ENDOMETRIUM IN POOR RESPONDERS

BENEFITS FROM EXPOSURE TO LOWER LEVEL OF ESTROGEN?

Professor T C LI

Sheffield, UK

19 March 2010

What do we already know? -1

- The implantation rate in normal responders is ~30%
- The implantation rate in poor responders is reduced to ~10%

Why is implantation rate reduced in poor responders?

- Is it ooctye quality?
- Is it endometrium receptivity?

Oocyte Quality in Poor Responders

- The viability of oocytes in poor responders is more related to the limited possibility of performing embryo (and oocyte) selection than to a comprised viability of the oocyte itself.

Cristina Magli, Luca Gianaroli, Anna Ferraretti

Why is implantation rate reduced in poor responders?

- Is it ooctye quality?
- Is it endometrium receptivity?

What do we already know? -2

- In over-responders, the very high E2 levels (>20,000pmol/l) adversely affect endometrial development and function and reduces implantation rate
- In normal responders, the moderately high E2 levels seem to affect endometrial morphology but no major detrimental effect on implantation rate (~30%)
- In poor responders, the E2 levels are lower than normal responders but still higher than in natural cycles, the implantation rate is reduced (~10%)

ENDOMETRIUM IN POOR RESPONDERS

BENEFITS FROM EXPOSURE TO LOWER LEVEL OF ESTROGEN?

Would a strategy of mild ovarian stimulation or natural cycle IVF in poor responders improves outcome by improving endometrial receptivity?

Embryo implantation rates in natural and stimulated assisted reproduction treatment cycles in poor responders

Ata et al 2008, RBM on line 17:207

- Retrospective study of cycles treated over ~10 year period
- 304 women who had poor response to ovarian stimulation in the previous cycle, defined as recovery of 5 or less oocytes
- Only cycles in which there was a single embryo available for transfer were included

Cycle type	Clinical pregnancy rate
Natural	6/30 (20%)
Gonadotrophin only	3/54 (5.6%)
Long GnRH agonist	2/52 (3.8%)
Co-flare	1/52 (1.9%)
Micro-dose flare	4/26 (15.4%)
antagonist	13/90 (14.4%)

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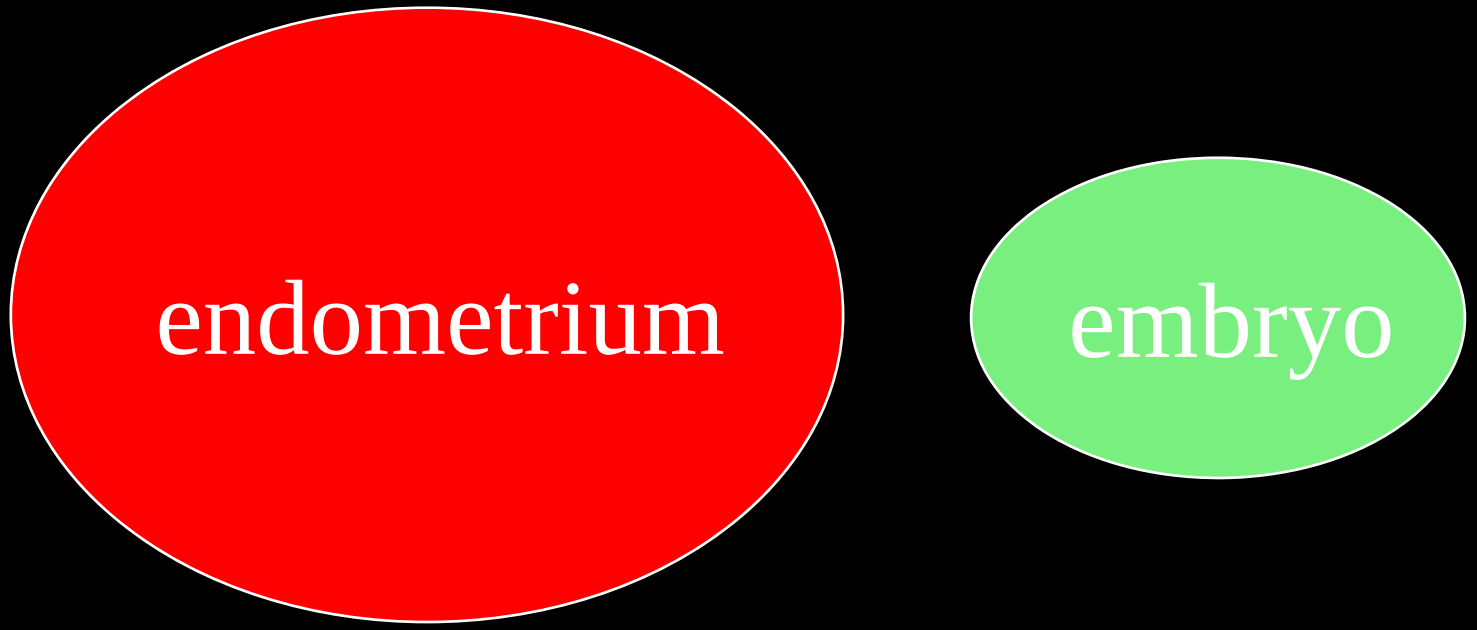
Bias

Natural cycle	Stimulated cycle	
Embryo suitable for transfer	5 follicle	Up to 5 embryo
Embryo not suitable for transfer	4 follicles	Up to 4 embryo
No fertilisation	3 follicle	Up to 3 embryo
No oocyte	2 follicle	Up to 2 embryo
No follicle	1 follicle	**Up to 1 embryo**

Inadmissible

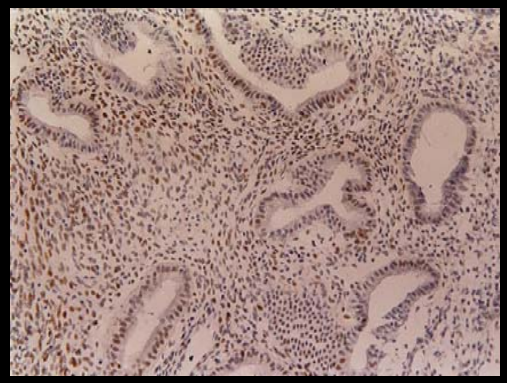
IMPLANTATION

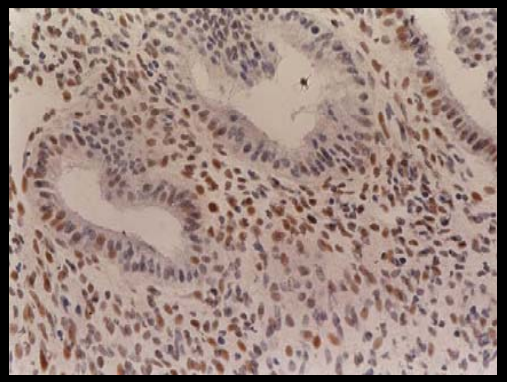


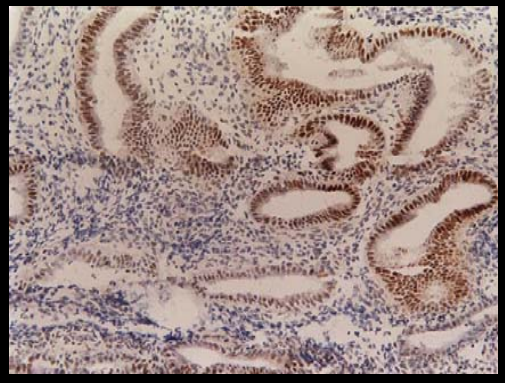
1. Intrinsic difficulty of Endometrial Studies

