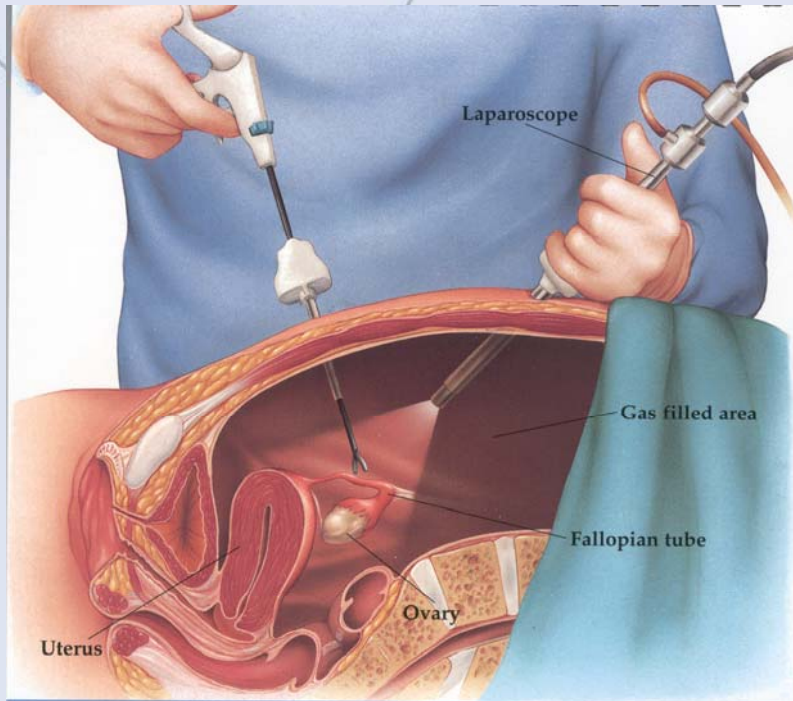
Background

- ASRM supports the use of L/S in UI
 - *Fertil Steril 2006;86 (5 Suppl):S264-S7*
- Others argue against L/S
 - *Balash Hum Reprod 2000;15:2251; Fatum Hum Reprod 2002;17:1-3*
- IVF is a cost-effective treatment
 - *Reindollar et al, FASTT Trial, FertilSteril 2010*
- IVF not covered by insurance in most states in the US
- Endometriosis reduces IVF success
 - *Barnhart et al, Fertil Steril 2002*
- IVF failures may do better after L/S
 - *Littman et al., Fertil Steril 2005*

Infertility and Endometriosis

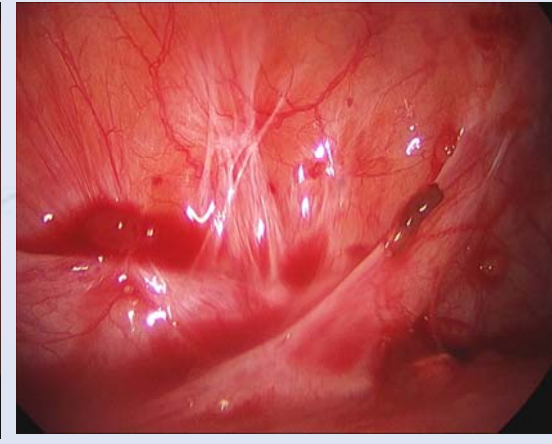
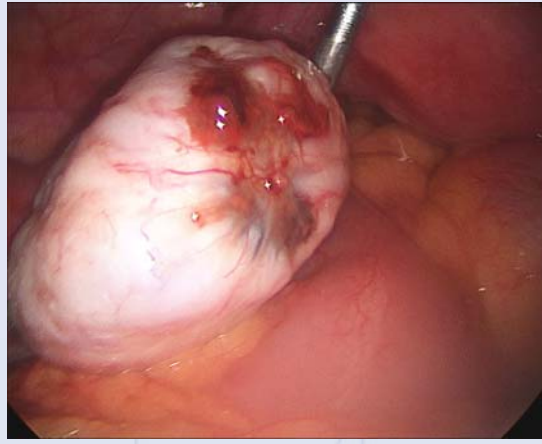
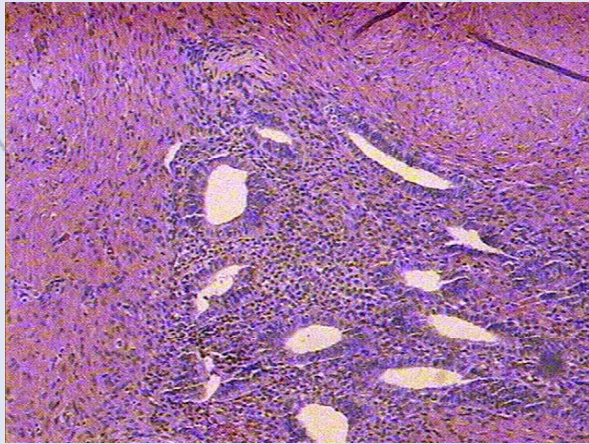
- Evidence for this association
 - Animal models
 - Donor insemination
 - Prevalence of endometriosis in normal fertile women vs. the infertile woman
 - Progesterone resistance phenomena and DNA microarray studies
 - Treatment data (surgical, not medical)
 - IVF data (Barnhart et al)

Laparoscopy



- Required to diagnose endometriosis
- It can be therapeutic as well as diagnostic
- Useful in patients with pain or UI

What is Endometriosis?



- Fragments of the endometrium that grow outside the uterus
- Defined as the presence of glands and stroma outside the uterus

Signs of Endometriosis

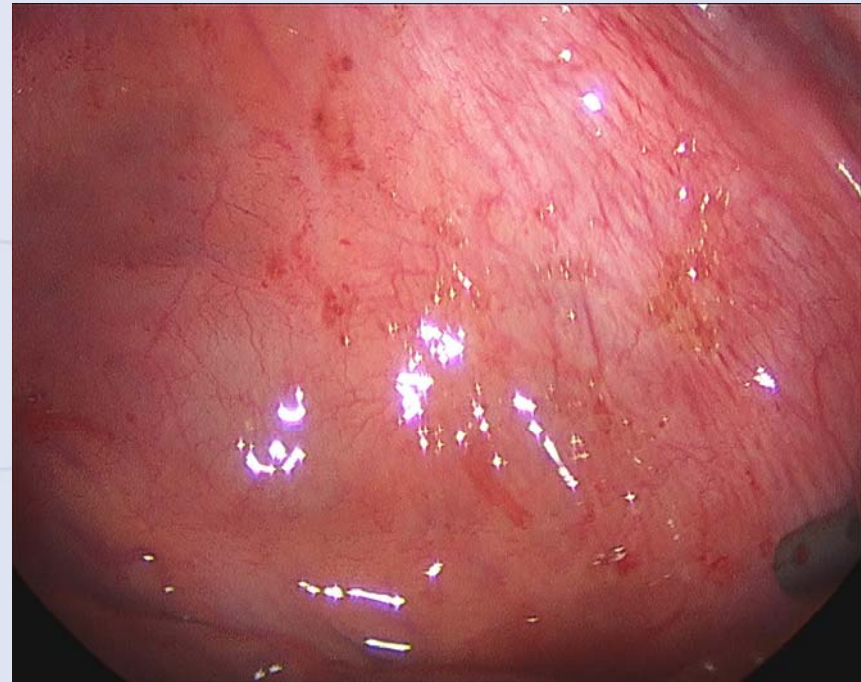
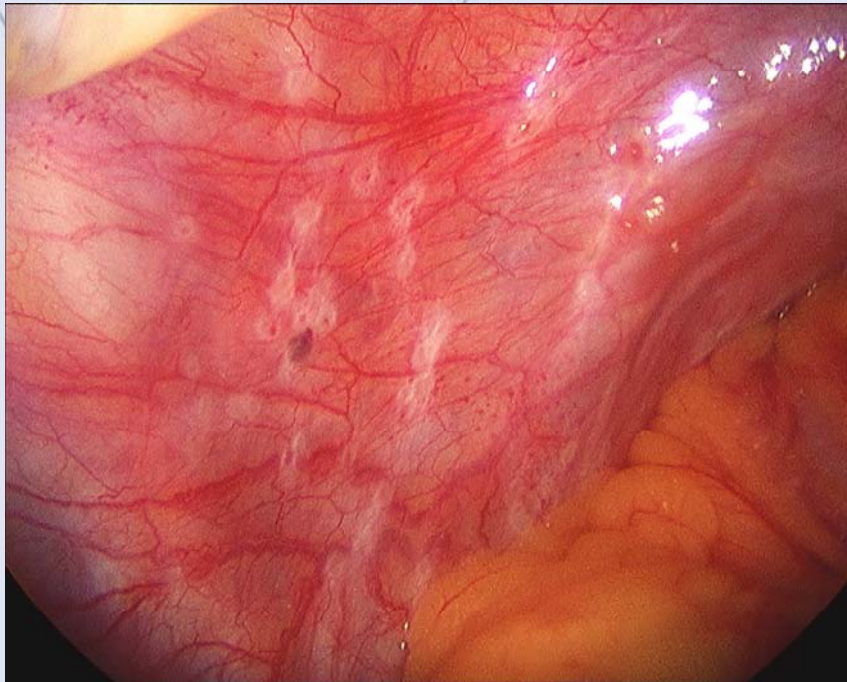
- Dysmenorrhea
- Dyspareunia
- Infertility
- Late luteal spotting
- Bladder symptoms
- Bowel symptoms
- Nausea during the menses
- Nothing!

