GP Fertility Autumn Series

Endometriosis and Infertility

Speaker: Dr Jodie Semmler
Date: 23rd May 2024

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Introducing

Dr Jodie Semmler

MBBS FRANZCOG

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Endometriosis and Infertility

- Understanding impact of endometriosis on fertility
- How does endometriosis cause infertility
- Surgery and potential problems and benefit
- Endometriosis fertility index
- Who might need IVF and IVF principles
- Oocyte vitrification for fertility preservation

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Endometriosis and Infertility

- Endometriosis is characterized by endometrial like lesions outside the uterus.
- It can be present on any pelvic organ, on bowel and between uterus and bowel (POD). It can occasionally be present on distant areas such as diaphragm
- It affects 9 -10% of women in their fertile years
- It causes two main health issues: Pain and Infertility
- No direct correlation between severity of endometriosis and inability to conceive
- Some women with severe endometriosis manage to conceive naturally whilst some women with mild endometriosis require IVF

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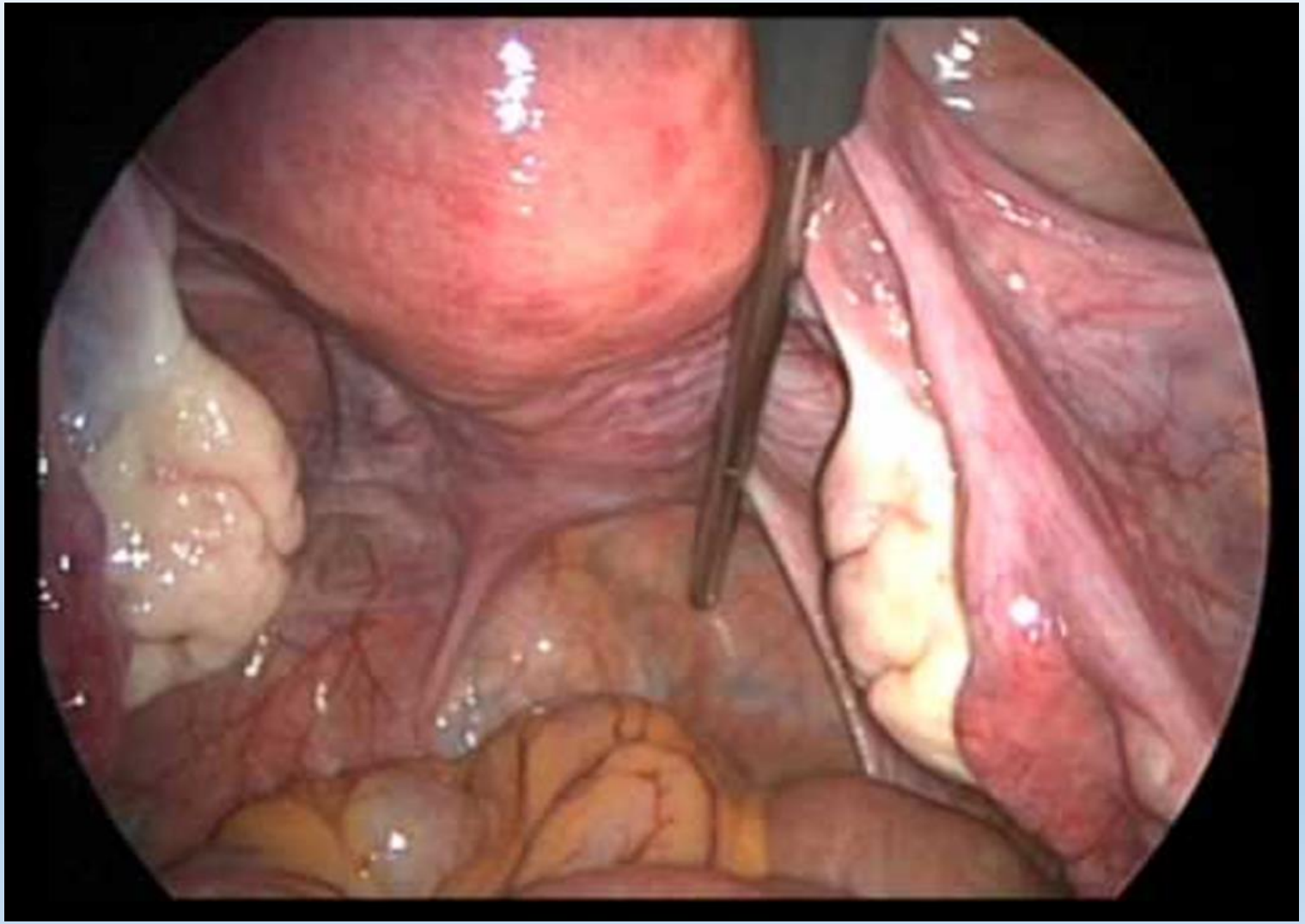
Diagnosing endometriosis

- Laparoscopy is still the gold standard
- Specialised “endometriosis ultrasound” done at the right place can find nodules of endometriosis (and endometriomas) but not superficial endometriosis
- MRI can also diagnose nodules of endometriosis, endometriomas, degree of bowel involvement but cannot diagnose superficial endometriosis

Endometriosis and Infertility – Normal pelvis



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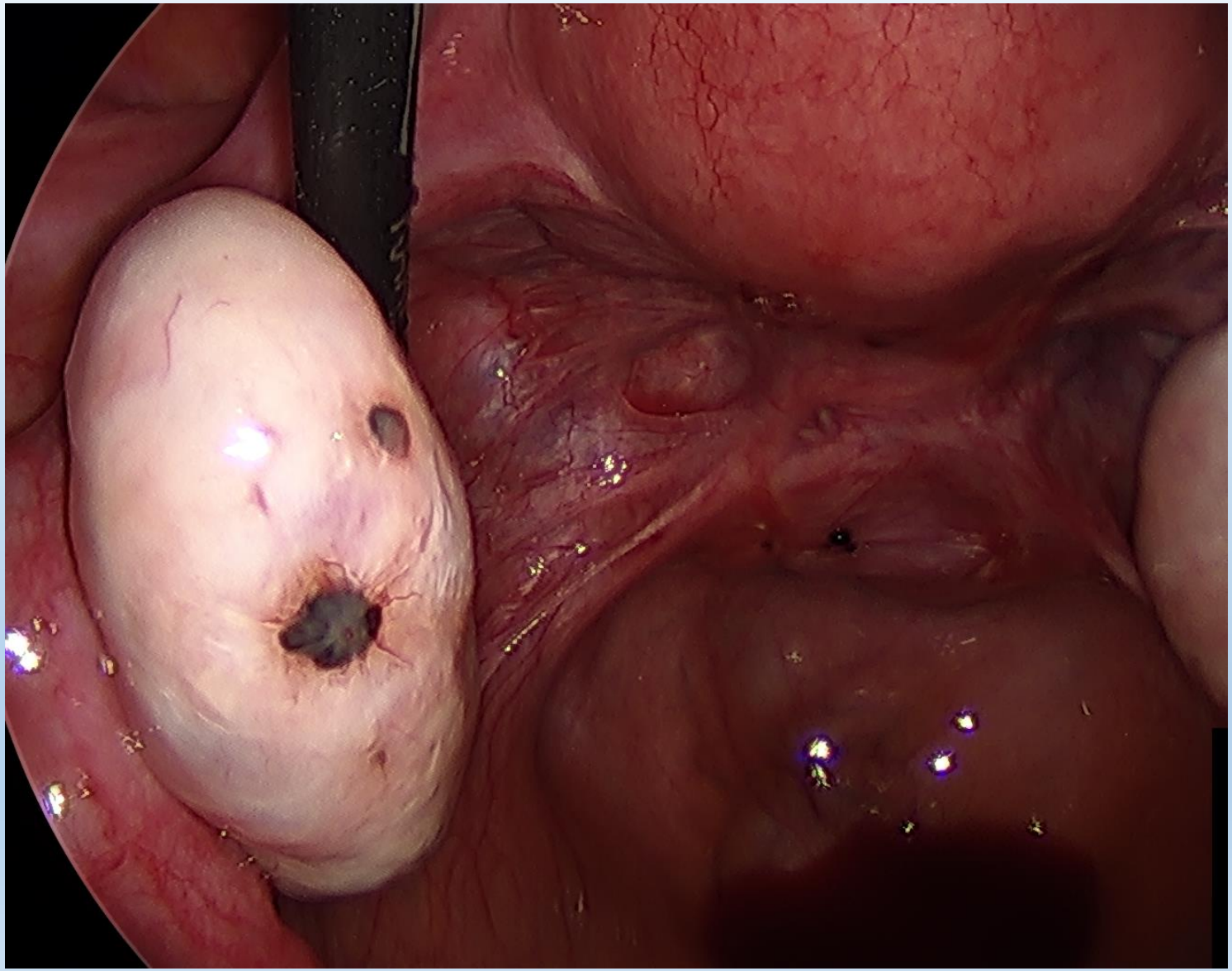
Endometriosis and Infertility – stage 2 endometriosis (Mild)