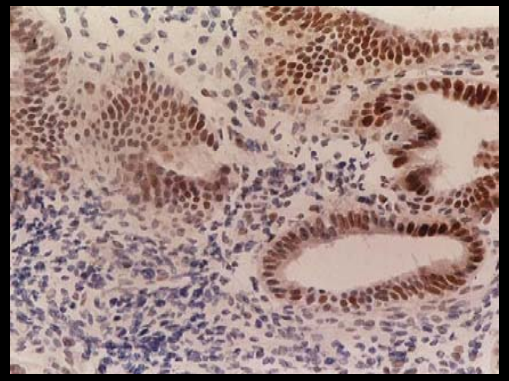
Tissue-heterogenity

Expression of ER in the same endometrial biopsy



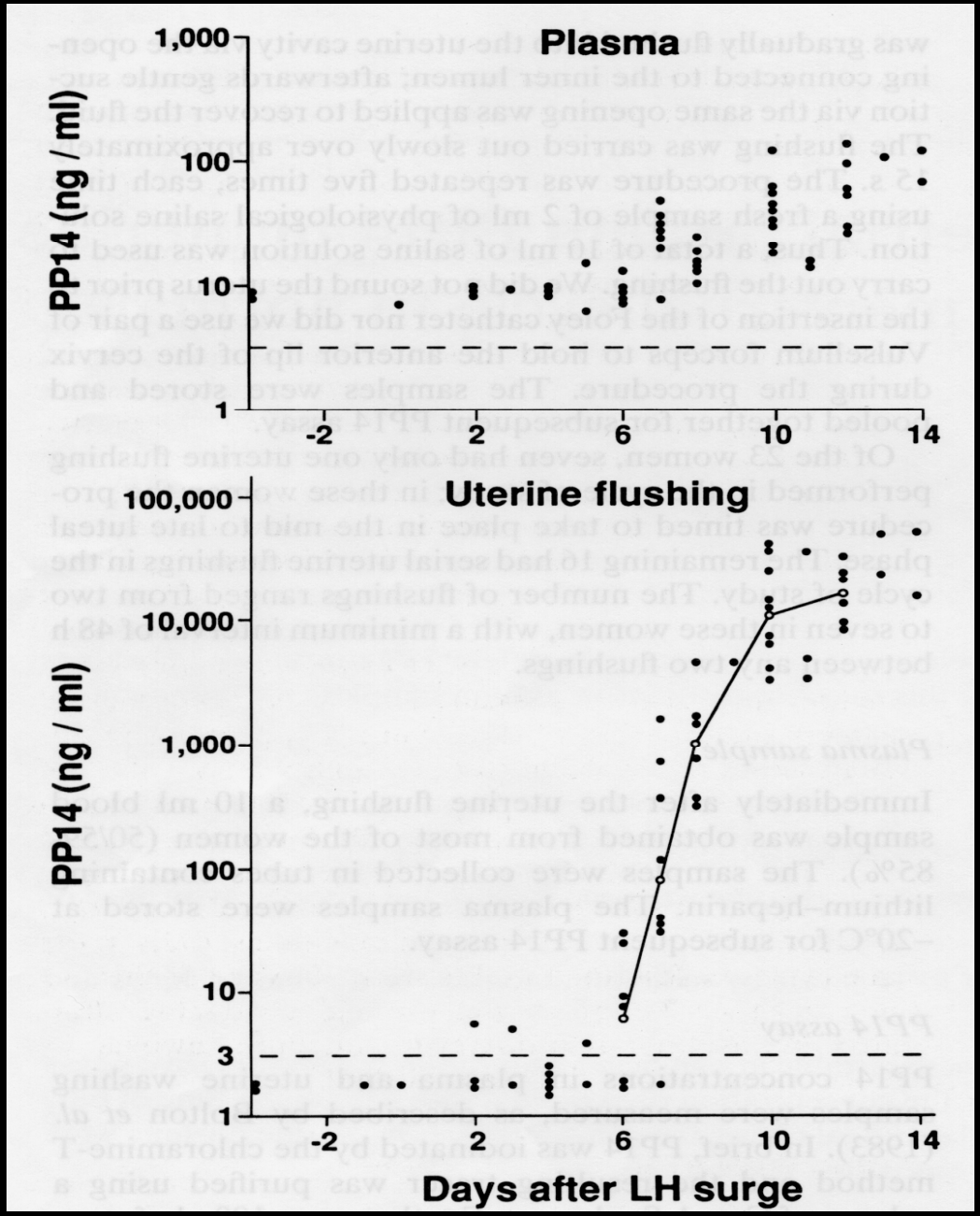






2. Specimens must be precisely timed

Glycodelin A (PP14) concentration in uterine flushing in Fertile Subjects



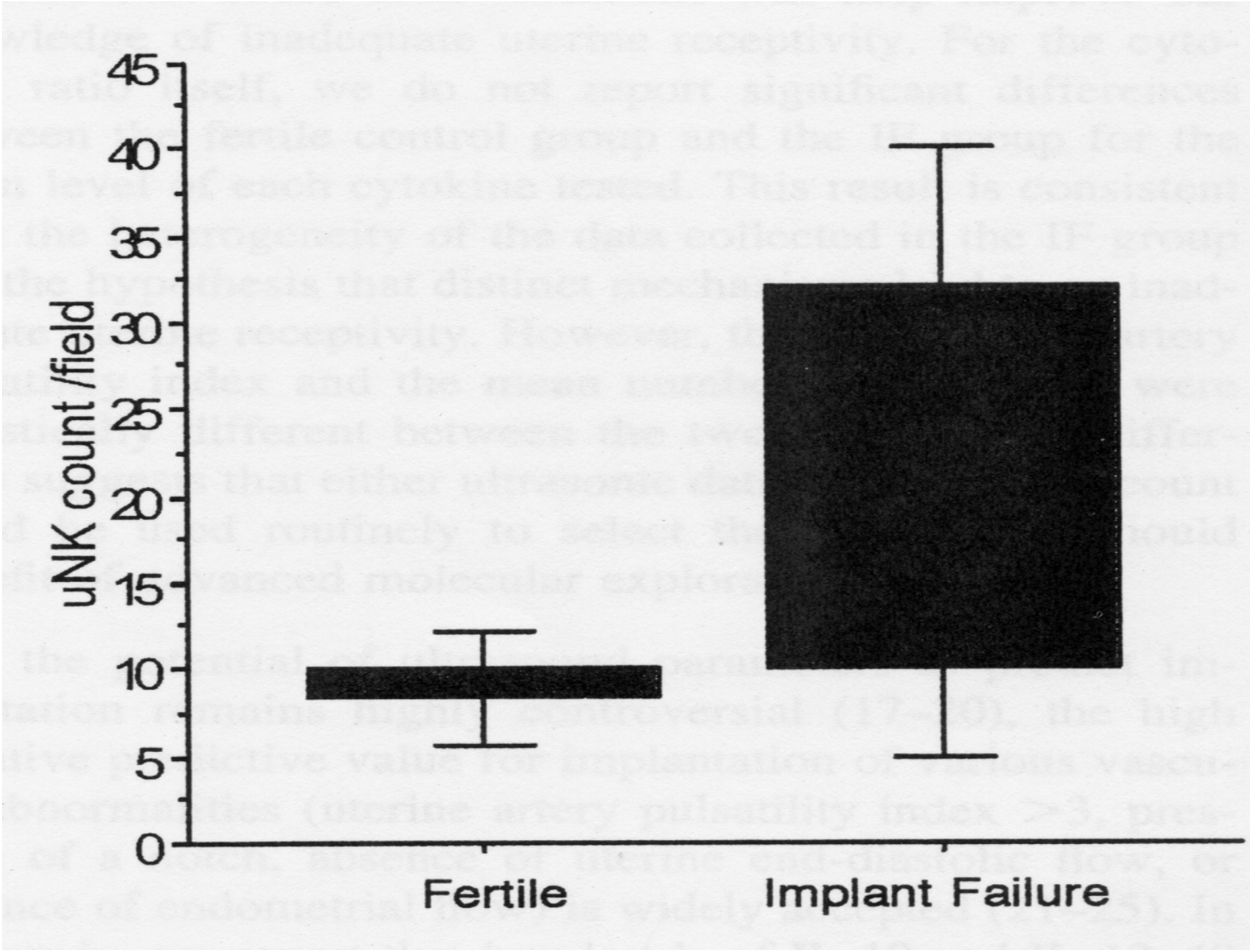
3. Prognostic Significance of putative marker ought to be demonstrated

Endometrial Markers of Successful Implantation still Unconfirmed

- Morphological markers – Noyes Critera, pinopods
- Endometrial protein – Glycodylin-A
- Steroid receptors
- Adhesion molecules – integrins
- Cytokines – LIF, IL6….
- Stromal cell marker – IGFBP-I
- Immune cells – CD56+ (NK cells)

Uterine NK cells & Reproductive failure

- 37% of women with RIF had increase number of uNK cells (Ledee-Bataille, 2004)
- Women with recurrent miscarriage and RIF had increase number of uNK cells compared with control subjects (Sheffield data)


uNK count /field
0
5
10
15
20
25
30
35
40
45
Fertile
Implant Failure

4. Endometrial function may be affected by steriod hormones

Ovarian steroid hormones

- Estrogen
- Progesterone
- androgen

Could the abnormality be treated by hormone manipulation?