Appearance

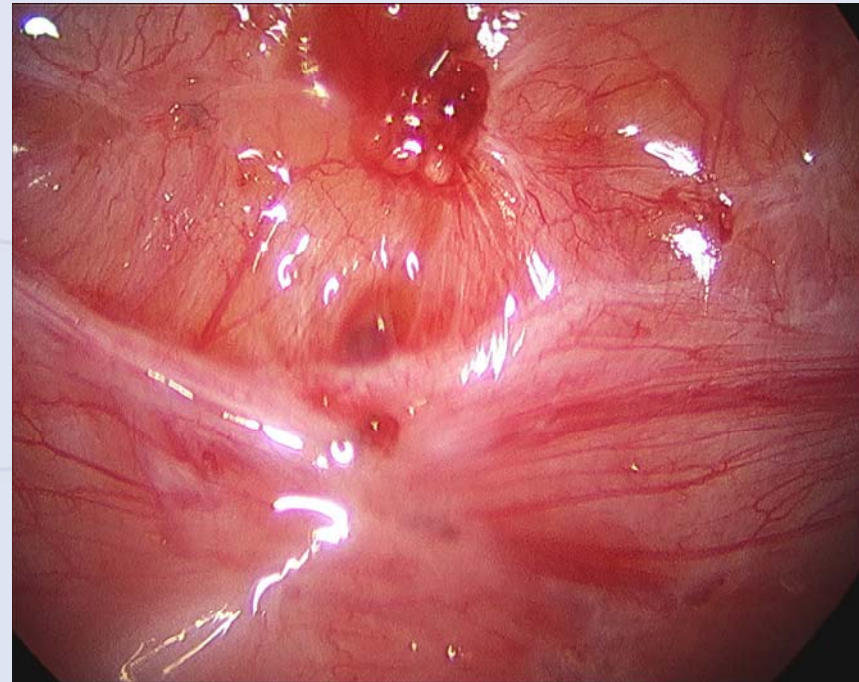
Endometriosis can be subtle or obvious

- Blue/black “Powderburn” lesions
- White - opacified
- Red flame like lesions
- Vesicular lesions
- Peritoneal windows
- Nodular (deep) endometriosis
- Adhesions/alterations in blood vessel pattern
- Invisible?

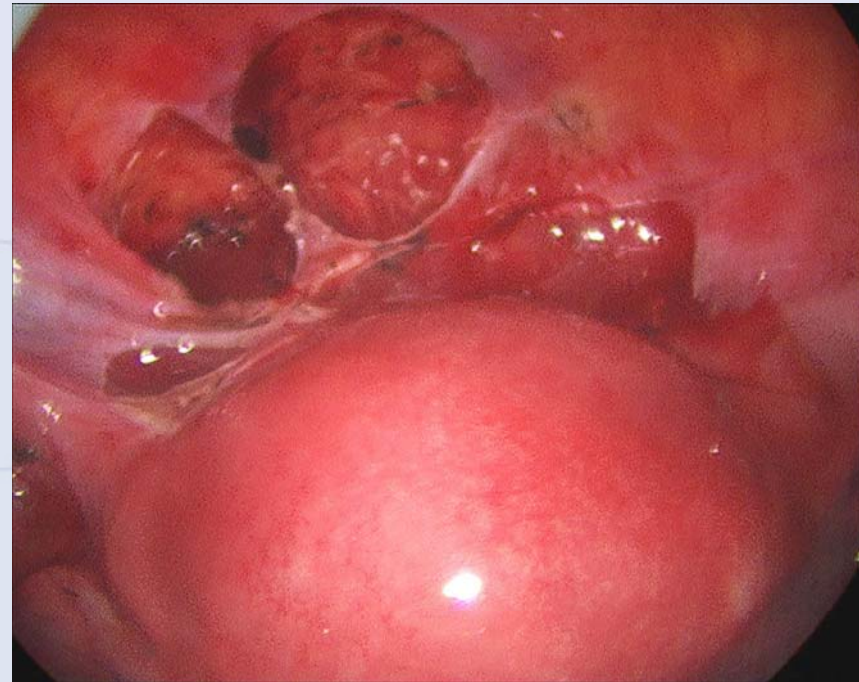
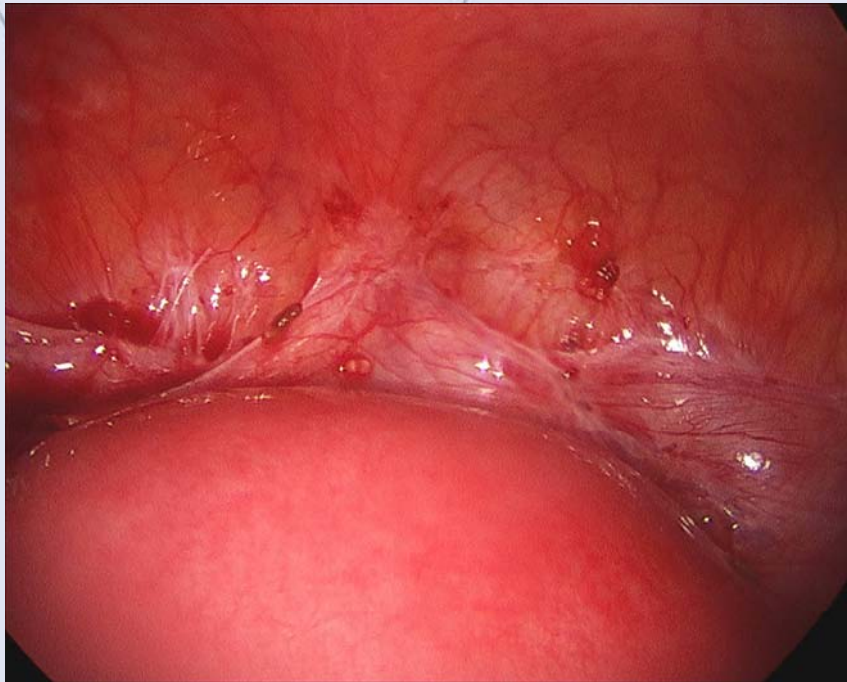
Subtle Endometriosis



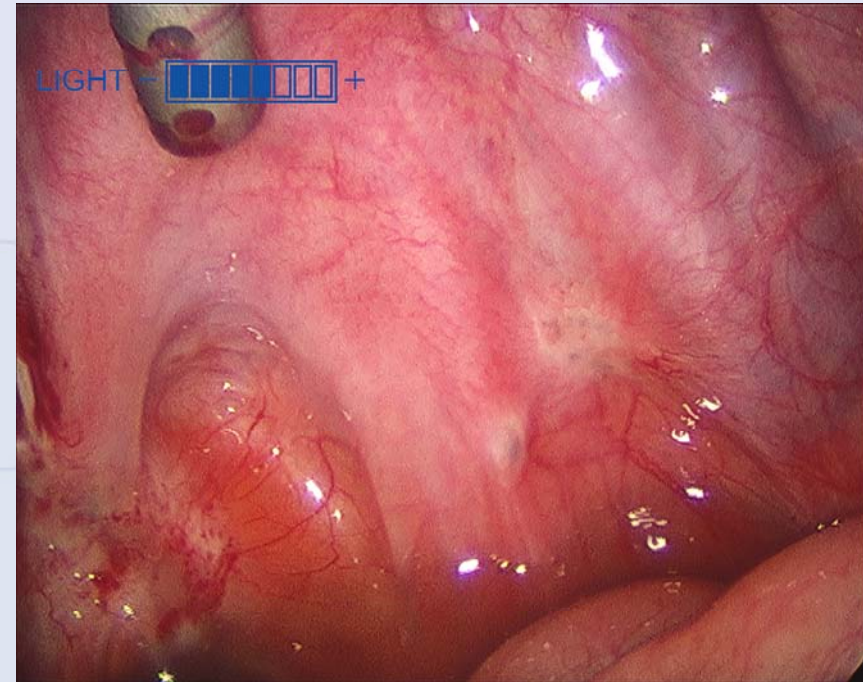
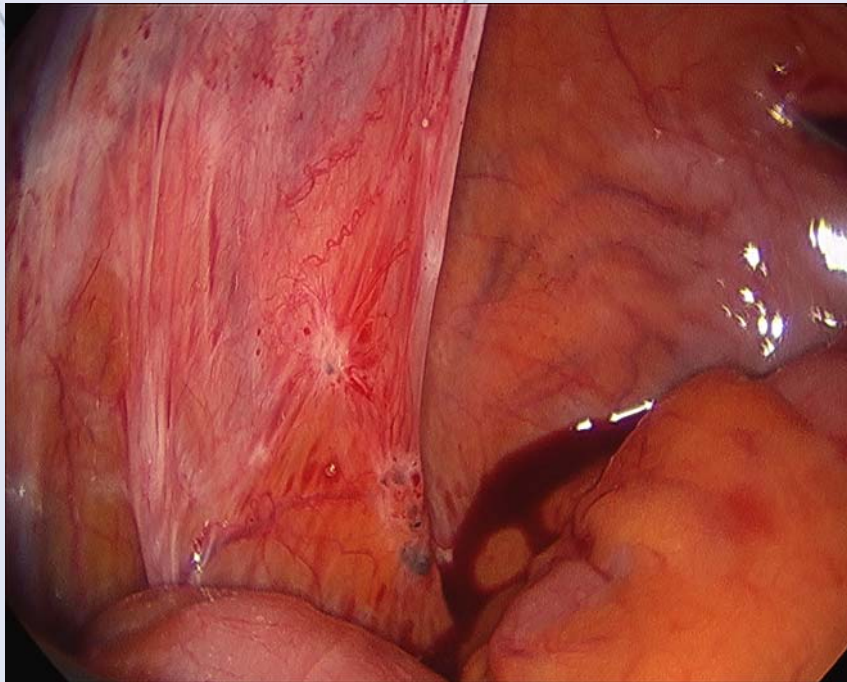
Typical – with scarring