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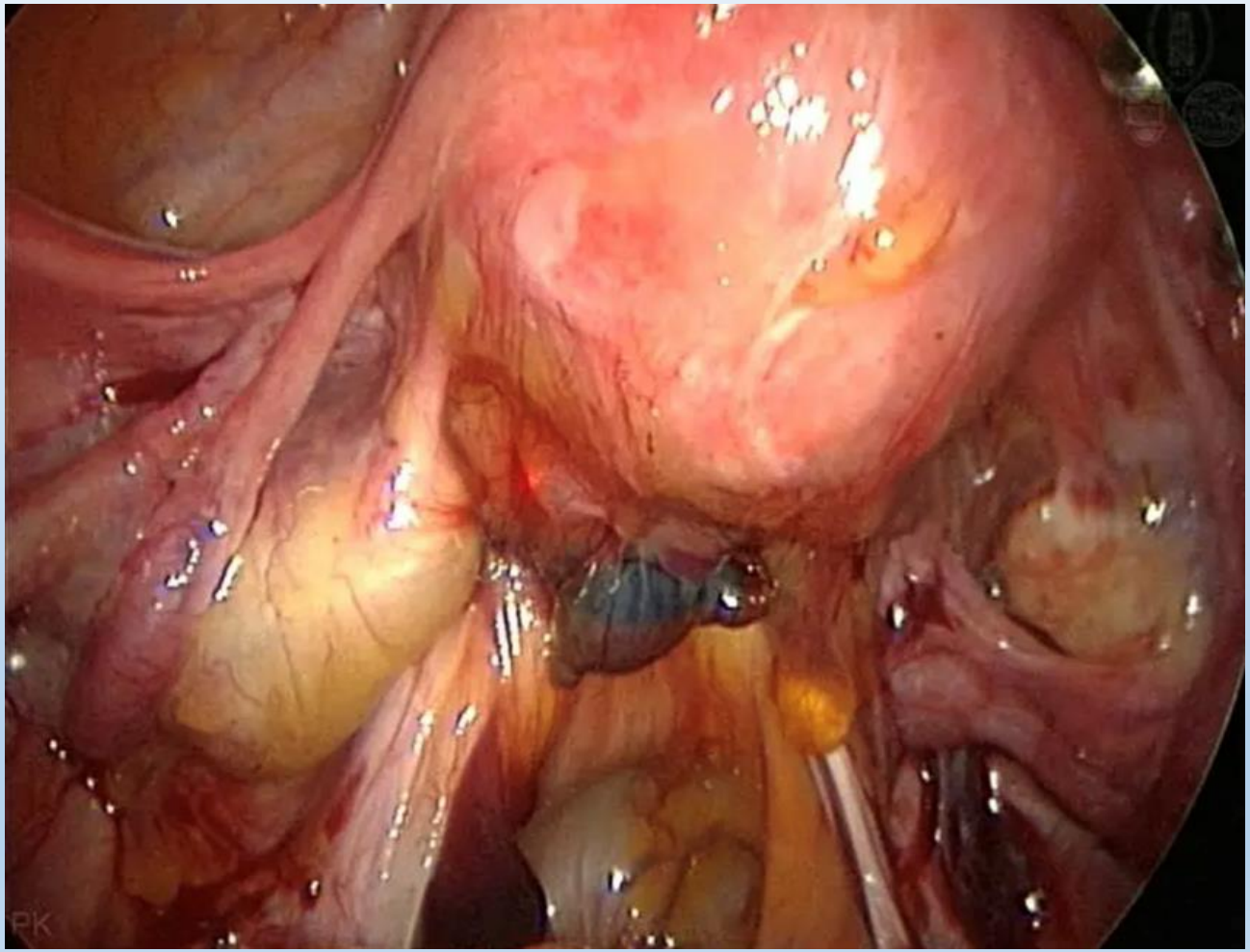
Endometriosis and Infertility – stage 4 endometriosis (Severe)



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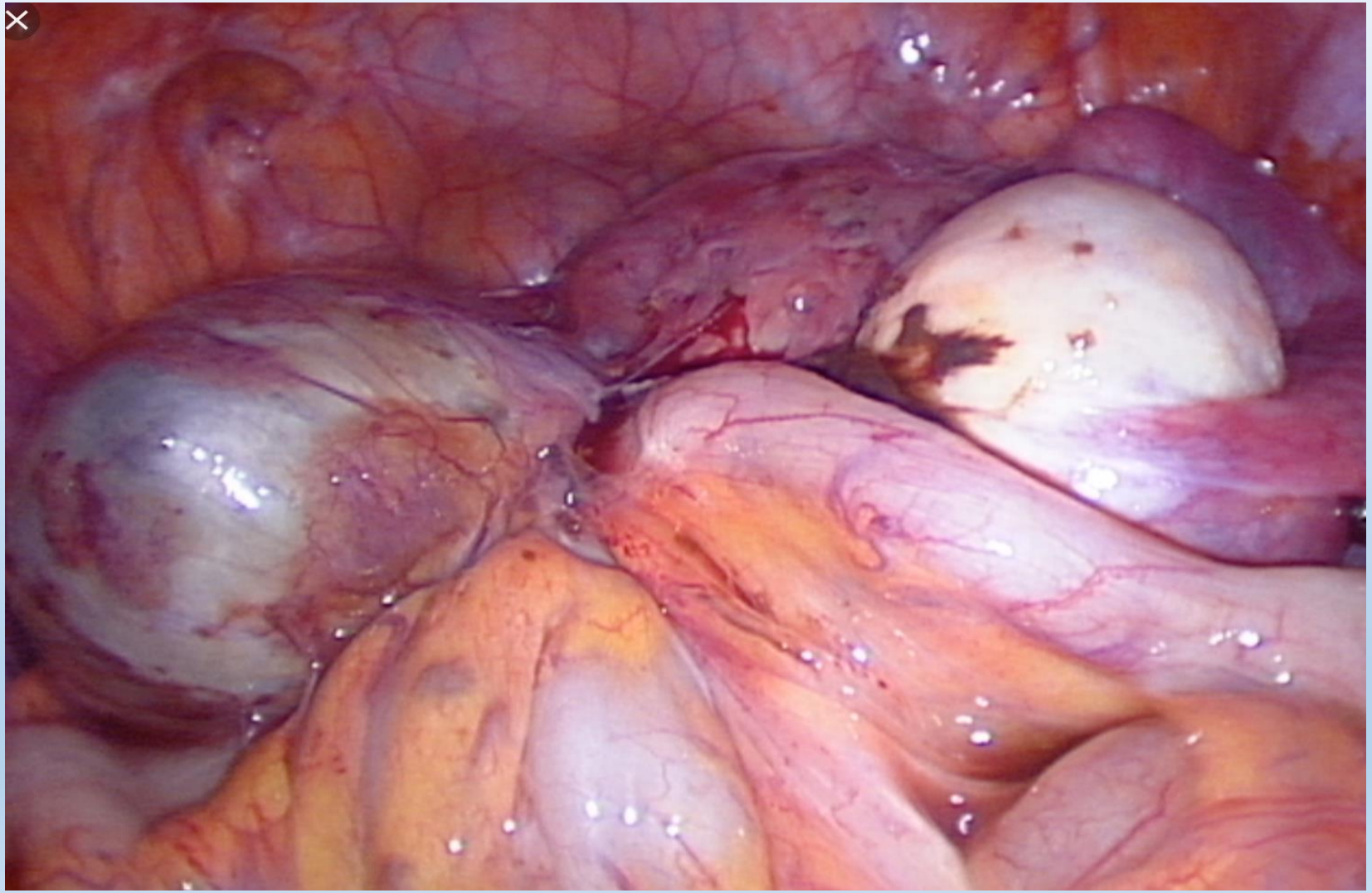
Endometriosis and Infertility – stage 4 endometriosis (Severe)



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Prevalence of endometriosis

Most recent systematic review by Ghiasi. 69 studies describing prevalence and incidence of endometriosis.

When defined by indication for diagnosis.

Indication	No of studies	Overall Endo %	Prevalence %
Chronic pelvic pain	11	**29%**	**15.4-71.4%**
Infertility	17	**27%**	**9-68%**
Tubal sterilisation	4	**5%**	**3.7-43.3%**

M Ghiasi et al JMIG 2020

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What patients with a diagnosis of endometriosis want to know

What is the chance that I will have infertility?

What is the chance that I will conceive naturally?

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Nurses' health study II prospective cohort

The prospective relationship between a history of laparoscopically confirmed endometriosis and infertility risk, in a large, well-characterized cohort of women.

History of laparoscopically confirmed endometriosis and risk of incident infertility among married women in Nurses' Health Study II from 1989 to 2005.

Laparoscopically confirmed endometriosis	No	Yes	*P*-value
Cases, *N*	4429	183	
Person-years	353 490	8730	
Age-adjusted HR (95% CI)	1.00 (ref)	2.12 (1.76–2.56)	<0.0001
Multivariate-adjusted HR[a] (95% CI)	1.00 (ref)	2.11 (1.74–2.54)	<0.0001
Multivariate-adjusted HR[b] (95% CI)	1.00 (ref)	1.78 (1.48–2.15)	<0.0001

A prospective cohort study of endometriosis and subsequent risk of infertility. J Prescott et al 2016

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Nurses health study II prospective cohort

The good news is: among all women with endometriosis, 83% were parous by age 40 years.

15% reported ever use of clomiphene or gonadotrophin to stimulate ovulation, and 2% reported ever use of IVF.

The low percentage of IVF use is possibly related to the lower success rate of IVF during the course of the study

Natural Fecundity: No endometriosis versus Endometriosis

15-20% per month

5-10% per month

Chandra A, Mosher WD. Infertil Reprod Med Clin North Am 1994;5: 283–96.; Schwartz D, Mayaux MJ. N Engl J Med 1982;306:404–6; Hughes EG, Fedorkow DM, Collins JA. Fertil Steril 1993;59:963–70.

Acknowledgement Prof Ying Cheong

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Natural Fecundity after laparoscopy (stage 1-2)

20% per month

5-10% per month

10-15% per month over next 6 months

Marcoux S, Maheux R, Be´rube´ S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997;337:217–22.

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How does endometriosis cause infertility?