5. Endometrial function may be adversely affected by factors other than steroid hormones

Non-steroidal factors

- Intra-cavity pathology
- Structural uterine anomalies
- Inhibitors of implantation

Non-steroidal factors

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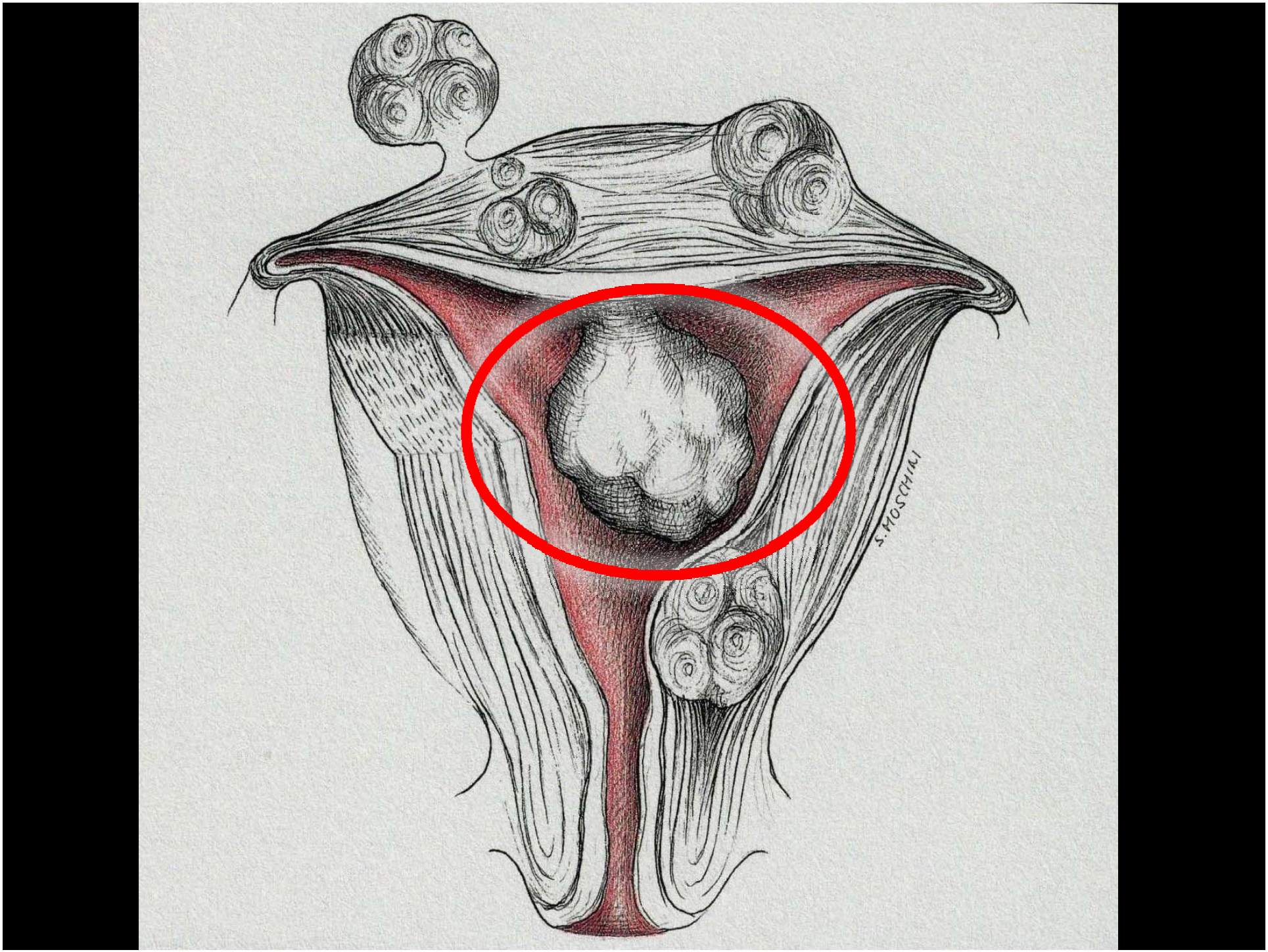

S. MOSCHINI

Fibroids and infertility: an updated systematic review of the evidence

Elizabeth A. Pritts, M.D.,[a] *William H. Parker, M.D.,*[b] *and David L. Olive, M.D.*[a]