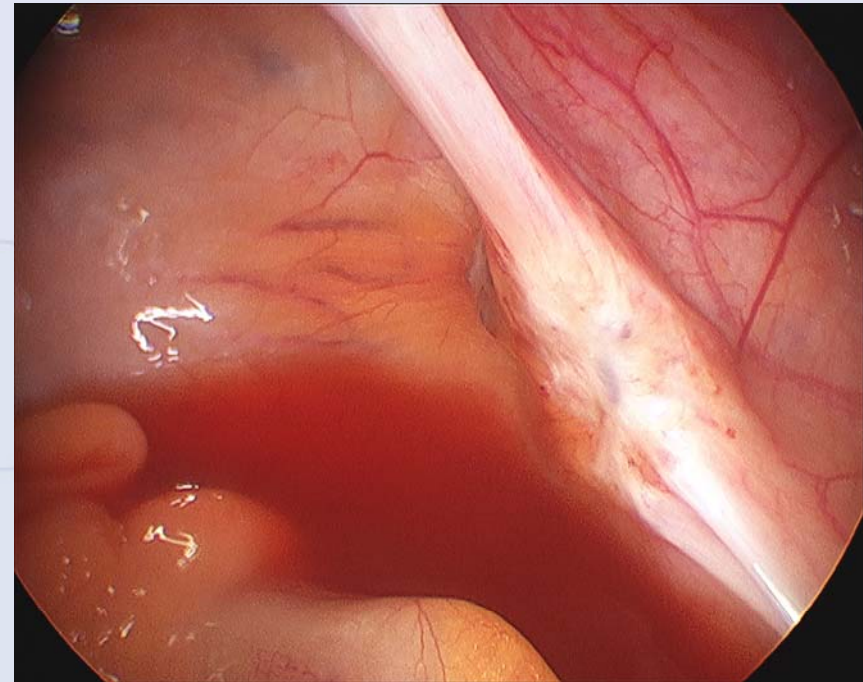
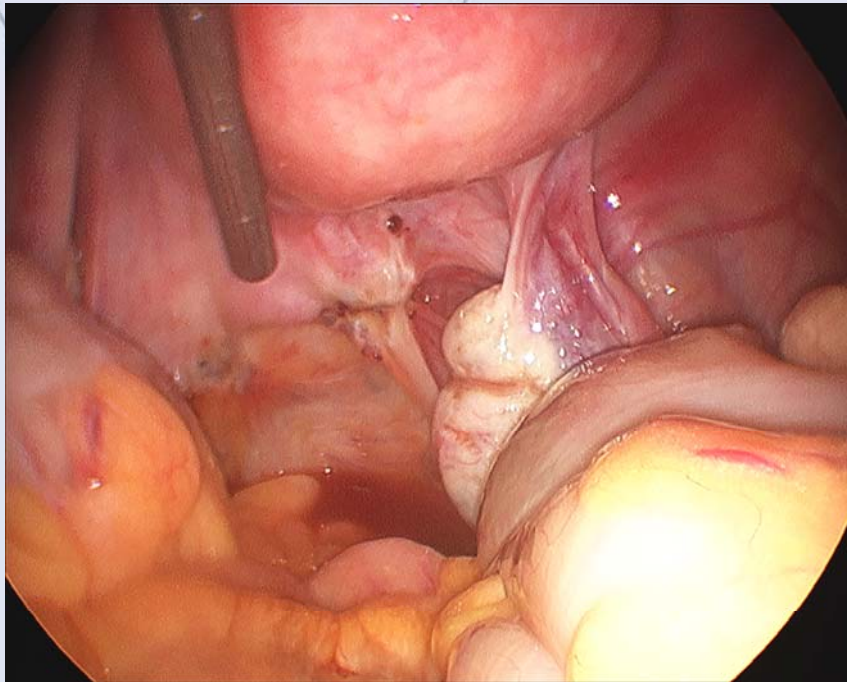
Bladder Endometriosis



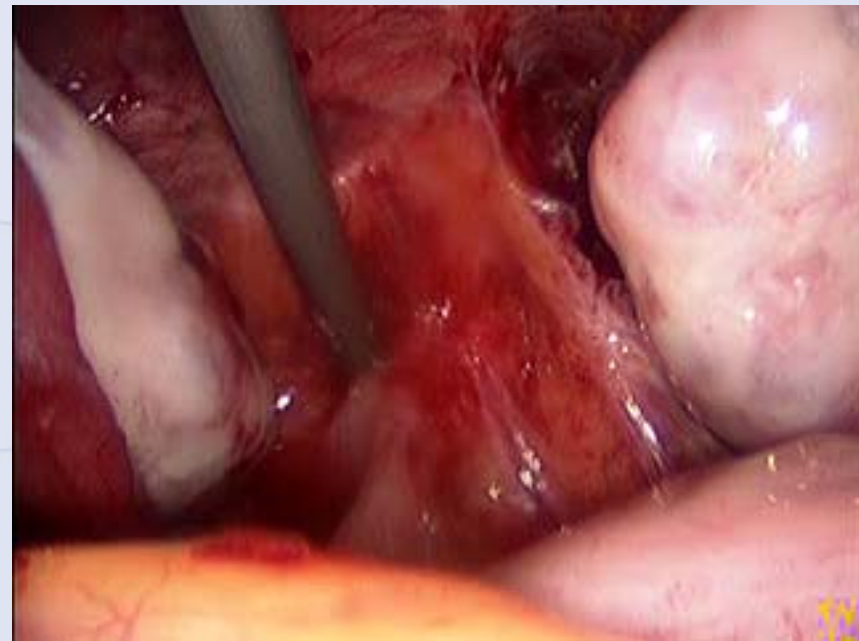
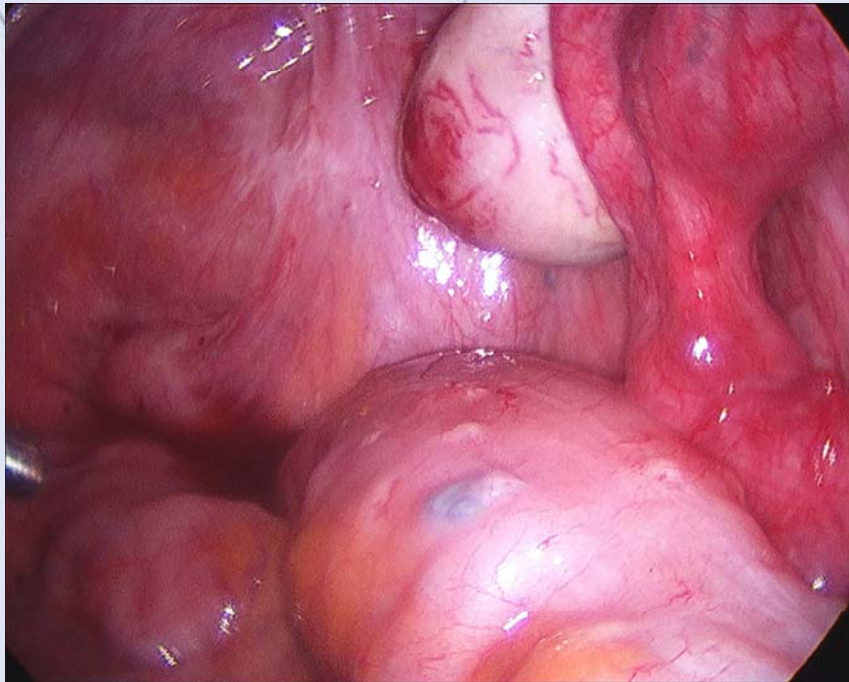
Powderburn Lesions