- Dyspareunia and sexual dysfunction
- Pelvic adhesions and anatomic distortions. Tubal damage such as hydrosalpinges
- Reduced ovarian reserve related to endometrioma surgery
- Altered oocyte quality. Reduce oocyte quality due to reactive oxidative stress, increased IL6, altered mitochondria. (Lecture notes. Prof Antonio Pellicer, ESHRE 2020
- Endometrial dysfunction and reduced implantation
- Dysregulated endometrial function due to progesterone resistance, chronic inflammation, impaired decidualization and reduced embryo implantation. Prof Velja Mijatovic, New theories on the aetiology of endometriosis-associated infertility. ESHRE course, Milan, 23-24 Jan 2020)

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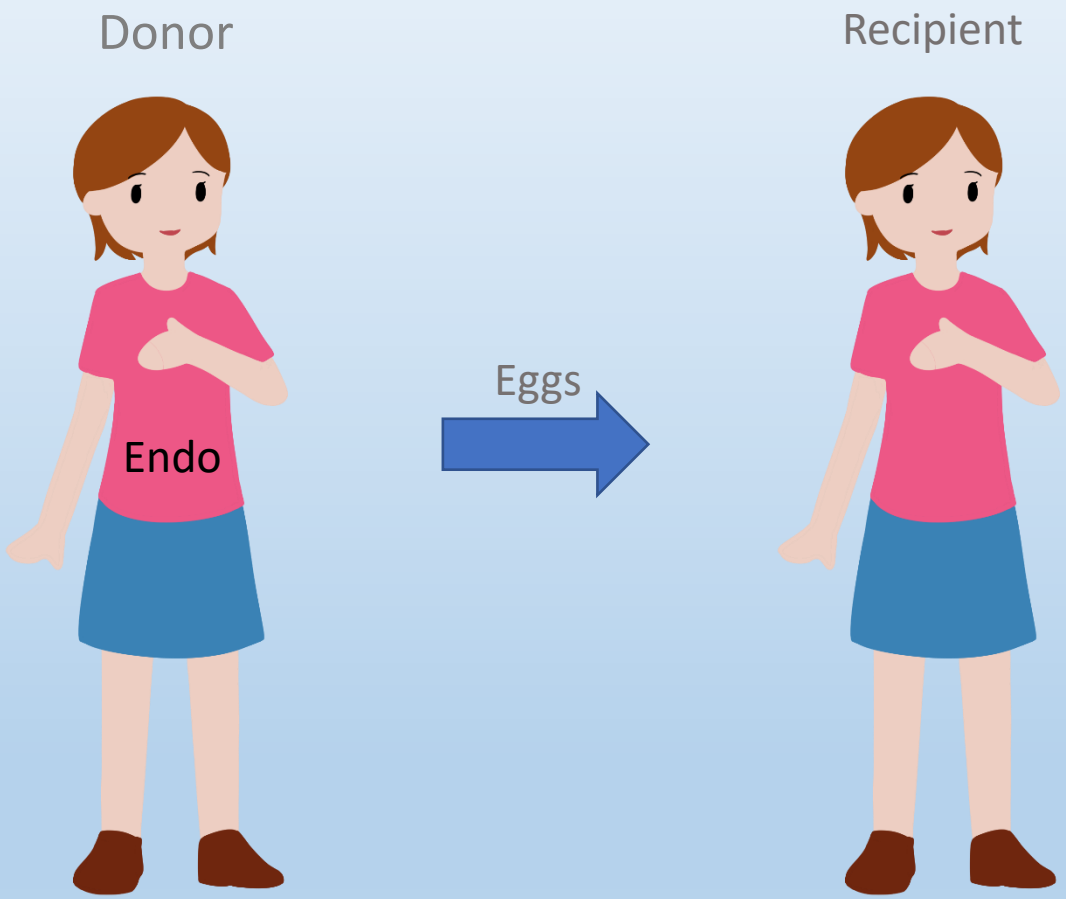
Donor Recipient model



Reduce implantation rate
Reduce quality of embryo
Reduce pregnancy rate

Embryos derived from donor with endometriosis have reduce ability to implant

Simons et al 1994, Pellicer et al, 1994; Diaz et al, 2000

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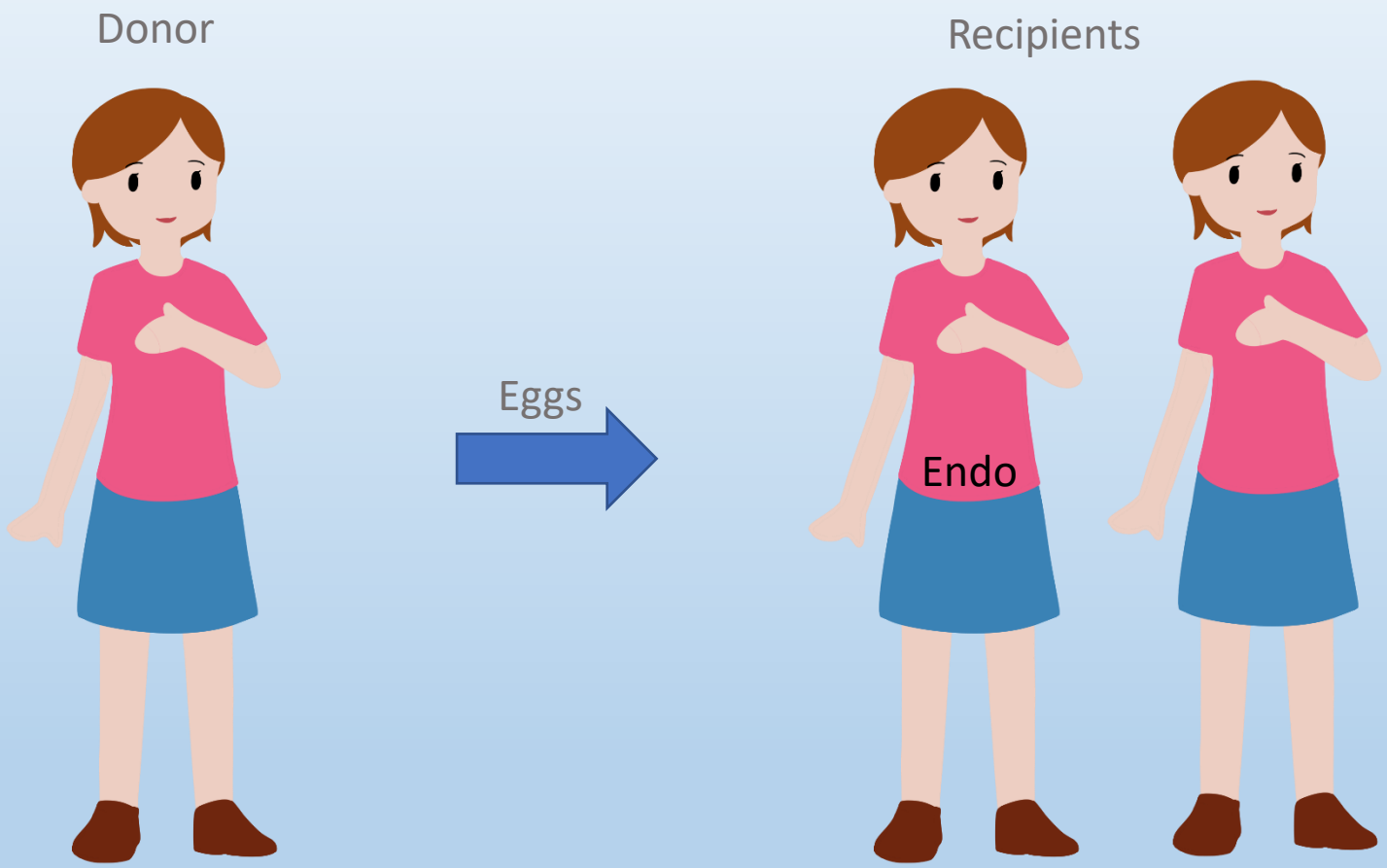
Donor recipient model



Controversial:
Earlier studies suggested similar pregnancy rates

Later study suggested lower pregnancy rate in recipients with endometriosis suggesting endometrium is affected in women with endometriosis

Simons et al 1994, Pellicer et al 1994, Diaz et al 2000, Sung et al 1997, Prapas et al, Reprod Biomed Online 2012;25:543–8