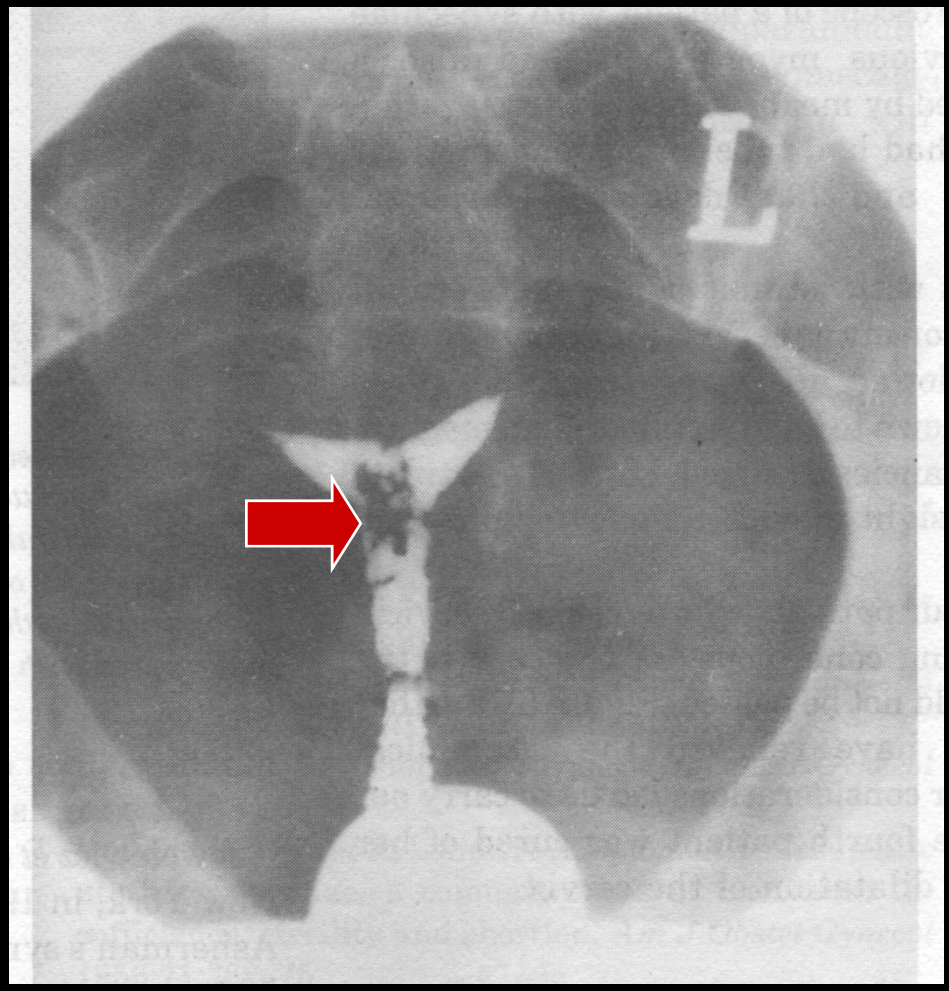
TABLE 3

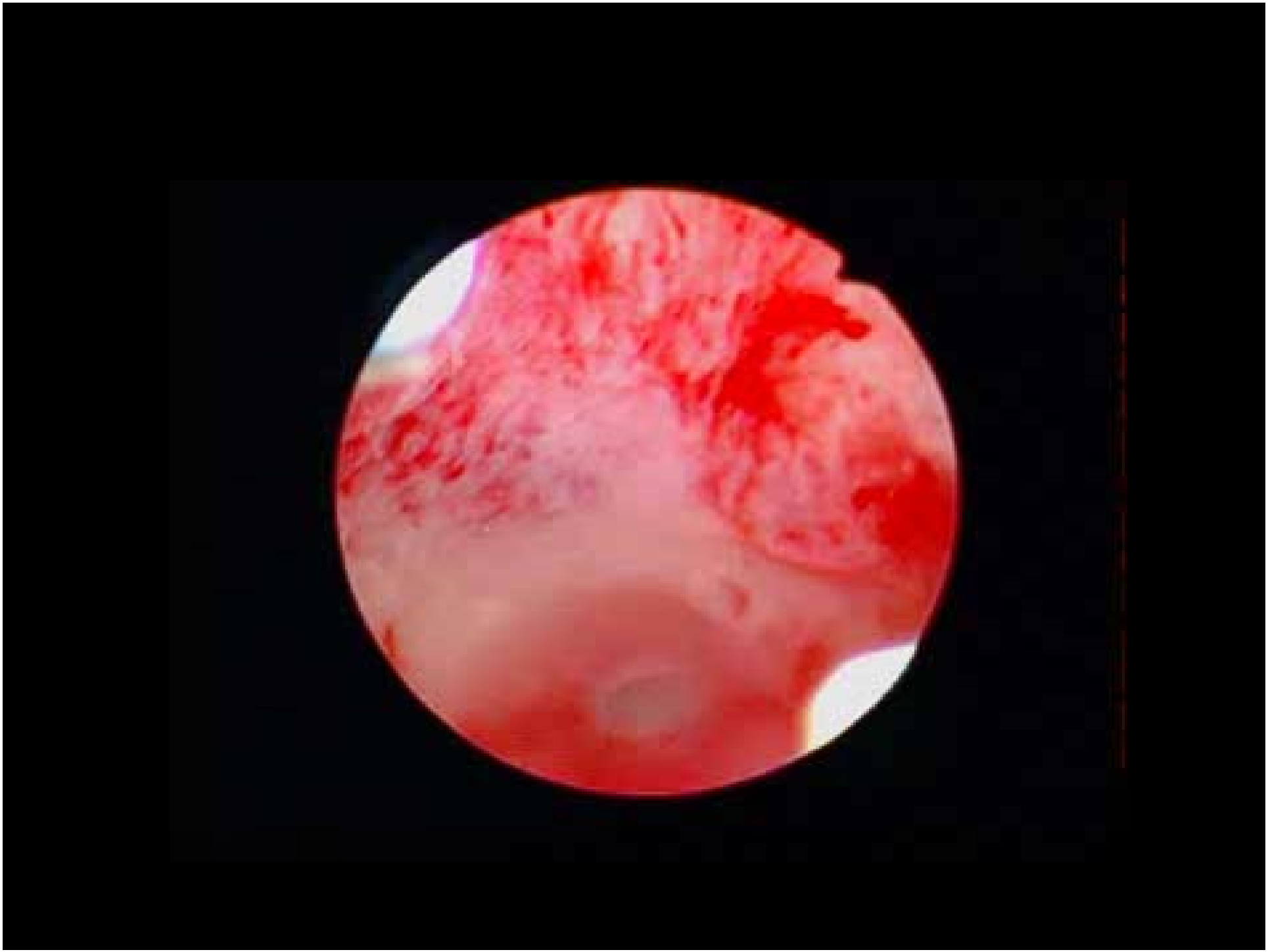
Effect of fibroids on fertility: submucous fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	4	0.363	0.179–0.737	$P=.005$
Implantation rate	2	0.283	0.123–0.649	$P=.003$
Ongoing pregnancy/live birth rate	2	0.318	0.119–0.850	$P<.001$
Spontaneous abortion rate	2	1.678	1.373–2.051	$P=.022$
Preterm delivery rate	0	–	–	–

Pritts. Fibroids and infertility. Fertil Steril 2009.

INTRAUTERINE ADHESIONS





HYSTEROSCOPY

- RCT by Demirol & Gurgan (2004)
- 421 women with 2 or more IVF failures
- 56 out of 210 (26%) women with normal HSG had intrauterine leisons detected by office hysteroscopy, and treated
- The subsequent pregnancy rate in the treated group (30.4%) and the group with normal hysteroscopy (32.5%) was significantly higher than the group who did not undergo hysteroscopy (21.6%)

Non-steroidal factors

- Intra-cavity pathology
- Structural uterine anomalies
- Inhibitors of implantation