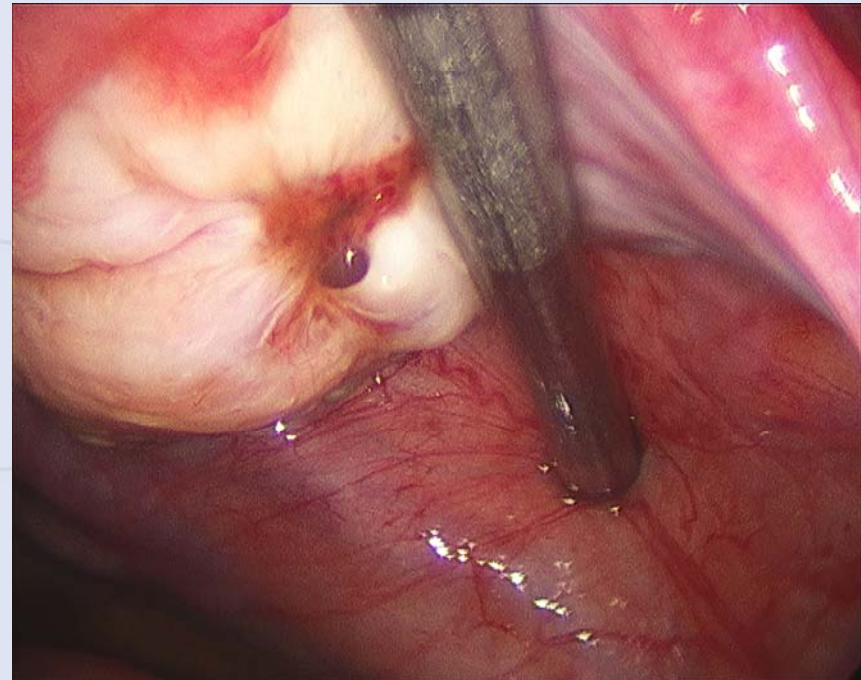
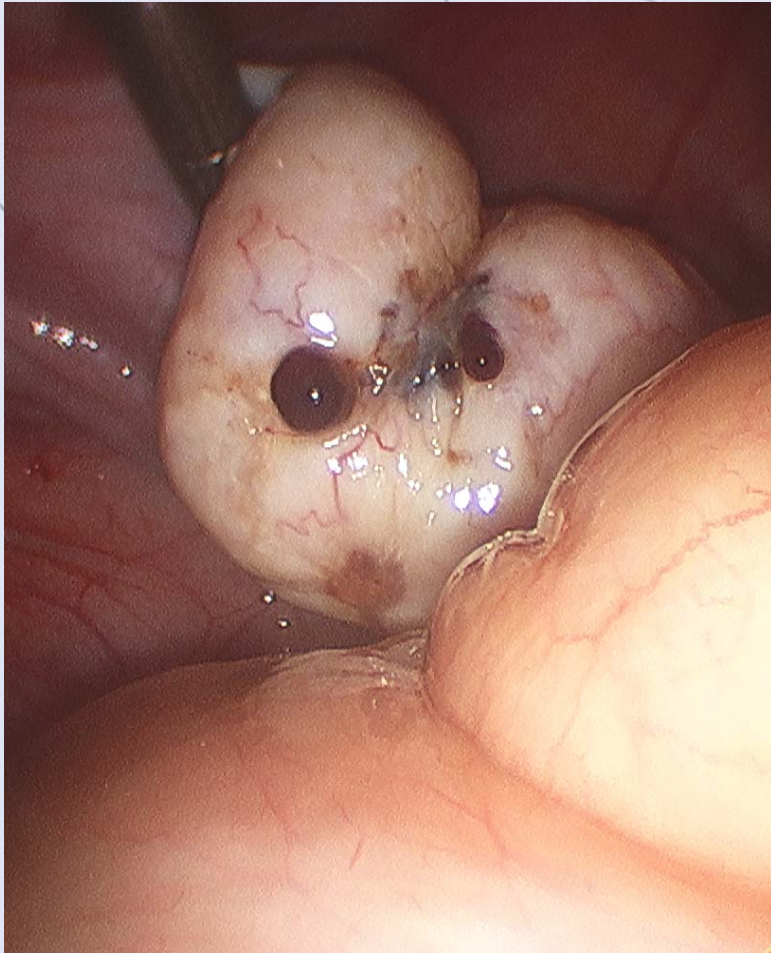
Nodular Endometriosis



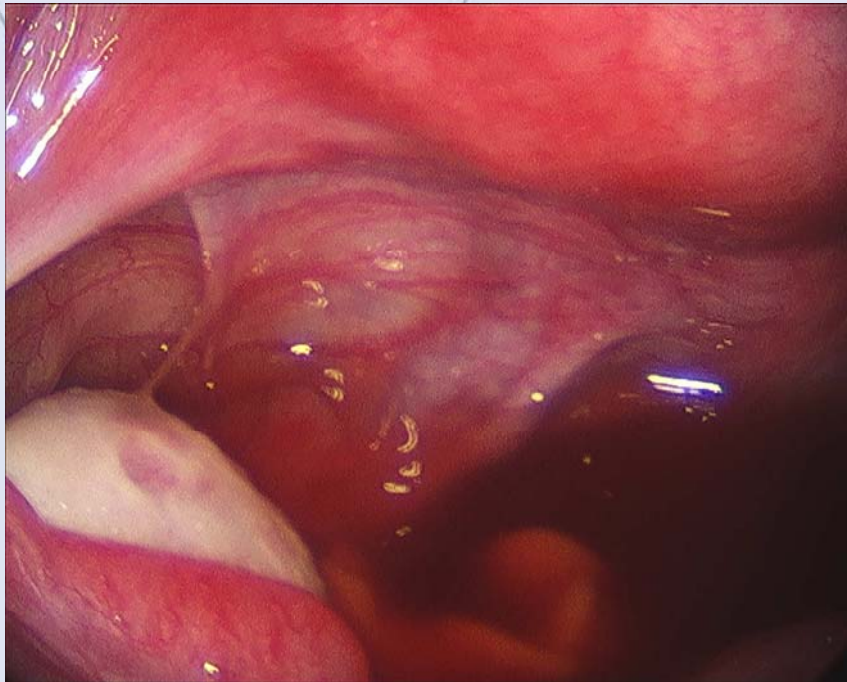
Bowel Endometriosis



Ovarian Endometriosis



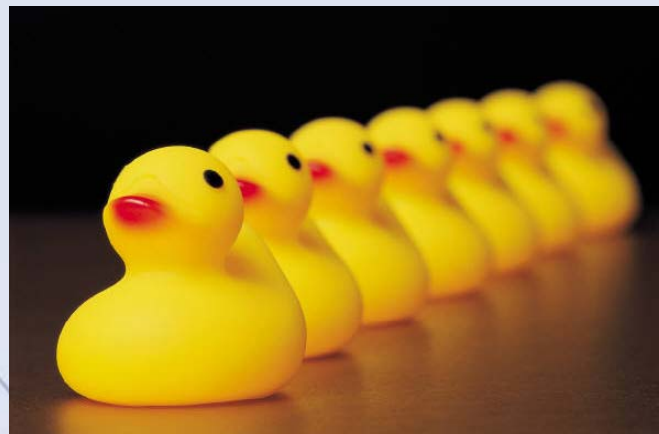
Invisible Endometriosis



Inclusion Criteria

Inclusion Criteria

- At least 12 months of unexplained infertility
- Normal sperm count
- Open tubes
- Ovulatory, and regular cycles
- No pelvic abnormality on exam



Methods

Evaluation –Case Cohort Study

- Laparoscopy was offered to all patients
- Monitored cycles in UI patients that did or did not undergo L/S
- Video photo taken of all implants, and tissue sent to pathology for histological diagnosis
- Patients were followed for up to 12 months
- IVF pregnancies were not included in this analysis

Methods

- Kaplan-Meier Life Table Analysis was performed on each group (Graph Pad Software®)
- Stage of endometriosis was evaluated and compared by Kaplan-Meier Life Table Analysis in those that conceived (AFS Score I-II vs III-IV)

Results

- Total of 67 UI patients were identified between February 2003 and July 2010
- 57 underwent laparoscopy
- 209 monitored cycles before and 182 after L/S
- Age and BMI were similar between data sets
- Successful pregnancy was achieved in 70.1% of L/S group and 12.5% in those before laparoscopy