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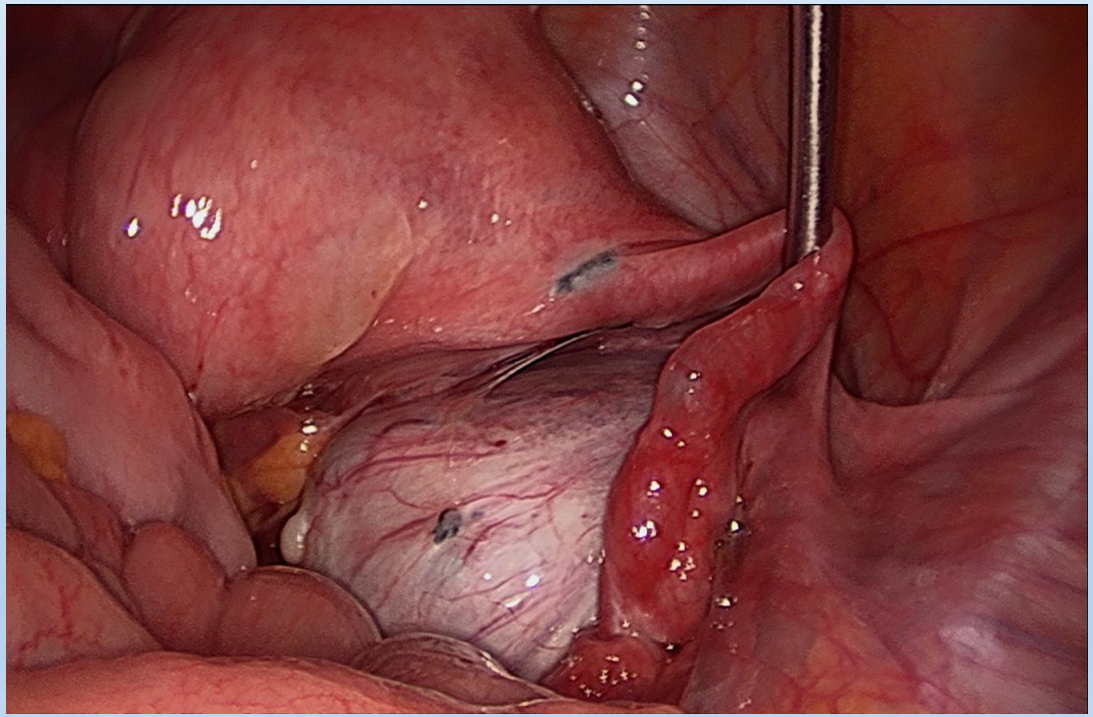
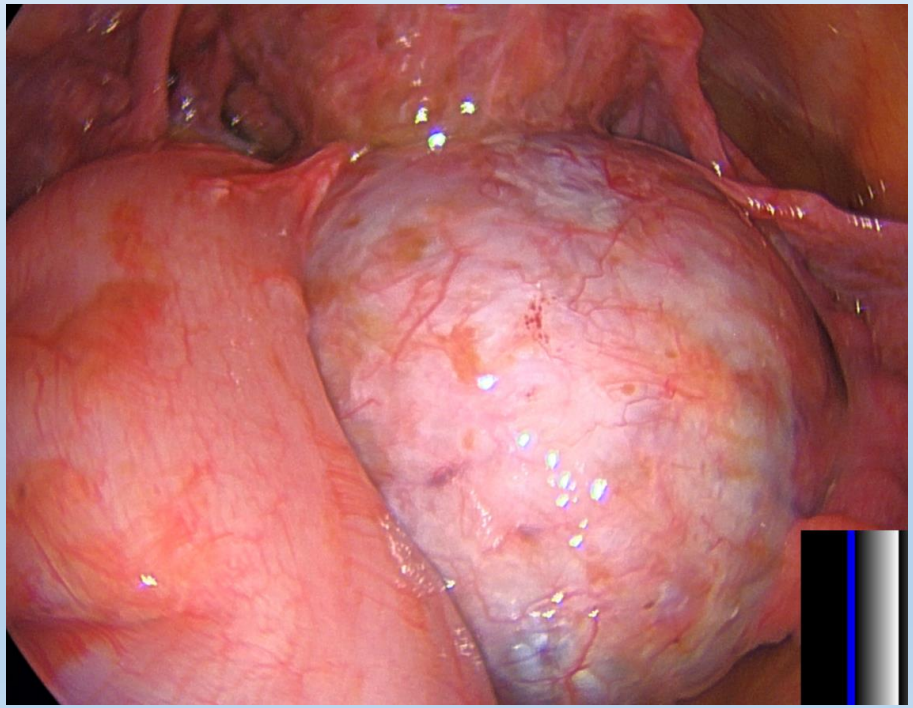
The dilemma with endometriomas

To operate or not to operate?

- For women presenting with pain, decision is easier to proceed with surgery
- What about the incidental finding of endometriomas, and those with no symptoms?





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The dilemma with endometriomas

Risk of endometriomas to fertility

- Presence of endometrioma has a toxic effect on remaining ovarian parenchyma
- Anatomical distortion
- Toxic effect of ROS, iron, inflammatory factors causing ischaemia, fibrosis and loss of ovarian follicles
- Lower rate of spontaneous ovulation in unoperated ovary
- Progressive decline in AMH and ovarian reserve

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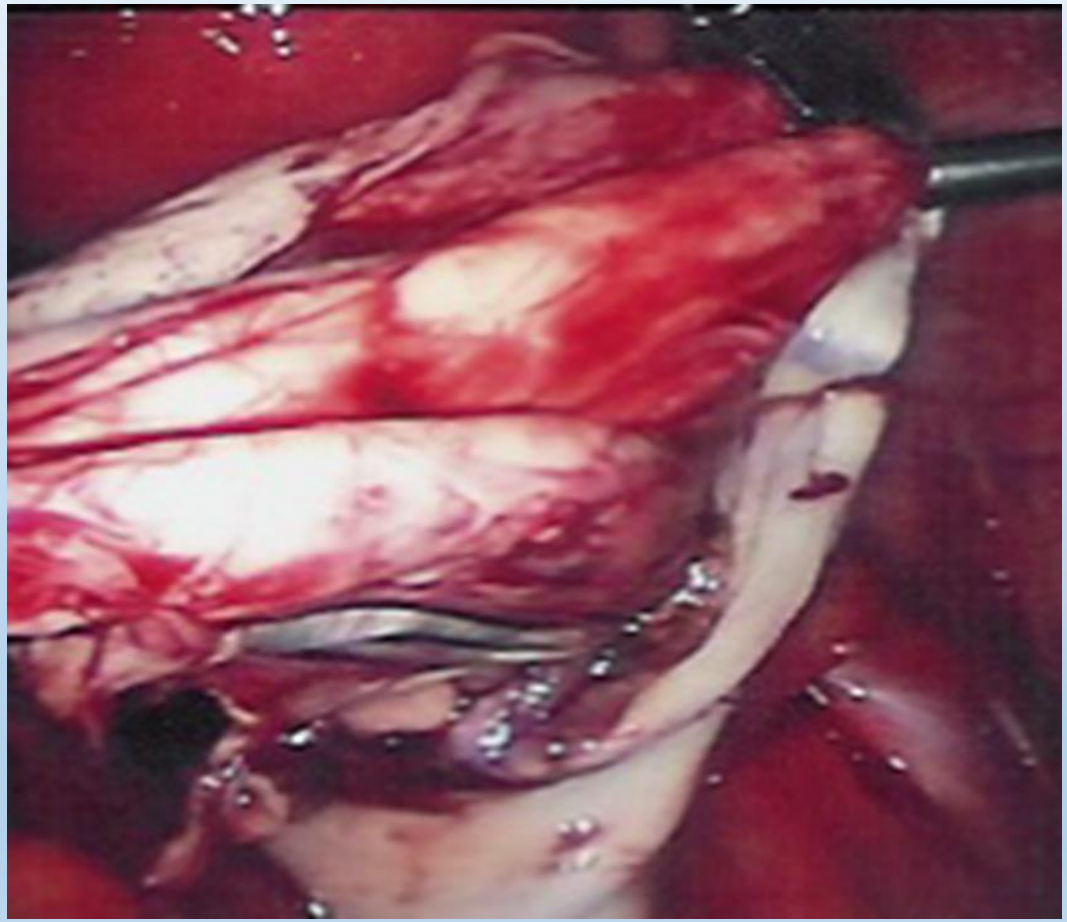
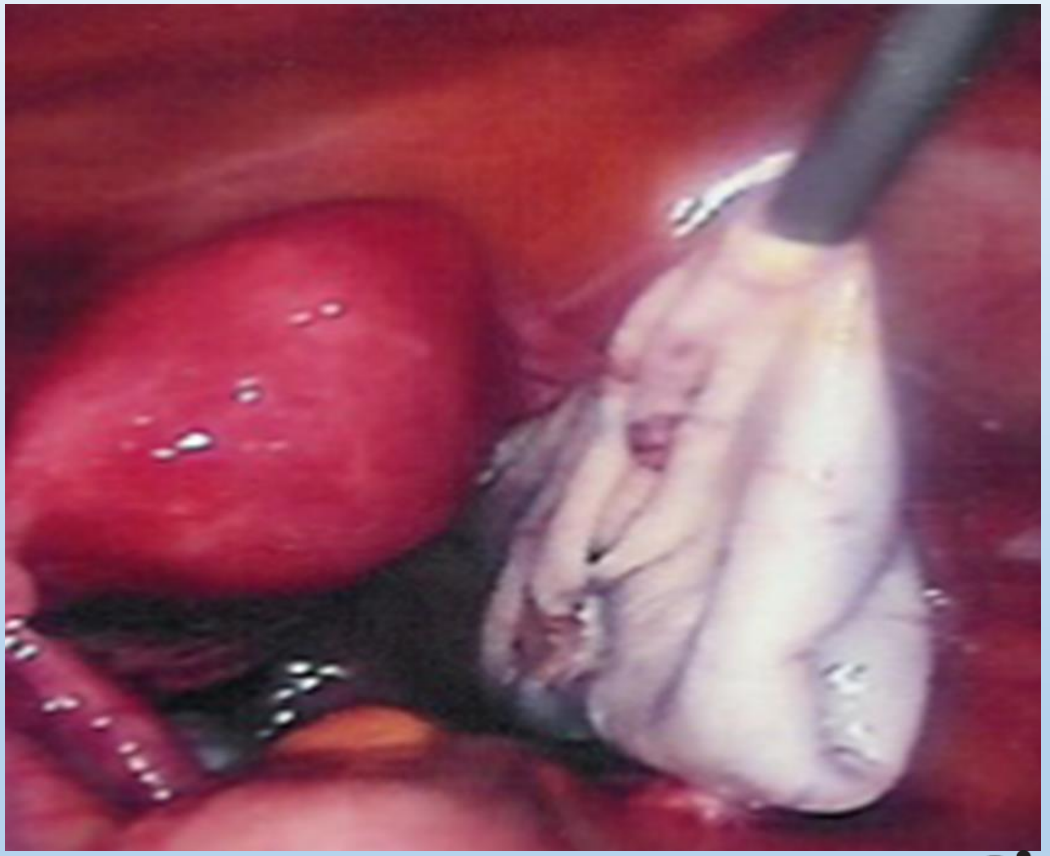
(M Busacca et al Human Reprod 2010)

Surgery for endometriomas





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The dilemma with endometriomas

Risk of surgery to fertility

- Removal of healthy tissue during stripping of ovarian cyst
- Vascular compromise due to coagulation
- Technical skill of surgeon – hard to find the “plane”
- Progressive decline in AMH after surgery
- 2.4% risk of premature ovarian failure after bilateral endometrioma cystectomy!