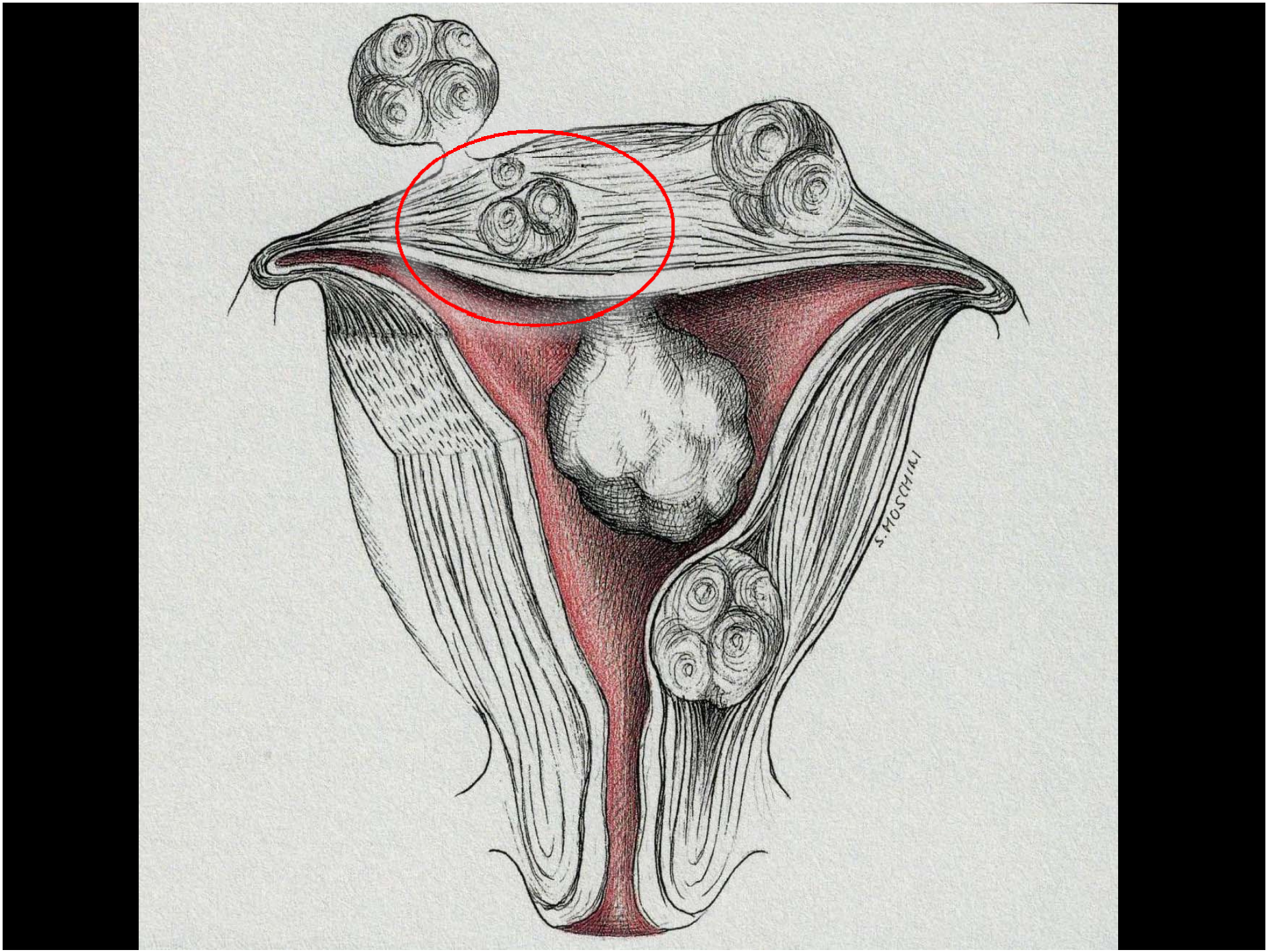

S. MOSCHINI

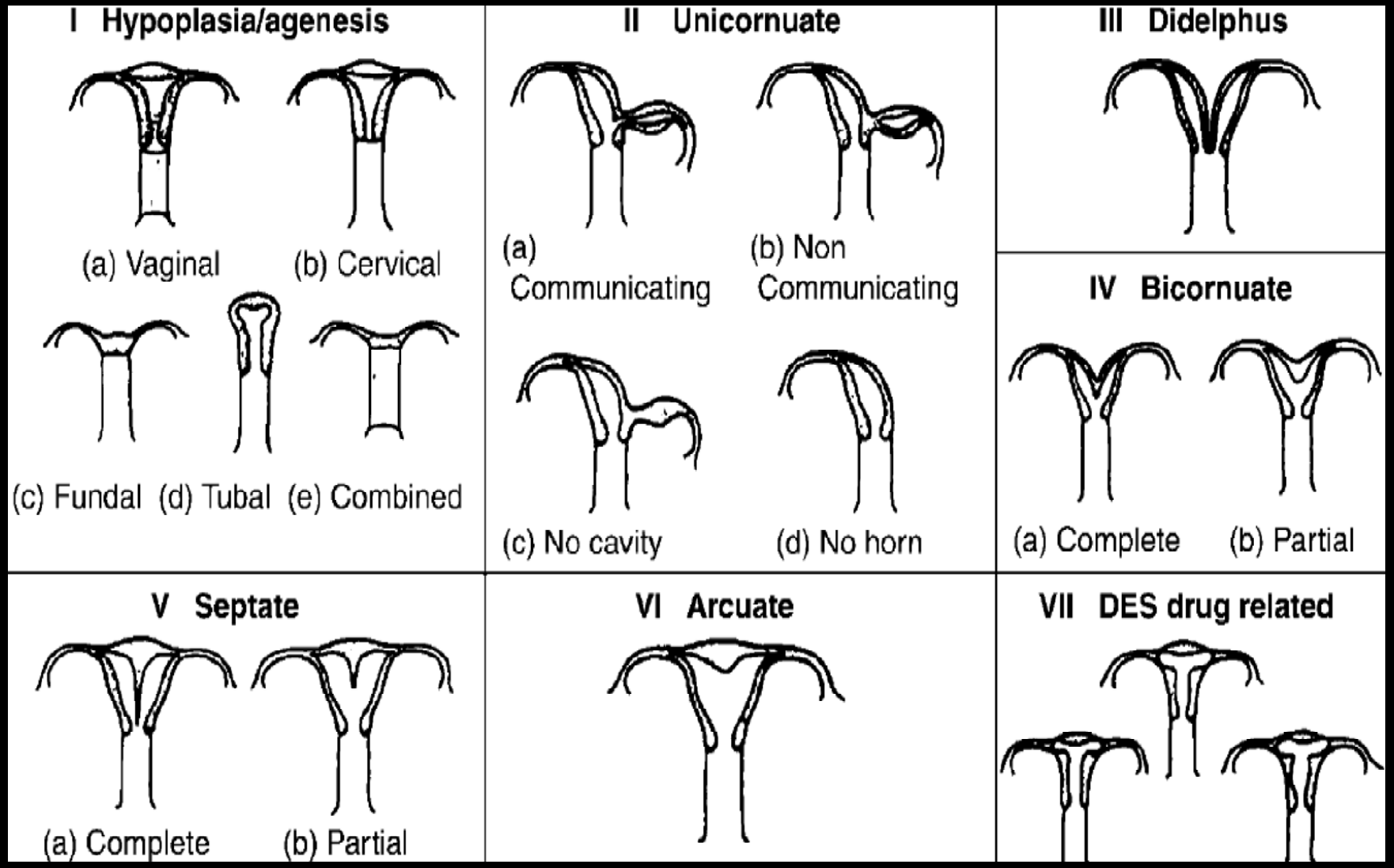
TABLE 5

Effect of fibroids on fertility: intramural fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
A. All studies				
Clinical pregnancy rate	12	0.810	0.696–0.941	P=.006
Implantation rate	7	0.684	0.587–0.796	P<.001
Ongoing pregnancy/live birth rate	8	0.703	0.583–0.848	P<.001
Spontaneous abortion rate	8	1.747	1.226–2.489	P=.002
Preterm delivery rate	1	6.000	0.309–116.606	Not significant
B. Prospective studies				
Clinical pregnancy rate	3	0.708	0.437–1.146	Not significant
Implantation rate	2	0.552	0.391–0.781	P=.001
Ongoing pregnancy/live birth rate	2	0.465	0.291–0.744	P=.019
Spontaneous abortion rate	2	2.384	1.110–5.122	P=.002
Preterm delivery rate	0	—	—	—
C. Studies using hysteroscopy in all subjects				
Clinical pregnancy rate	2	0.845	0.666–1.071	Not significant
Implantation rate	1	0.714	0.547–0.931	P=0.013
Ongoing pregnancy/live birth rate	2	0.733	0.383–1.405	Not significant
Spontaneous abortion rate	2	1.215	0.391–3.774	Not significant
Preterm delivery rate	1	6.000	0.309–116.606	Not significant