Results

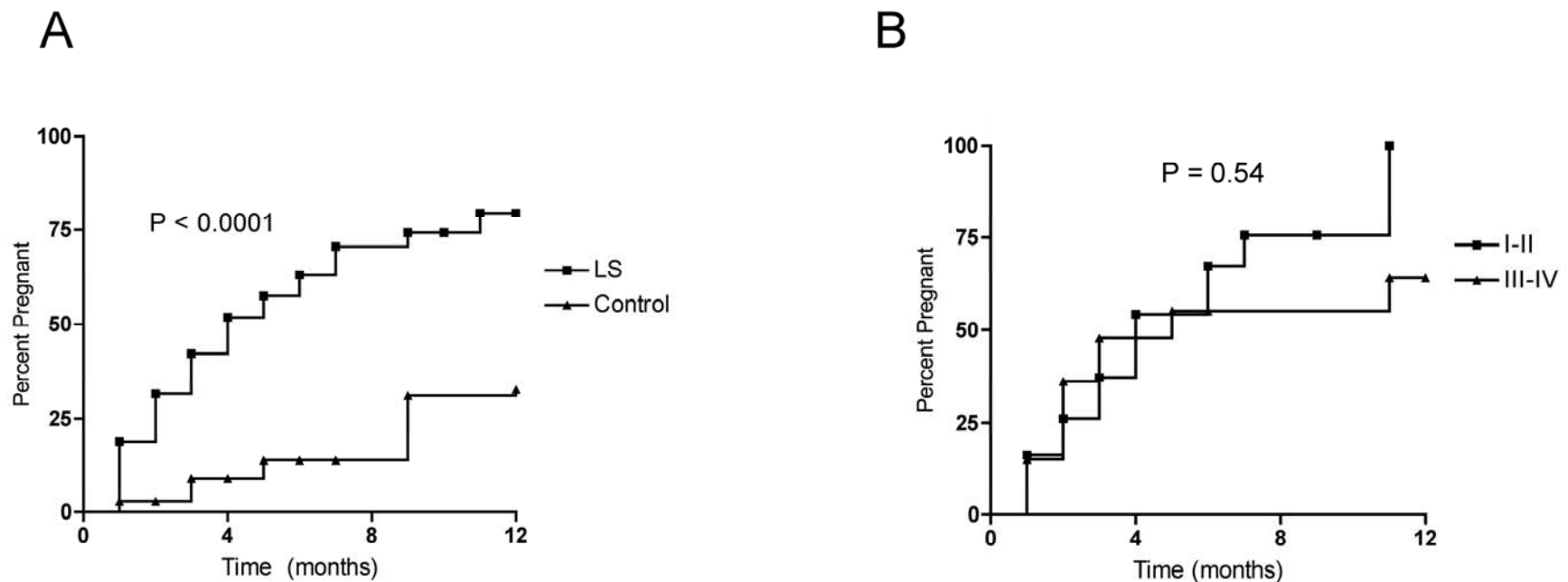


FIGURE 1: A – Comparison of pregnancy rates in without laparoscopy compared to treatment after laparoscopy
B – Comparison of pregnancy rates by stage of disease (I-II vs. III-IV)

Results

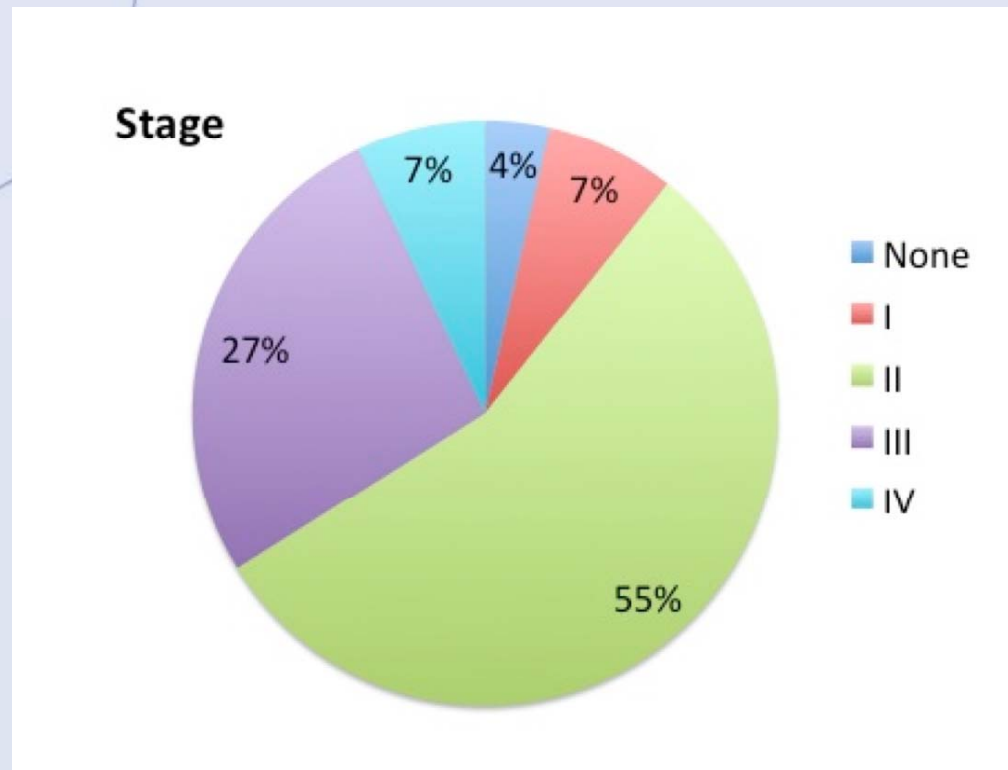
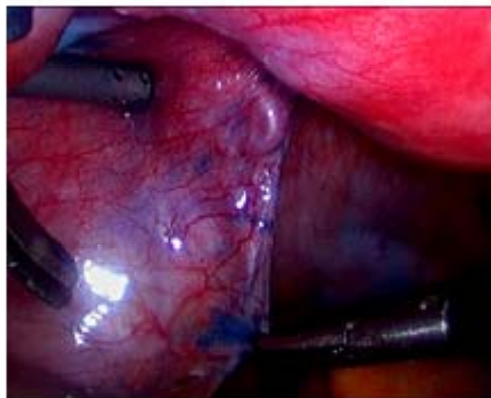
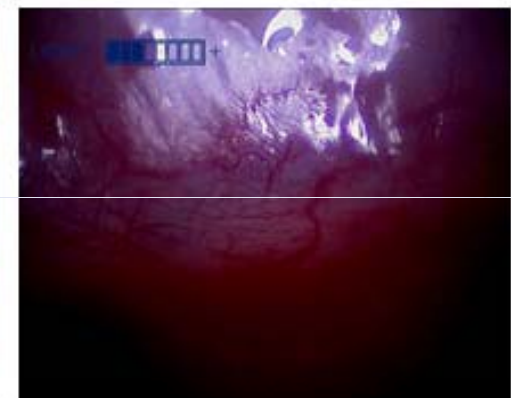
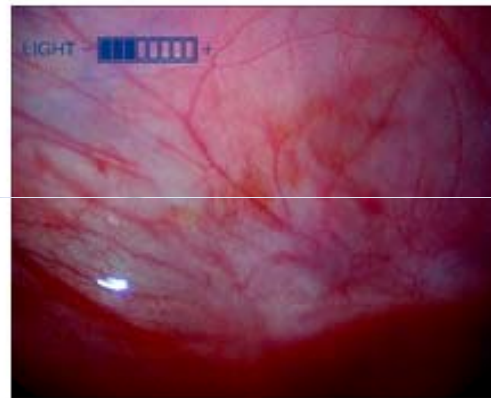