(M Busacca et al Human Reprod 2010)

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Indications for surgery, removal of endometriomas

- Investigation of infertility with symptoms of pain or concern of malignancy in complex cyst
- To reduce risk of pelvic infection during IVF
- To allow access to the follicles during transvaginal oocyte retrieval
- Not all endometriomas, especially if small, need to be removed

ESHRE guidelines on management of Women with endometriosis, endometriomas

- When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces endometriosis-associated pain and reduces recurrence rates (Hart, et al., 2008). Grade of recommendation: A
- After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe hormonal contraceptives for the secondary prevention of endometrioma (Vercellini, et al., 2010). Grade of recommendation: A
- In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase pregnancy rates (Jacobson, et al., 2010, Nowroozi, et al., 1987). Grade of recommendation: A

Endometriosis fertility index

What to do after surgery? Options

- Try naturally
- IUI
- IVF
- ASRM classification does not predict post op fertility

Endometriosis Fertility Index = Outcome based classification for endometriosis

Based on: Historical factors, adnexal function after surgery and extensiveness of endometriosis.
Score of 0-10

Endometriosis Fertility Index calculator. (https://endometriosisefi.com/)
IVF can be advised or deferred based on objective judgement.

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Endometriosis fertility index

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description		Left	Right
4	=	Normal	Fallopian Tube		
3	=	Mild Dysfunction			
2	=	Moderate Dysfunction	Fimbria		
1	=	Severe Dysfunction			
0	=	Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score	Left	+	Right	=	LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	**Description**	**Points**	**Factor**	**Description**	**Points**
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			**Total Surgical Factors**		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:	Historical	+	Surgical	=	EFI Score

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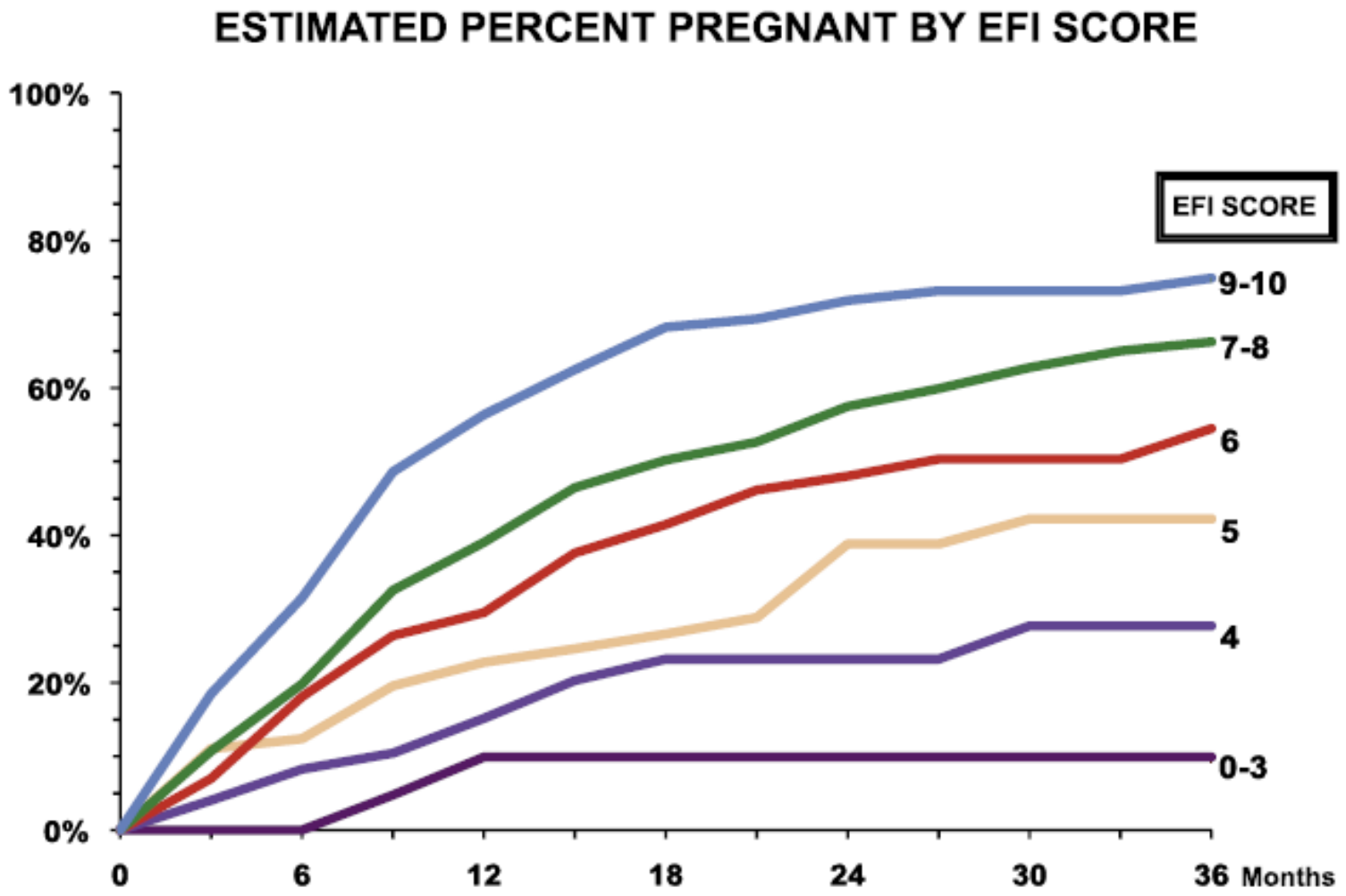
FIGURE 1



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Who to refer for IVF

- Women with low Endometriosis Fertility Index (EFI)
- Women with low ovarian reserve
- Advanced maternal age > 35yo
- Concurrent male factor
- Couples request

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Management of endometriosis patients with infertility - IVF

- Management of women with endometriosis and infertility has to take into account all fertility factors.
- Not all patients with severe endometriosis will require surgery, not all endometriomas should be removed prior to IVF.
- Conversely, not all patients with endometriosis will need IVF.
- Women with mild endometriosis have comparable ART outcomes in terms of live births to women without endometriosis, whereas those with severe endometriosis have inferior outcomes.
- There is insufficient evidence to recommend surgery routinely before undergoing IVF. (Hamdan 2015)
- IVF for patients with severe endometriosis can be challenging, with lower response, less oocytes and poorer embryo development. Patients need to be counselled fully before embarking on IVF.

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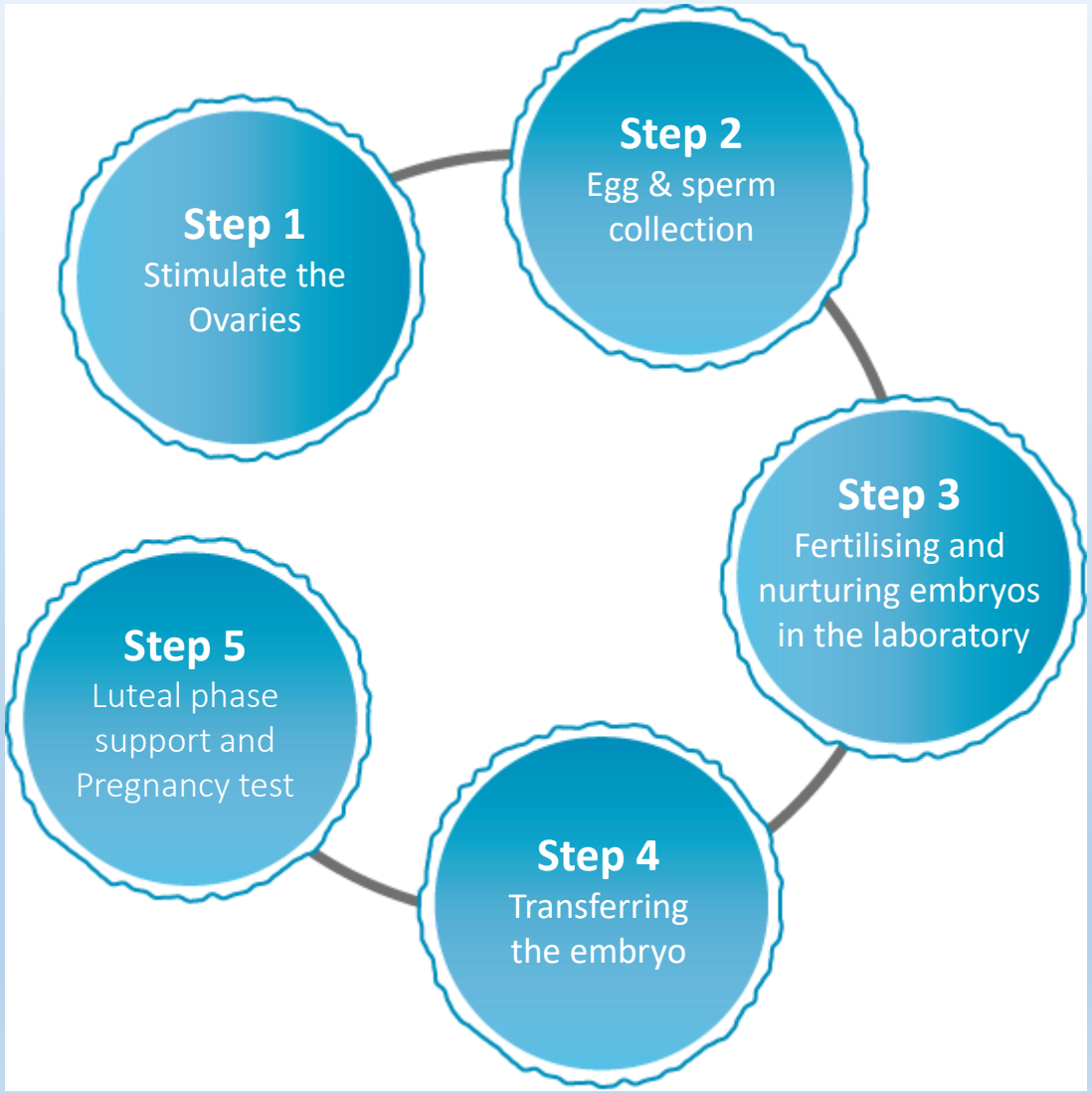
Principle of In vitro fertilisation (IVF)