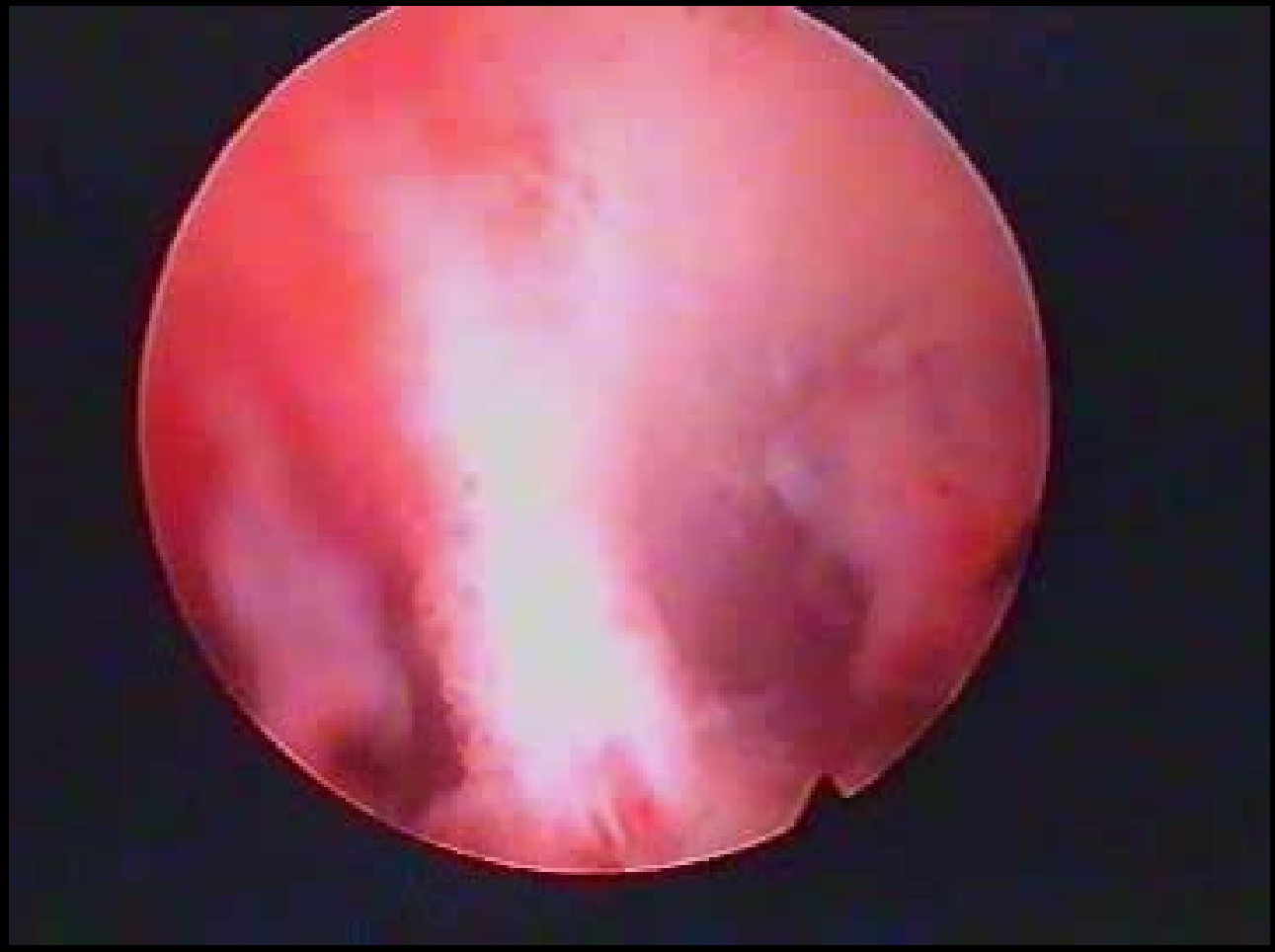
Pritts. Fibroids and infertility. Fertil Steril 2009.

Classification of congenital uterine anomalies



American Fertility Society. *Fertil Steril* 1988;49:944–955.

UTERINE SEPTUM



Prospective Controlled Trial

Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility : a prospective controlled trial

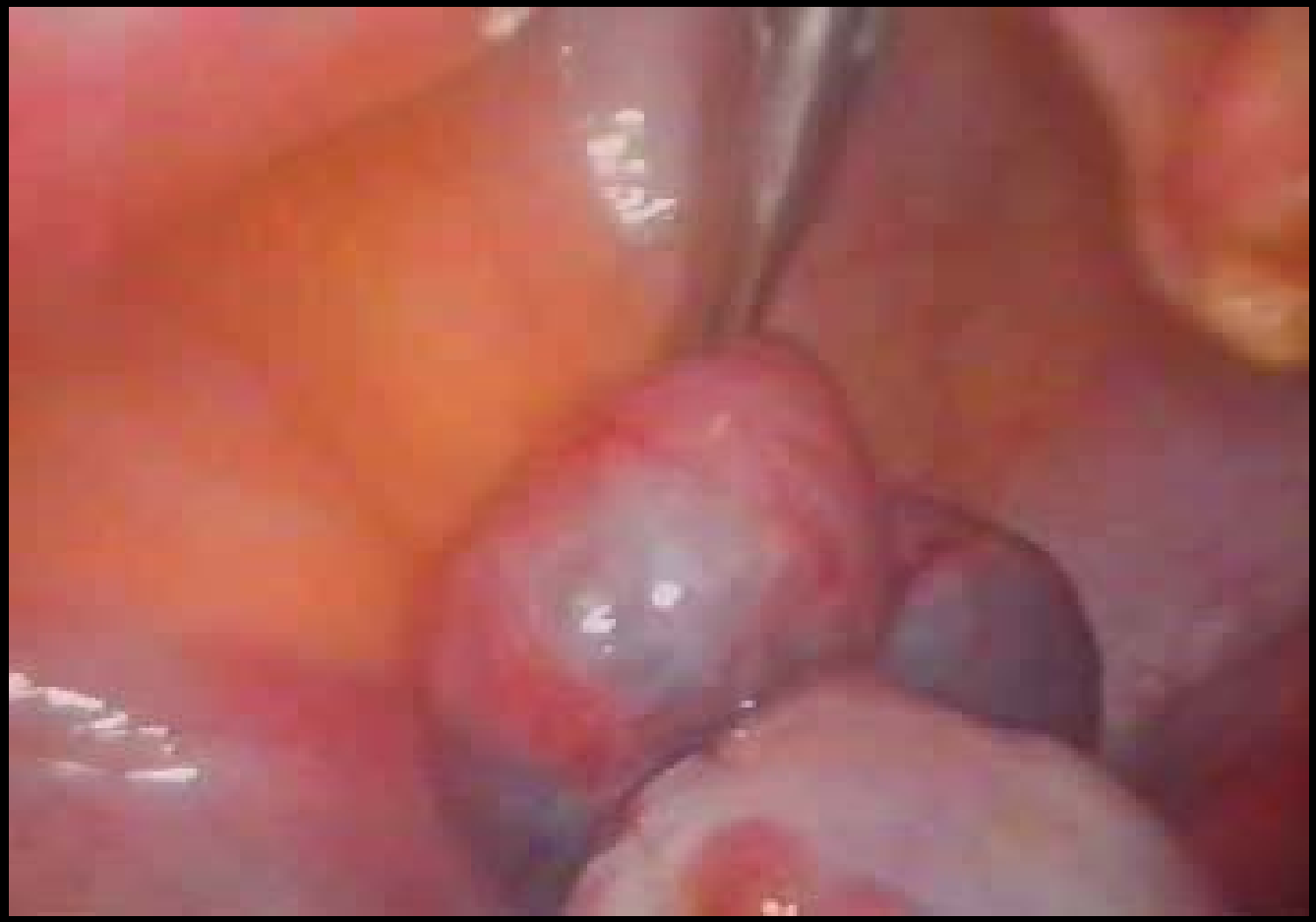
Mollo et al, Fertil Steril 2009

	Pregnancy rate	Live birth rate
unexplained infertility & septum removed	38.6%	34.1%
Unexplained infertility	20.4%	18.9%

Non-steroidal factors

- Intra-cavity pathology
- Structural uterine anomalies
- Inhibitors of implantation

HYDROSALPINX



Why does the presence of hydrosalpinges adversely affect IVF pregnancy rate ?