Figure 2A – Percent of patients with UI that had endometriosis present

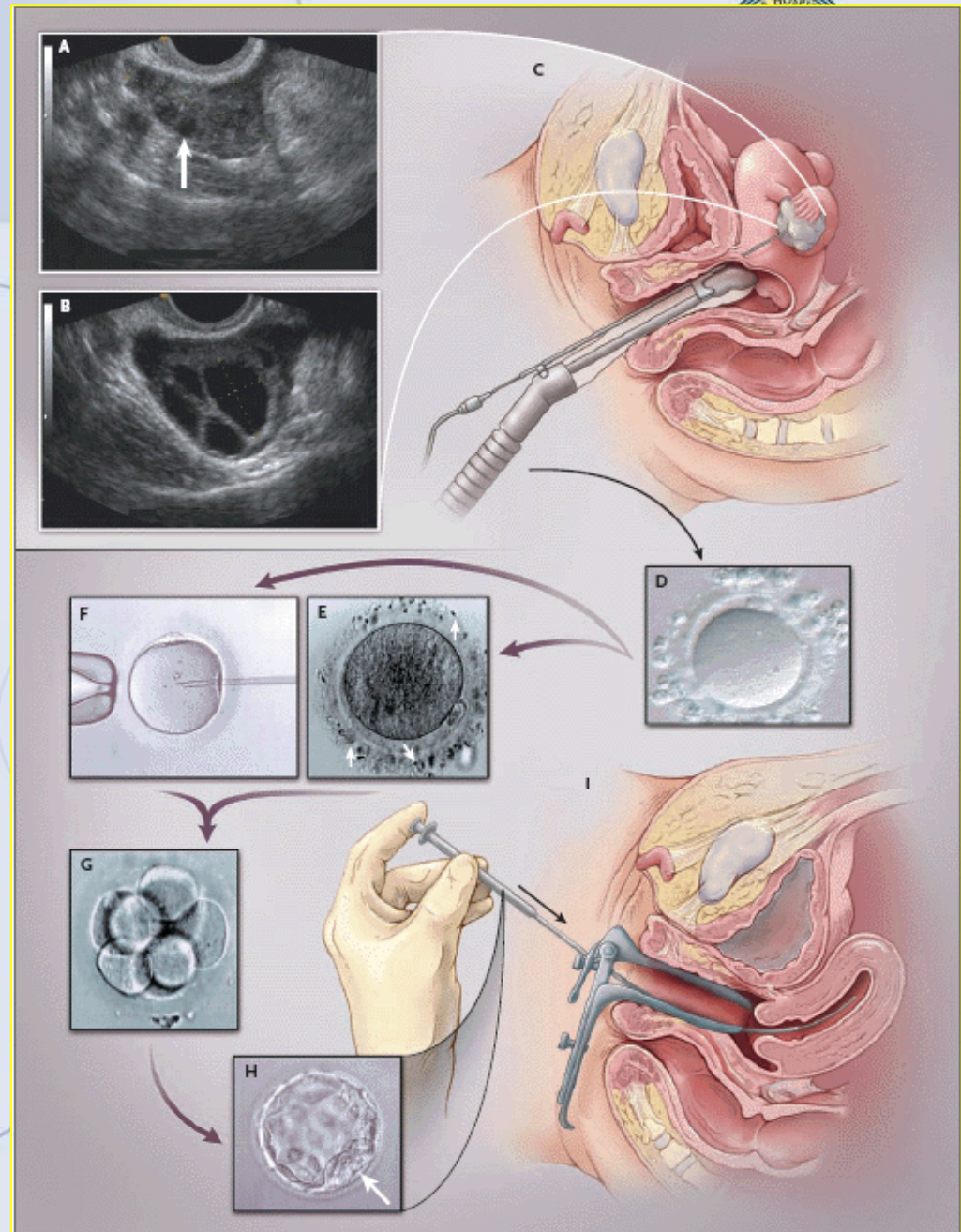
Discussion

- Cause and effect on fertility controversial
 - D’Hooghe 2003
- Many women have endometriosis
 - Balasch et al, *Hum Reprod* 1996; Evers et al, *Hum Reprod* 1998
- Some endometriosis is not visible or identifiable by traditional histologic methods
 - Murphy et al, *Fertil Steril* 1986
- Not all suspected endometriosis is verifiable by pathology
 - Stegmann et al, *Fertil Steril* 2008;89:1632-36
- A lower limit of endometriosis associated with infertility has not been defined

The "Blue" Effect



Endometriosis and IVF



Wilma

- 32 year old with UI
- Four failed fresh and 2 failed frozen IVF cycles
- No diagnosis, no pregnancy
- On laparoscopy had extensive surface endometriosis



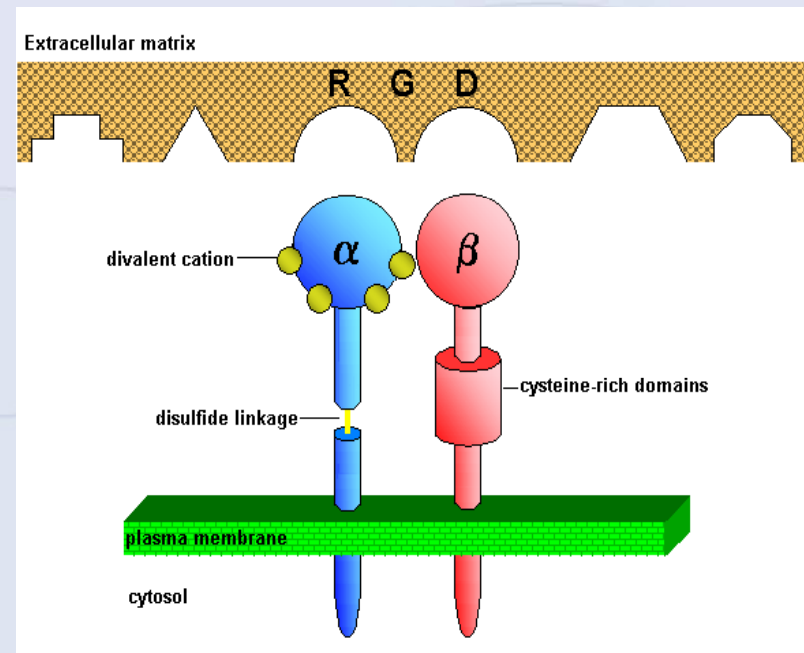
Endometriosis and IVF Failure

- Repeated, unexplained IVF failure patients exist in most practices
 - IVF centers may not have the inclination or skills to diagnose endometriosis
- Studies have suggested endometrial receptivity defects
 - (Steinleitner, 1998; Thomas et al., F&S, 2003; Littman et al., 2005; Arache et al., 2009)
- Meta-analyses suggest IVF is affected by endometriosis (Barnhart et al., F&S 2002)
- Brosens suggested aromatase expression is a marker of poor IVF performance (Brosens et al., HR, 2004)



Integrins and Implantation

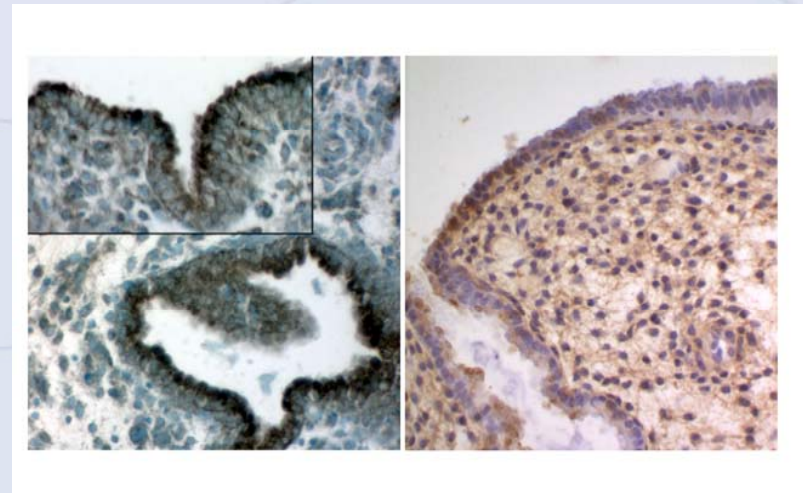
- Integrins are heterodimeric glycoproteins
 - Composed of α and β subunits
 - Reside in the cell membrane
 - Bind other CAMs and ECM





Presence or Absence of $\alpha v \beta 3$

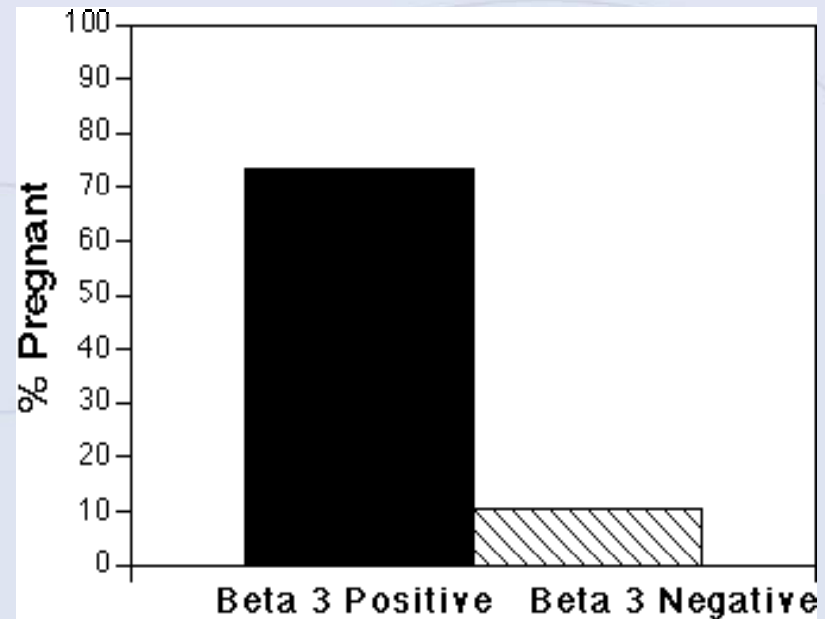
- Normally present after day 20 to 21 on glandular and luminal epithelium
- Aberrant lack of $\alpha v \beta 3$ associated with endometriosis
 - Type I defects → out of phase
 - Type II defects → in phase