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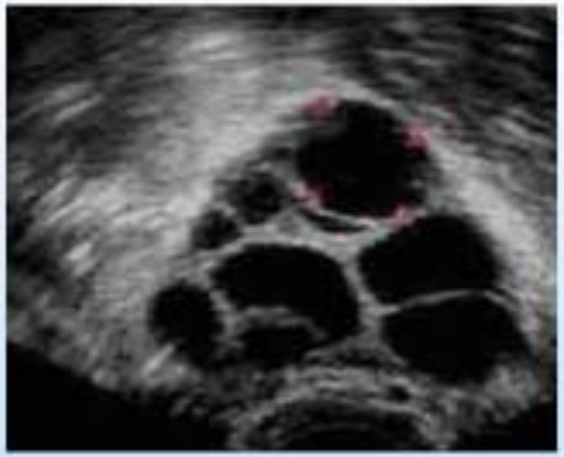
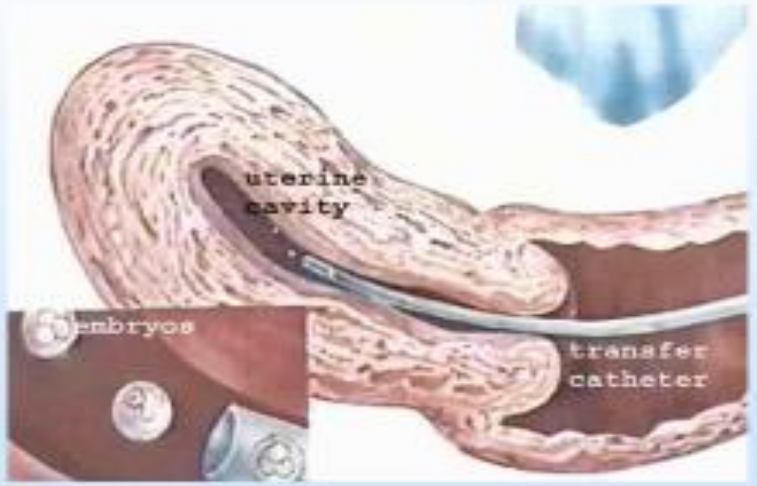
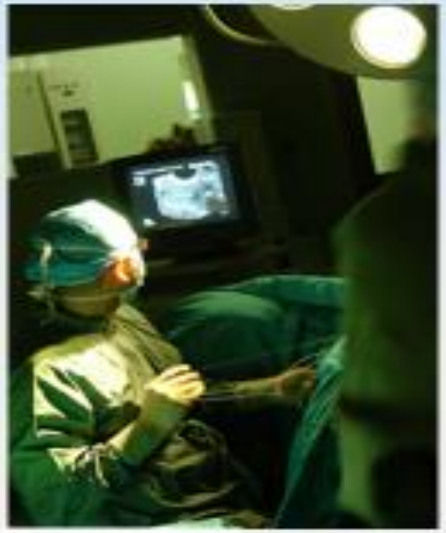
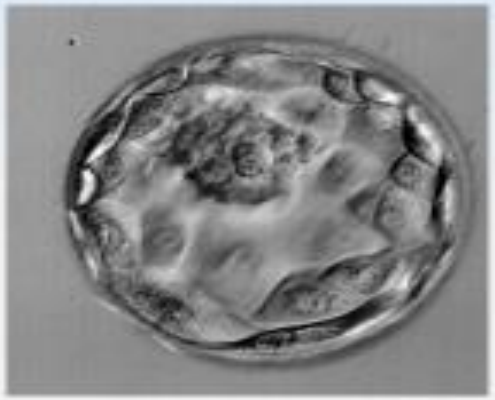
IVF









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IVF at a glance

- Antagonist cycle is the most frequently used in SA
- Approximately 2 weeks of injections
- Cycle starts with a period
- 1st week is stimulation only phase – FSH +/- LH or HCG
- 2nd week GNRH antagonist is introduced

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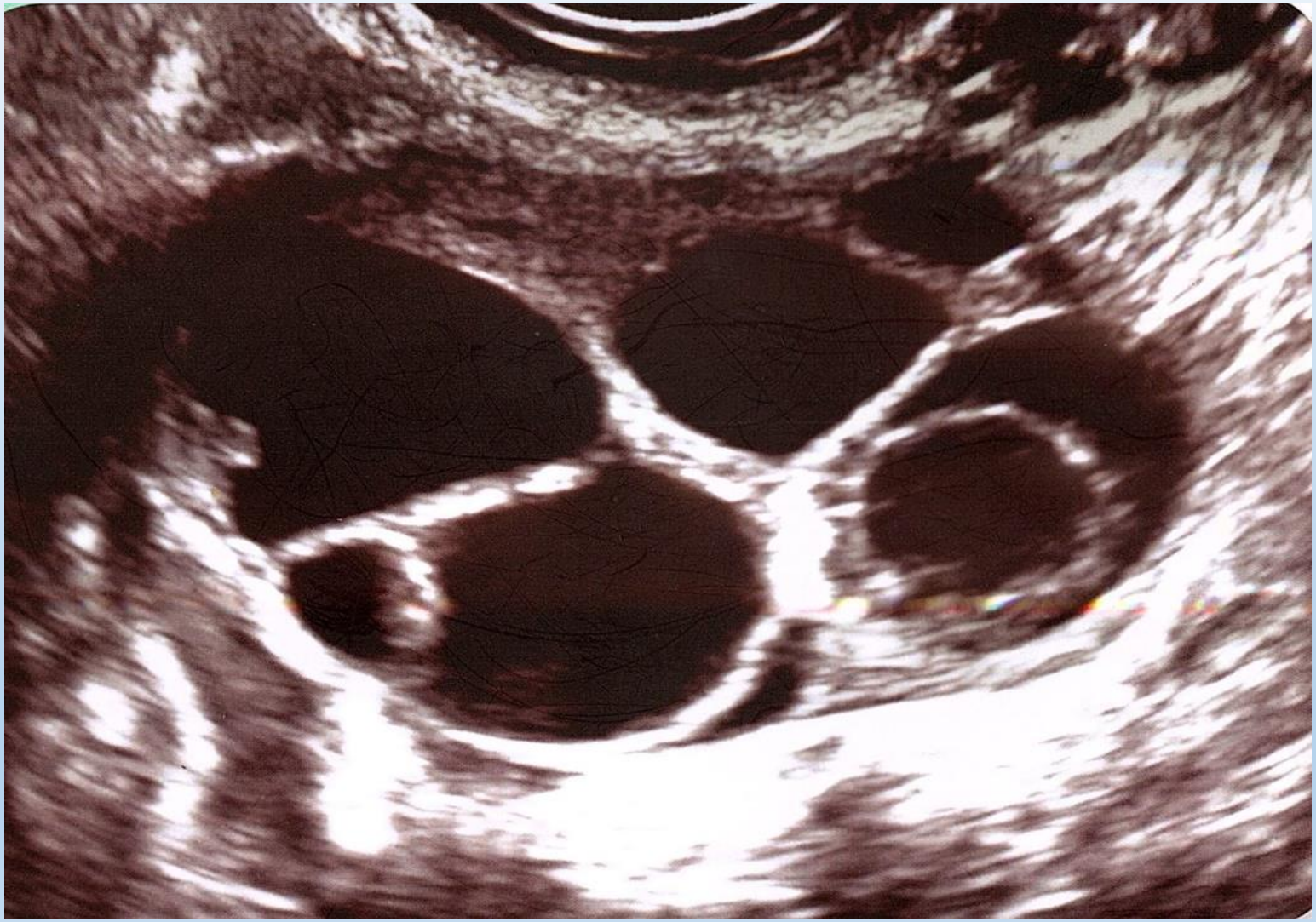
Scans and bloods are done during the 2nd week



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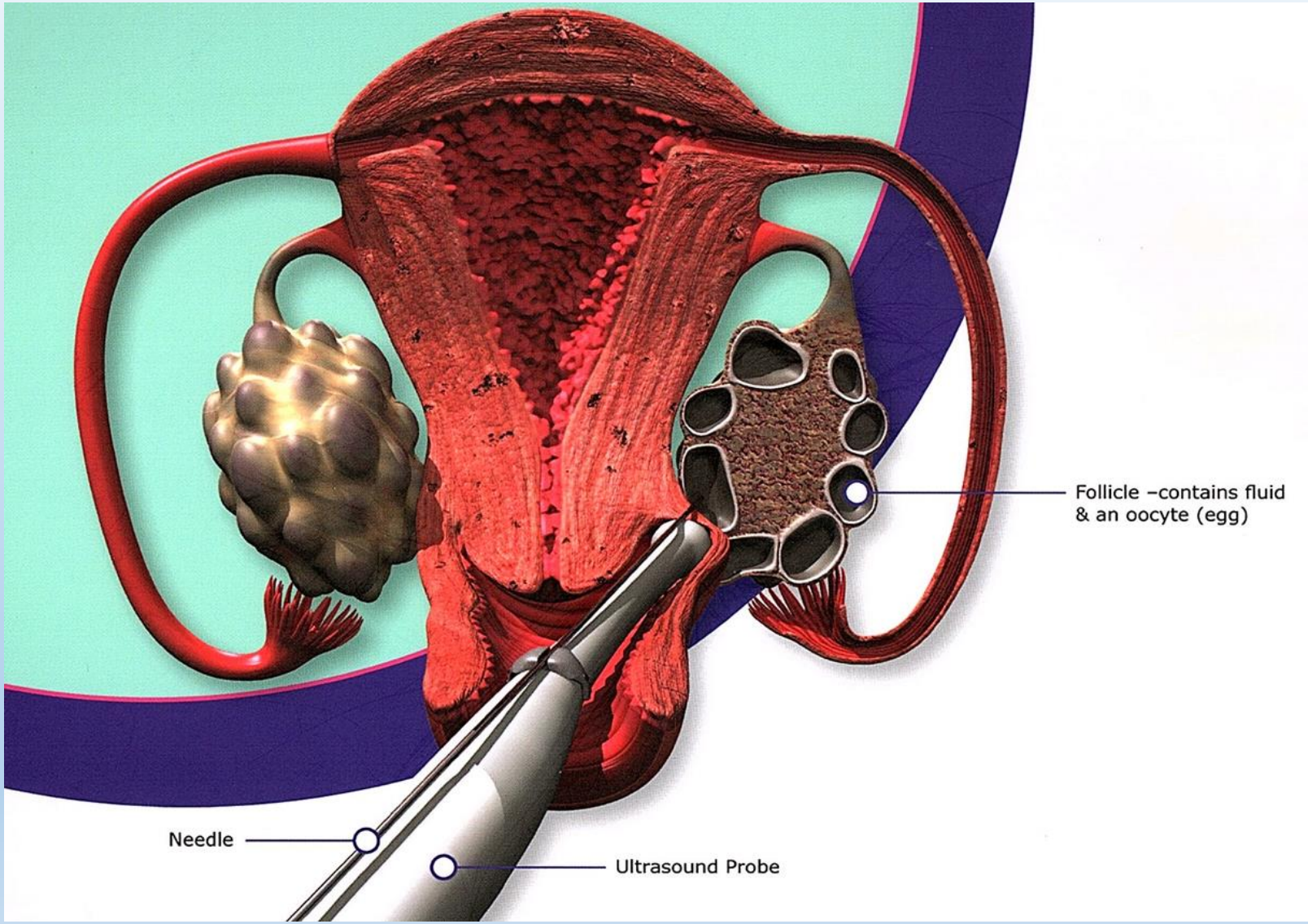
Transvaginal Oocyte Retrieval (TVOR)