Hydrosalpingeal fluid impairs endometrial function

Hydrosalpinges and Leukaemia inhibitory factor (LIF) expression in the endometrium

- LIF expression in the mid-luteal phase endometrium of infertile women (n=10) with hydrosalpinges was significantly lower than control fertile subjects
- Salpingectomy resulted in increase of LIF expression in 8/10 subjects with hydrosalpinges

Seli et al 2005

Human Reprod 20:3012

Hydrosalpinges and integrin expression (αvβ3) in the endometrium

- Integrin (αvβ3) expression in the mid-luteal phase endometrium of women with hydrosalpinges was significantly lower than control subjects
- Salpingectomy resulted in increase of integrin (αvβ3) expression

Meyer et al 1997
Human Reprod 12:1393

Bildirici et al 2001
Human Reprod 16:2422

Populaton Must be Thoroughly Investigated

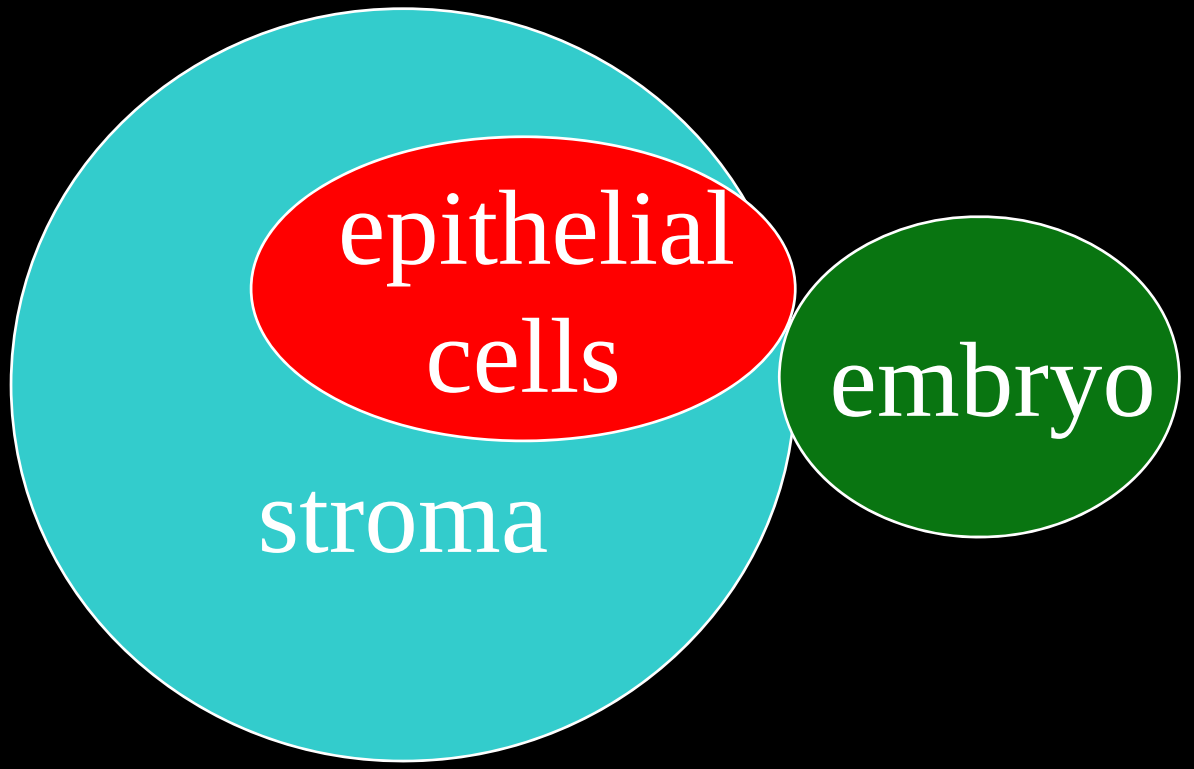
Uterine and tubal investigations need to be part of protocol