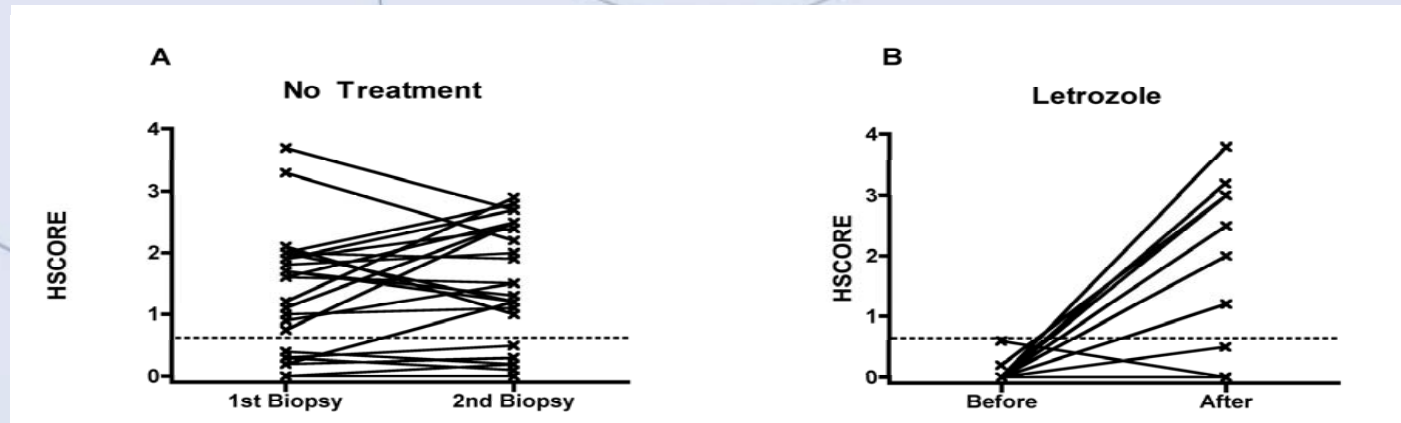
Lessey et al., 2000

Effect on Pregnancy in Women

- Women with endometriosis
 - Segregated by $\alpha v\beta 3$ integrin status
 - Marked reduction in pregnancy rates in affected individuals with type II defects
 - Can be reversed with GnRH agonist



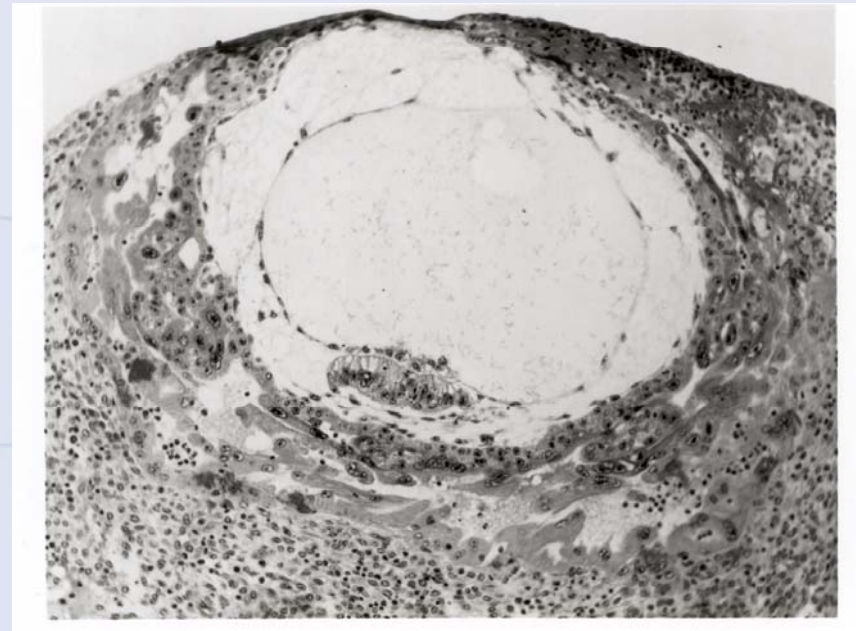
Integrin Testing



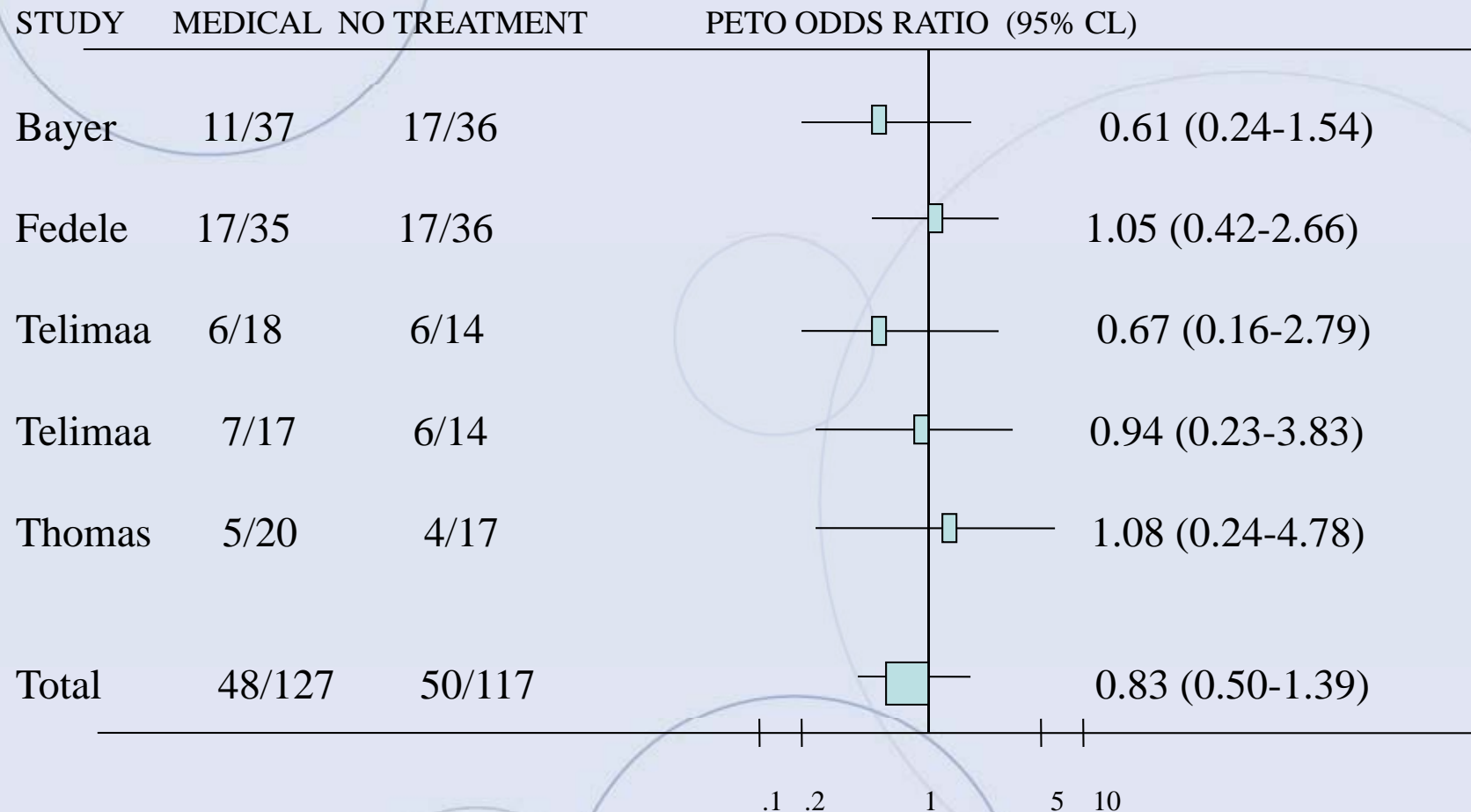
- Repeat biopsies in normal fertile controls showed consistent results
- Integrin negative patients who underwent a second biopsy on Letrozole generally improved their integrin score

Methods

- Integrin testing was performed prior to IVF
- Phase I – evaluate outcomes
- Phase II – prospectively determine integrin staining
- Treat integrin negative patients with aromatase inhibitor



Medical Therapy and Infertility



IVF Screening for $\alpha v\beta 3$

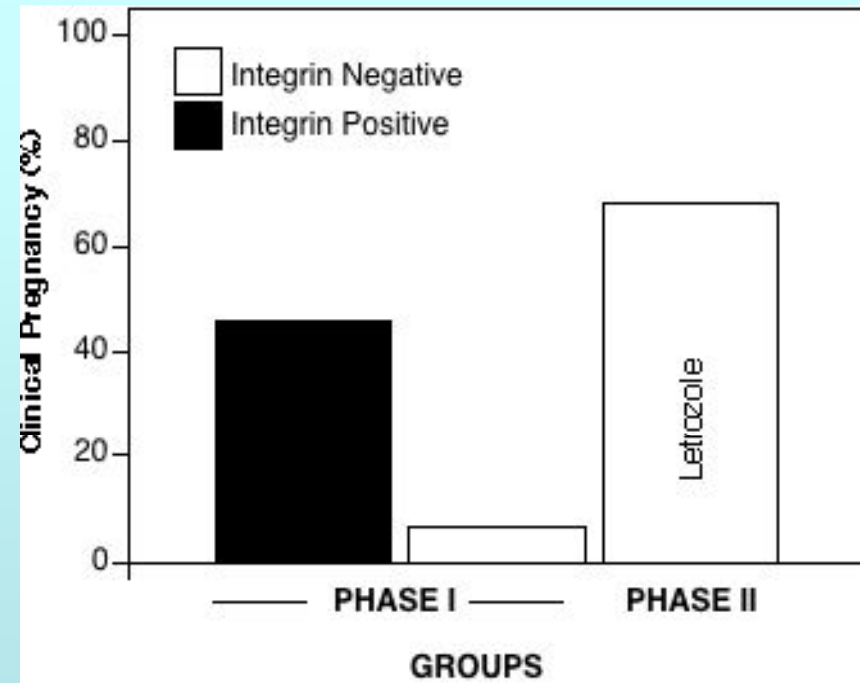
- In patients who completed IVF, the lack of the $\alpha v\beta 3$ integrin was highly predictive of failure