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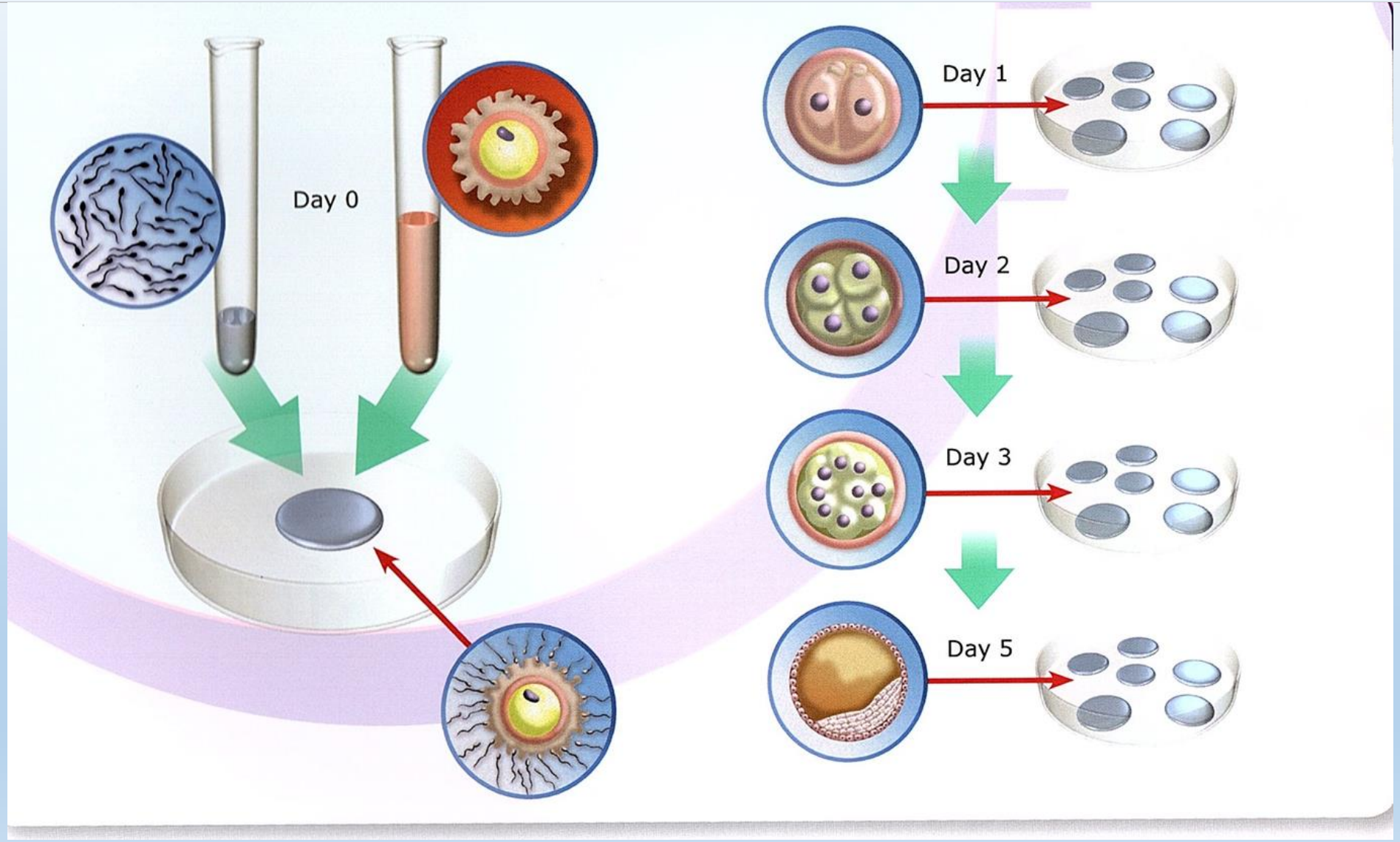
IVF at a glance



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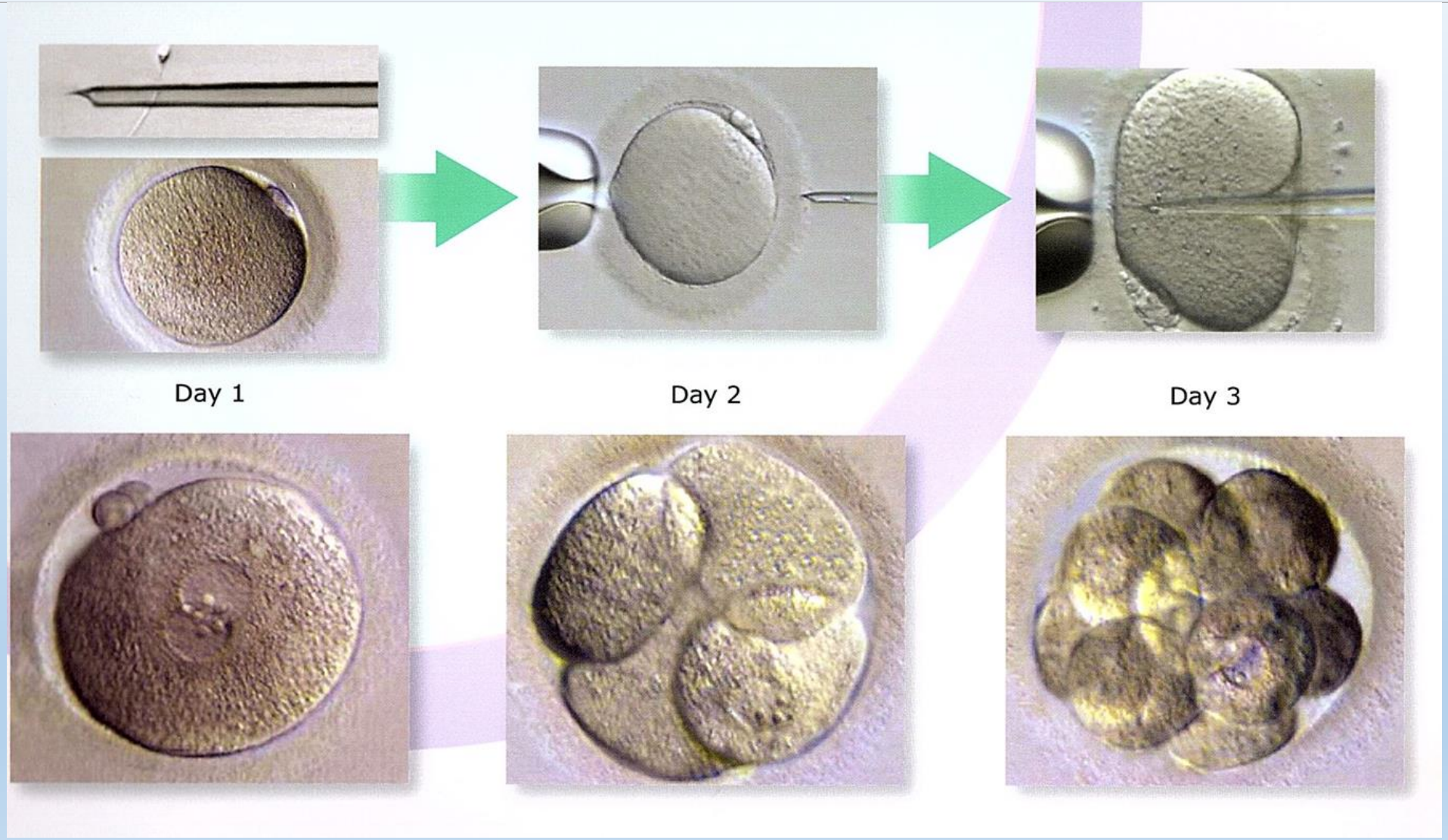
IVF at a glance