6. Implantation is a long process involving many steps

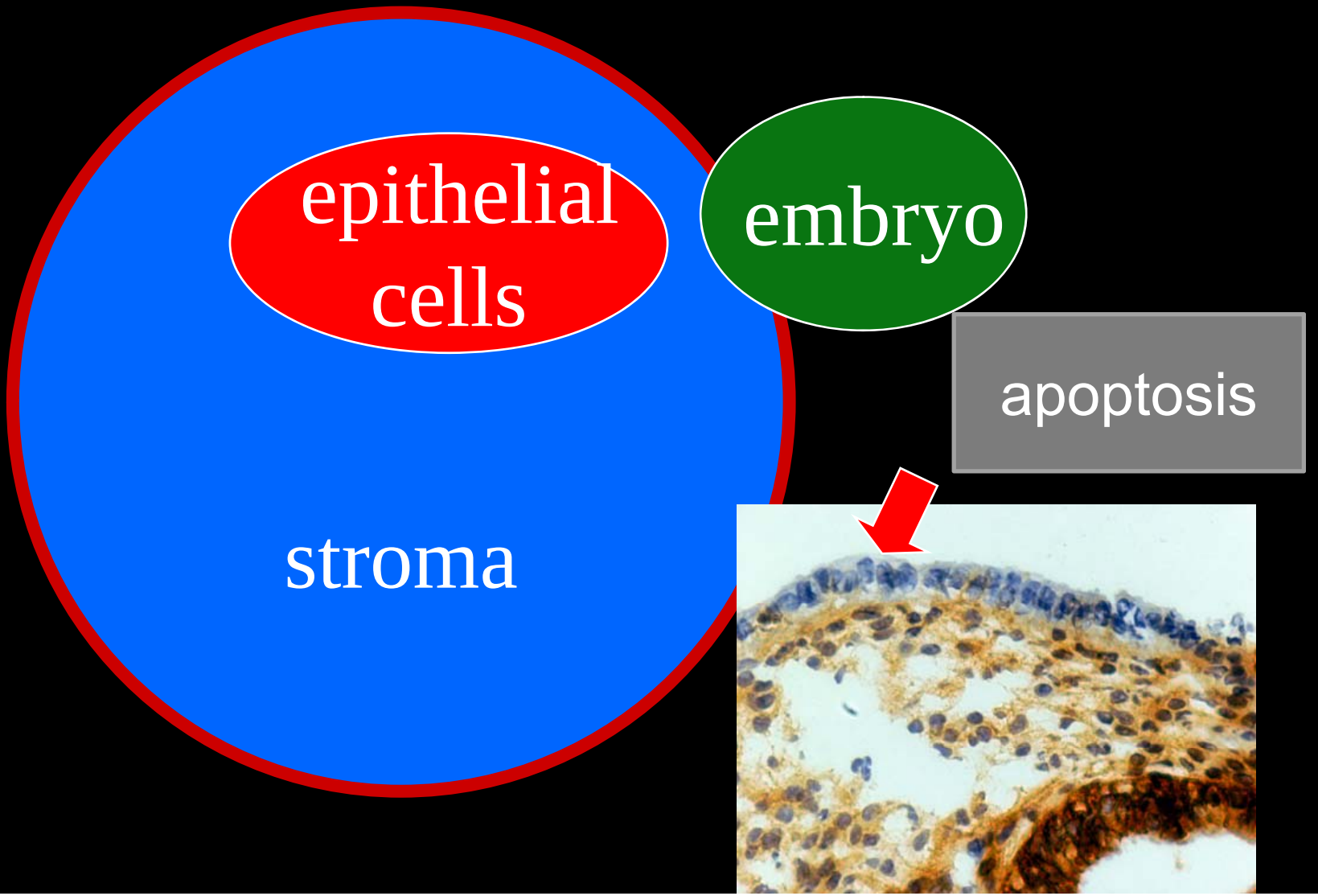
1. ATTACHMENT

ADHESION MOLECULES

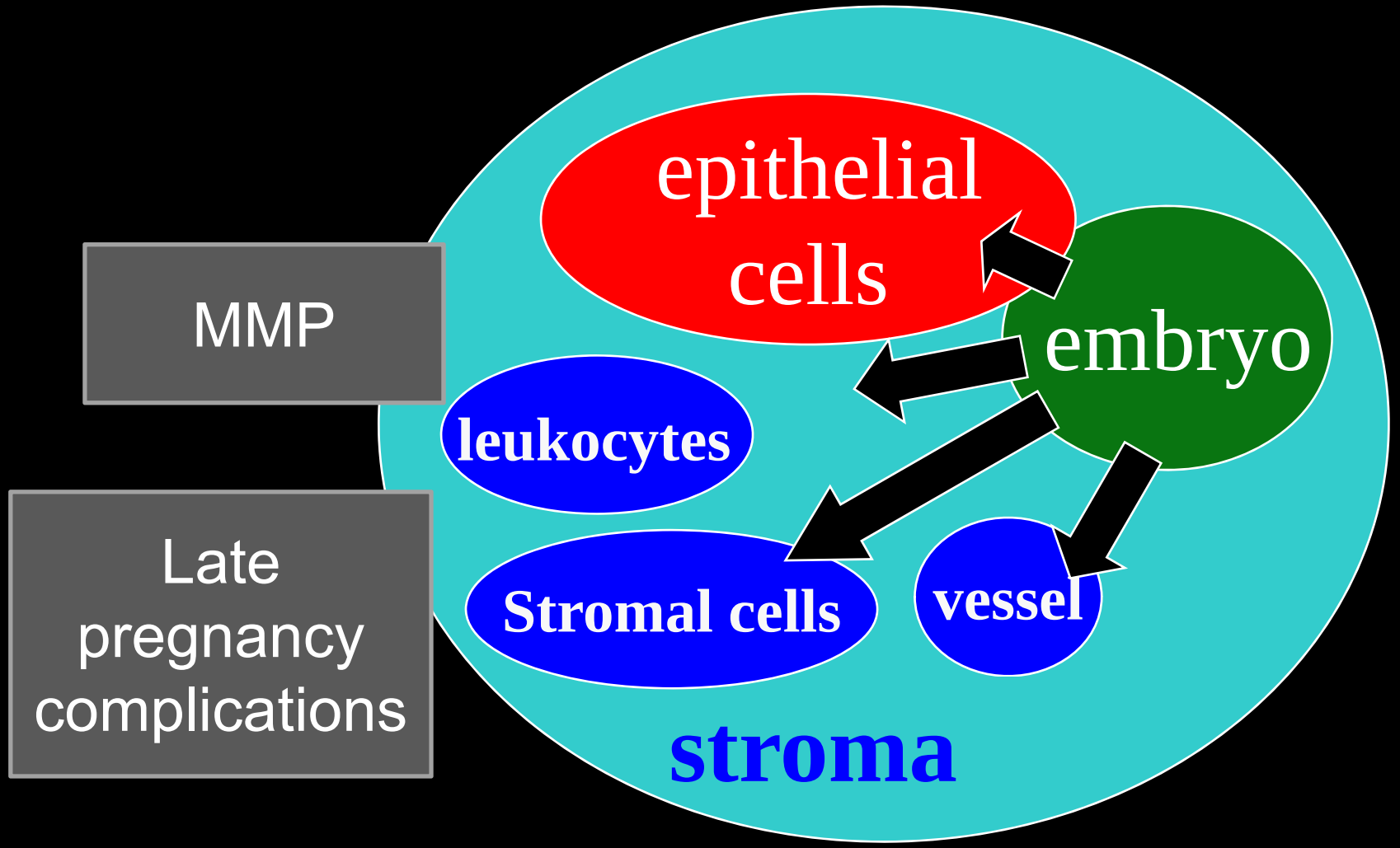
1. INTERGRINS
2. MUC1



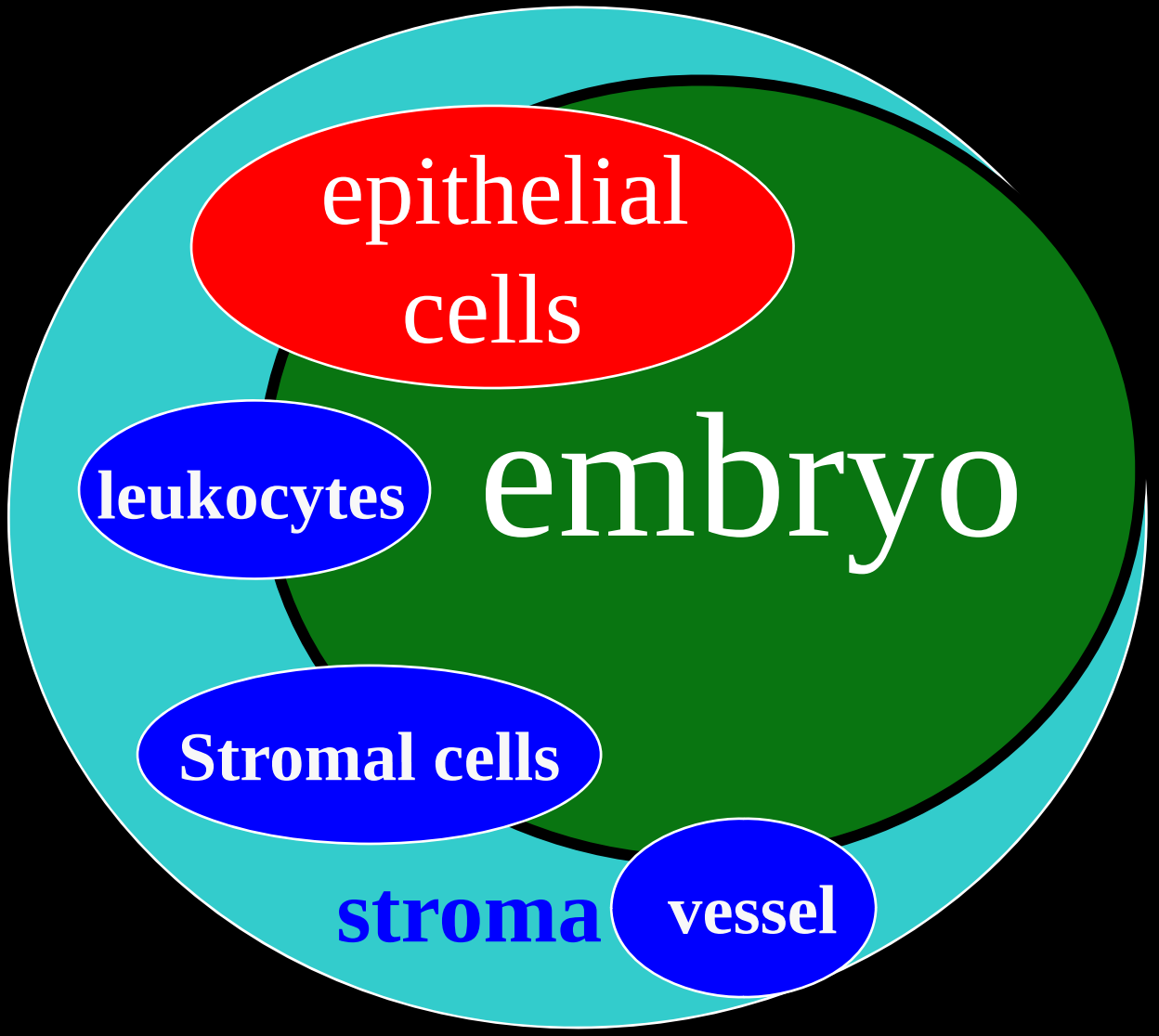
2. Migration via luminal epithelium



3. INVASION


epithelial cells
embryo
MMP
leukocytes
Late pregnancy complications
Stromal cells
vessel
stroma

4. GROWTH


epithelial cells
leukocytes
embryo
Stromal cells
stroma
vessel

CONCLUSION

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Any good quality data?

No

CONCLUSION

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Any data at all?

No

Pubmed search on:
Poor responder &
IVF &
endometrial receptivity

Result = 0

none

My Opinion

- The endometrium in poor responder is unlikely to be abnormal
- Poor responders usually have good implantation rate when they undergo oocyte donation
- The low implantation rate in poor responders is more likely a consequence of poor oocyte quality, partly a consequence of reduced number for selection

ENDOMETRIUM IN POOR RESPONDERS

BENEFITS FROM EXPOSURE TO LOWER LEVEL OF ESTROGEN?

Would a strategy of mild ovarian stimulation or natural cycle IVF in poor responders improves outcome by improving endometrial receptivity?

Uncertain, probably not

The Final Question

Is the endometrium of no relevance at all?

Poor responders

vs

Recurrent IVF
(implantation) failure

THANK YOU