	$\beta 3 +$	$\beta 3 -$
Preg	21	2
Not Preg	14	33

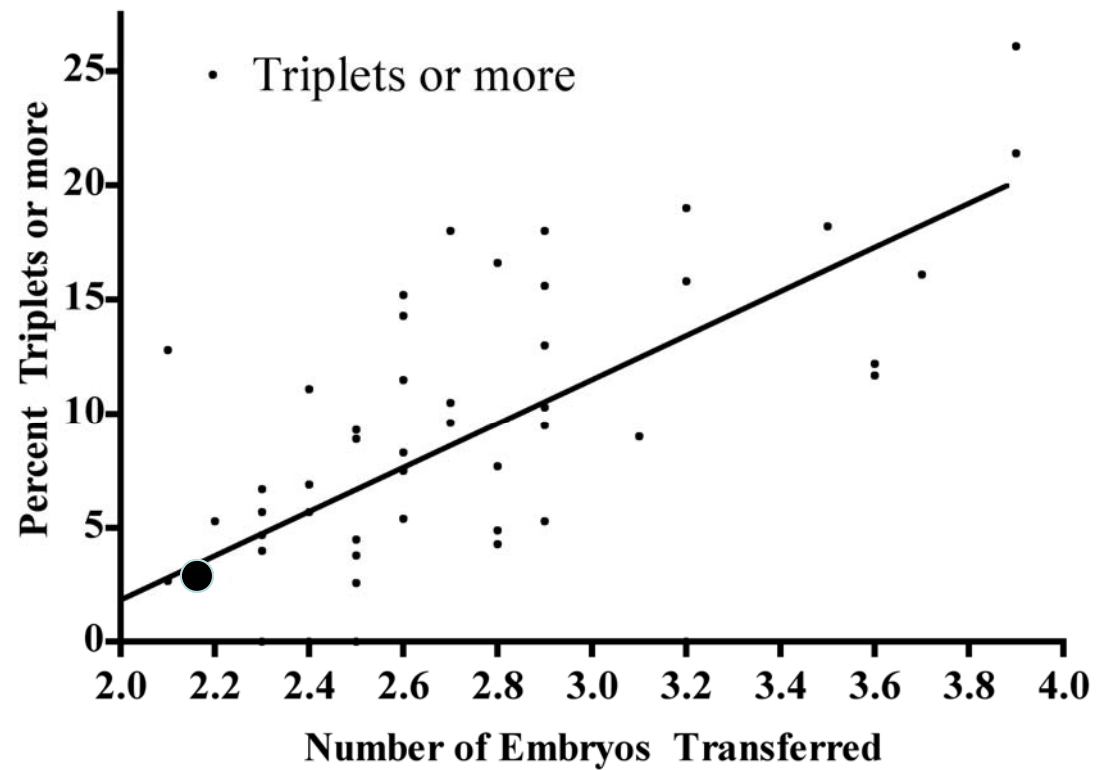
Chi Square = 25.46 $p = < 0.001$

Results

- Integrin expression was predictive of IVF success
- Addition of an aromatase inhibitor (Letrozole) on days 2 to 6 of stimulation increased IVF success



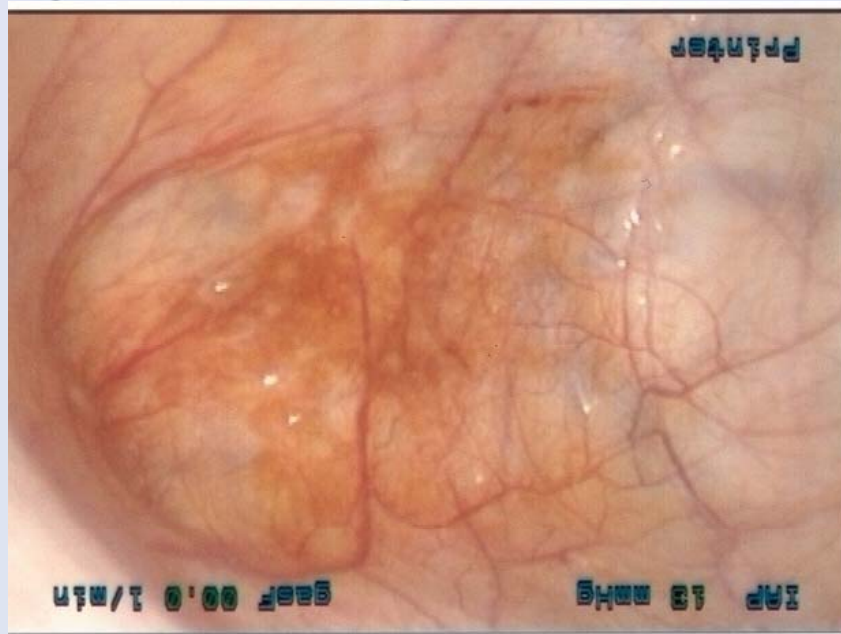
Number of Embryos Transferred



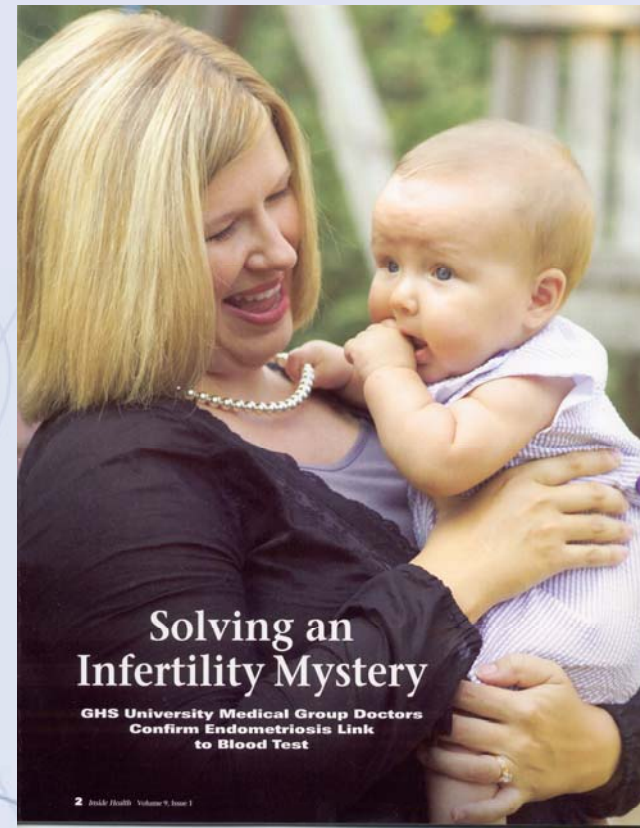
Miller et al., JSCMA 101:373-7 2005

Endometriosis and Pregnancy Loss

Minimal endometriosis



Five previous losses



Discussion

Debate on how to treat

- In most states, in the USA, IVF is not covered
- The bias toward IVF for everyone discriminates against those that can't afford the technology
- IVF doesn't work in all patients
- Endometriosis has the potential to harm if left untreated

However...

- IVF is an efficient method to improve fertility in MOST couples
- Mild endometriosis might be an epiphenomena unrelated to the real cause of fertility
- Decisions on how to treat are often based on a belief system, rather than scientific evidence

Concluding Remarks

- Most women with UI had endometriosis at laparoscopy (L/S)
- Diagnostic accuracy was improved through the use of L/S
- Ablation and resection of all visible or bearly visible endometriosis shortened time to successful pregnancy ($P < 0.001$)
- Just because some women are fertile with mild endometriosis, doesn't mean everyone is

Comments

- 1) Unusual disease – paradoxical effects
- 2) Complexities –
 - Pain doesn't correlate with disease
 - Infertility only seen in 50% of those affected
 - Medical Tx doesn't work but surgical Tx does
- 3) Chicken and egg questions
 - Which comes first? The changing endometrium or the endometriosis

Questions to Address

- 1) Why are some women with endometriosis infertile while others are not?
- 2) How is the presence of endometriosis communicated to the endometrium?
- 3) If very minimal endometriosis is damaging to fertility in some women, how can we identify them?



GREENVILLE HOSPITAL SYSTEM
UNIVERSITY MEDICAL CENTER
ghs.org

Questions?