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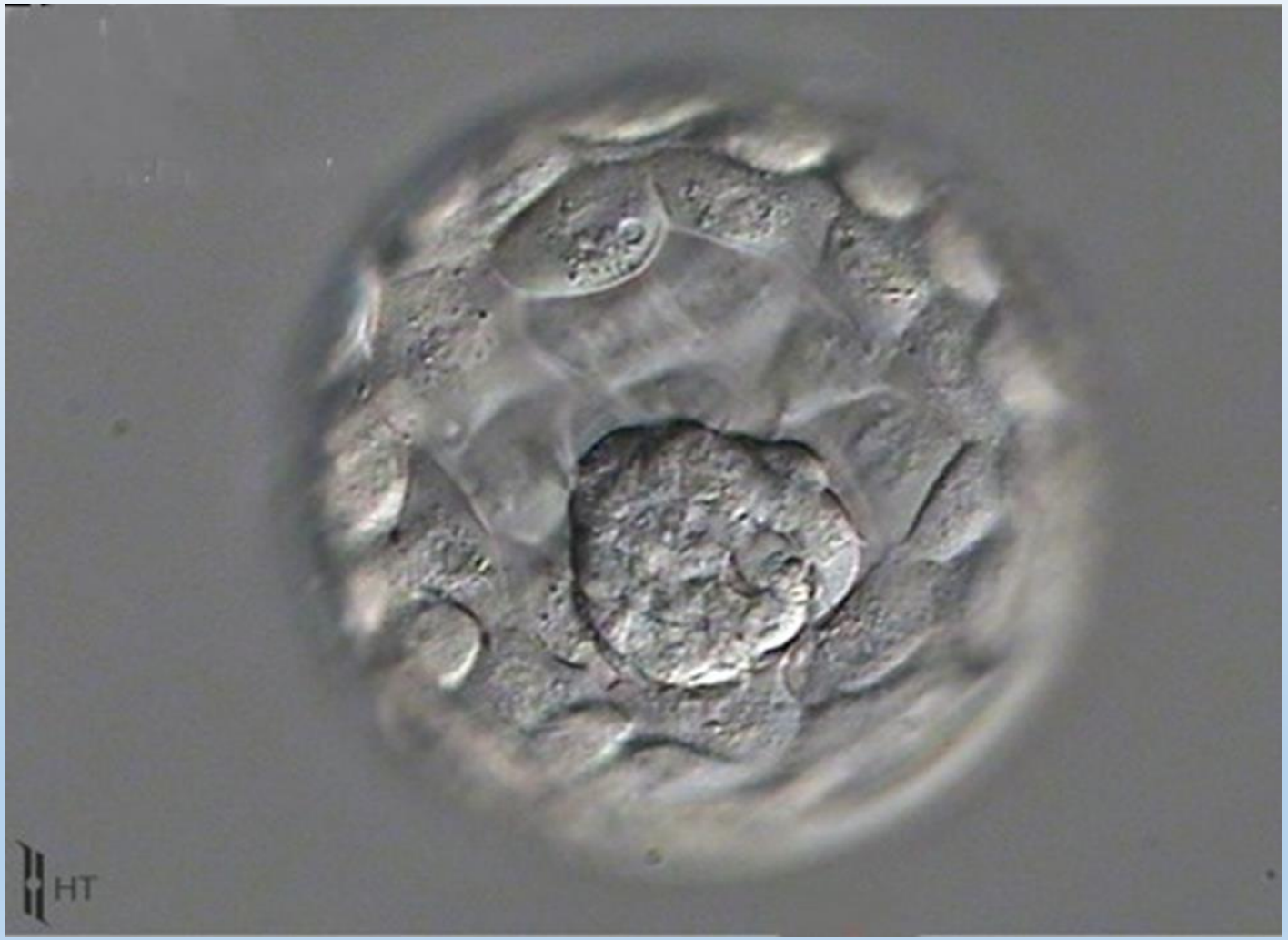
Blastocyst



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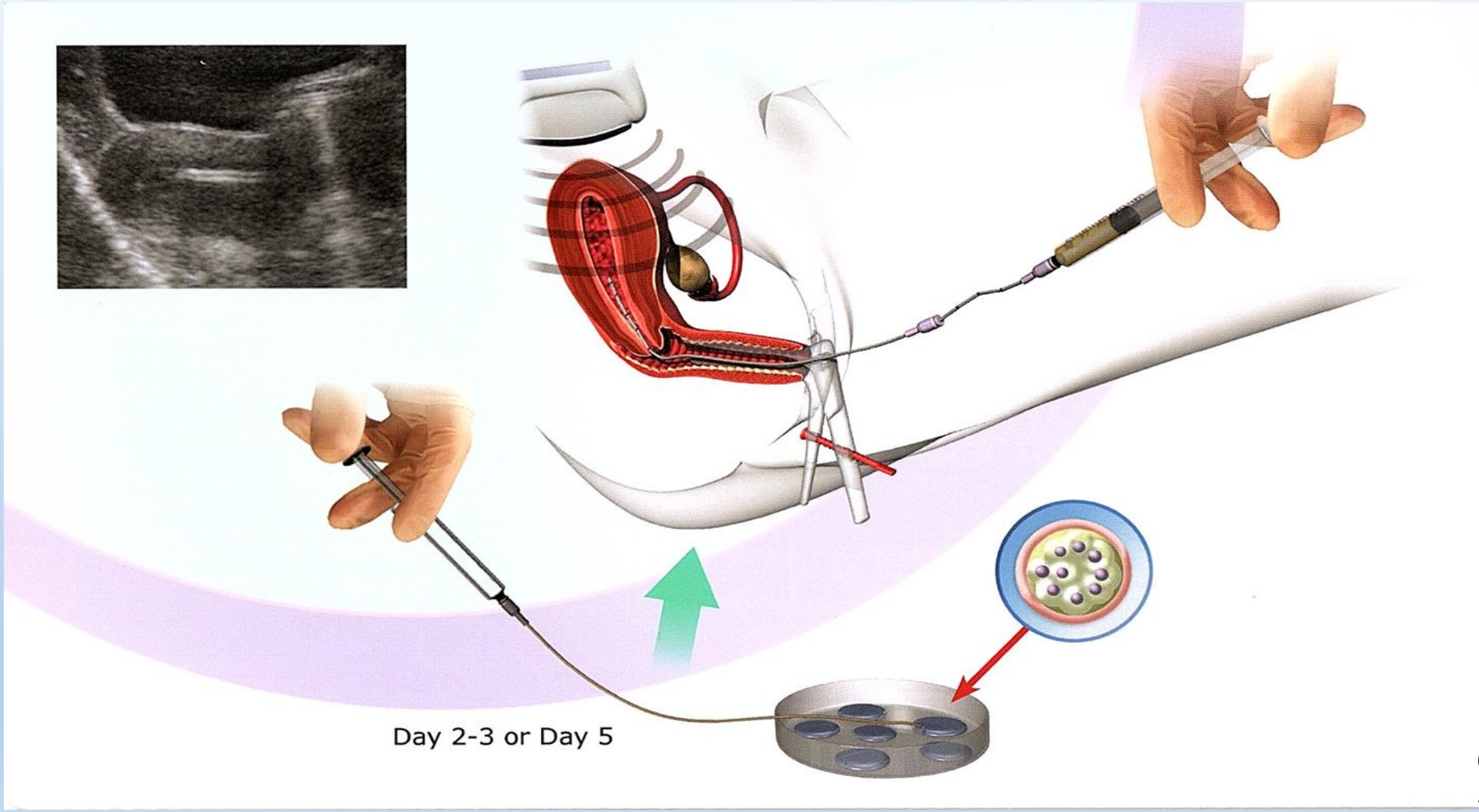
Embryo Transfer



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Fertility preservation for endometriosis

Endometriosis and endometriomas can impact on fertility, and surgery for endometrioma will further decrease ovarian reserve. Oocyte vitrification is therefore a feasible option for women with severe endometriosis wanting to preserve fertility.

More oocytes frozen
Higher oocyte survival
Higher CLBR 70%

Less oocytes frozen
Lower oocyte survival
Lower CLBR 50%

Take home message
Not to perform surgery before FP in asymptomatic patients with endo

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Oocyte vitrification for fertility preservation in women with endometriosis: an observational study. A Cobo et al Fert Ster 2020

Take home messages

- Management of women with endometriosis needs to be individualised
- Approximately ¼ of women with infertility will have endometriosis
- Chances of infertility is increased 2-fold in women with confirmed endometriosis
- Most women with endometriosis will conceive successfully
- Careful consent is required before surgery to remove endometrioma because of its impact on ovarian reserve
- Not all endometriomas should be removed because of the impact on ovarian reserve
- Women should be offered the opportunity to freeze eggs prior to surgery for severe endometriosis/endometriomas

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References

European Society of Human Reproduction and Embryology. Guideline on the management of women with endometriosis. September 2013

Endometriosis fertility index: the new, validated endometriosis staging system. Adamson & Pasta. Fertility and Sterility Oct 2010

Is endometriosis more common and more severe than it was 30 years ago? M Ghiasi et al JMIG Feb 2020

A prospective cohort study of endometriosis and subsequent risk of infertility. J Prescott et al. Hum Reprod July 2016

Oocyte vitrification for fertility preservation in women with endometriosis: an observational study. A Cobo et al. Fertility and Sterility April 2020

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Questions?

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Case study – Mrs EB, 33 yo

- Periods regular on OCP. No pain
- Stopped the OCP and tried to conceive (TTC) for one month
- USS ordered by GP showed left ovary ?adherent to uterus. Endometriosis was mentioned as a possible cause (was not an "Endometriosis ultrasound")
- Went back on OCP awaiting surgery
- Husband has a son from a previous relationship
- What should my advice be?

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Case study – Mrs EB 33yo

- Advised doesn't need to have surgery before trying to conceive
- Advised to stop OCP and try to conceive
- Fertile times of cycle discussed
- See in 6 months if not pregnant

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Mrs EB, 34yo

- Returned in 9 months. No pregnancies
- Periods regular but increasingly painful. Pain with intercourse
- Endometriosis scan shows nodules of endometriosis both uterosacral ligaments and over bladder
- Other investigations normal, AMH normal but below average for age
- Semen analysis normal
- What should my advice be?

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Mrs EB, 34yo

- To proceed to laparoscopy and dye studies
- At laparoscopy endometriosis excised as per USS findings plus endometriosis under both ovaries excised
- Both tubes patent, both ovaries normal
- What should my advice be?

Mrs EB, 34 yo

- Continue to try on own for another 6 months
- Review if not pregnant after 6 months
- Can then discuss the option of IVF treatment versus continuing to try on their own

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