What is the ideal protocol for endometriosis in IVF?

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Clinical recommandations of the french college of Obstetrics and Gynecology

- 2006
- General recommandations on the clinical mamagement of endometriosis

Canadian recommandations (2010)

American recommandations (2012)

Endometriosis and infertility: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Women with endometriosis typically present with pelvic pain, infertility, or an adnexal mass, and may require surgery. Treatment of endometriosis in the setting of infertility raises a number of complex clinical questions that do not have simple answers. This document replaces the 2006 ASRM Practice Committee document of the same name. (Fertil Steril® 2012;98:591–8. ©2012 by American Society for Reproductive Medicine.)

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EHSRE recommandations (2005 revised 2013)

Management of women with endometriosis

Guideline of the European Society of Human Reproduction and Embryology

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ORIGINAL ARTICLE *Gynaecology*

Consensus on current management of endometriosis

Neil P. Johnson[1,2,3,*] and Lone Hummelshoj[1], for the World Endometriosis Society Montpellier Consortium[†]

Strong consensus issues

- Medical therapy of endometriosis is inefficient to restore fertility in endometriosis patients (1,2,3,4,5)
- No hormonotherapy is indicated, before or after endometriosis surgery in order to improve fertility (1,2,3,4,5)
- Stage AFS I and II lesions have to be excised or destroyed (1,2,3,4,5)
- If an endometrioma has to be operated, ablation is preferable to simple drainage (1,2,3,4,5)
- Information on the risk of decrease of the ovarian reserve after endometrioma surgery must be given to the patient (3,4,5)
- In case of failure of sugical treatment of endometriosis aimed at improving fertility, Assisted Procreation should be proposed (1,3,5)
- Insemination can be proposed in endometriosis patients with stage AFS I or II (1,2,3,4,5)
- Ovarian blockage by GnRH analog during 3 to 6 months is recommended before IVF or ICSI)
- Pregnancies in endometriosis patients are more complicated (3,4)

Virtually no place for medical treatment of endometriosis in infertile patients

- The treatment of endometriosis when the patient desires a pregnancy, if a treatment is necessary (symptomatic endometriosis, infertility), is surgical (laparoscopy)
  - Treatment of infertility by suppressive medical therapy is unefficient and should not be offered (SCOG)

- No medical therapy after surgery
  - After surgery, medical treatments are not recommanded (CNGOF grade B)
  - Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to have fertility benefits (Consensus de Montpellier)

Virtually no place for medical treatment of endometriosis in infertile patients

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes, et al., 2007).	**A**
In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking.	**GPP**
In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness, et al., 2004).	**A**

But exceptions !!!!!!!!!!!

- If…. pain++++++++++++++++++++++++
  - In case of association of infertility with persistant pelvic pain after initial surgery, it is recommanded to avoid a repeat surgery. Medical therapy is necessary, in particular in between assisted procreation cycles (CNGOF, AP)

- And if…..IVF
  - GnRHa administered for 3-6 months prior to IVF in women with endometriosis increases the clinical pregnancy rate (Consensus de Montpellier)
  - If a patient in whom endometriosis is documented has to undergo an IVF cycle, suppressive therapy with a GnRH agonist together with a substitutive therapy 3-6 months before ovarian stimulation is associated with an increase in pregnancy rates

Recommendation

Clinicians can prescribe GnRH agonists for a period of 3 to 6 months prior to treatment with assisted reproductive technologies to improve clinical pregnancy rates in infertile women with endometriosis (Sallam, et al., 2006).	**B**

When IVF ?

Recommendations

The GDG recommends the use of assisted reproductive technologies for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed.	GPP
In infertile women with endometriosis, clinicians may offer treatment with assisted reproductive technologies after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI (Benaglia, et al., 2011, Benaglia, et al., 2010, Coccia, et al., 2010, D'Hooghe, et al., 2006).	C
In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of ovarian abscess following follicle aspiration is low (Benaglia, et al., 2008).	D

When IVF ? ASRM

- IVF success rates in women with endometriosis apear to be diminished compared to women with tubal factor infertility. However, IVF maximizes cycle fecundity for those with endometriosis.
- For women with stage III/IV endometriosis who fail to conceive following conservative surgery or because of advancing reproductive age, IVF-ET is an effective alternative

- Meta-analysis 3 studies 165 patients
  - Dicker 1992 : 62 patients with severe endometriosis
    - 6 months GnRHa versus nothing
  - Rickes 2002 : 47 patients stage II - IV, after laparocopic treatment
    - 6 months GnRHa versus long luteal phase agonist protocol
  - Surrey 2002 : 51 patients with endometriosis without endometrioma
    - 3 months GnRHa versus long luteal phase agonist protocol

Sallam et al, Cochrane 2006

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman	1	67	Odds Ratio (M-H, Fixed, 95% CI)	9.19 [1.08, 78.22]
2 Clinical pregnancy rate per woman	3	165	Odds Ratio (M-H, Fixed, 95% CI)	4.28 [2.00, 9.15]
3 Miscarriage rate per clinically pregnant woman	1	14	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.02, 10.25]
4 Miscarriage rate per woman randomised	1	67	Odds Ratio (M-H, Fixed, 95% CI)	4.0 [0.42, 37.84]
5 Dose of FSH or HMG (ampoules)	2	118	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.70, 1.38]
6 Duration of FSH administration (days)	1	51	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.90, 0.98]
7 Number of oocytes per woman	2	150	Mean Difference (IV, Fixed, 95% CI)	2.05 [1.27, 2.84]

Use of oral contraceptives in women with endometriosis before assisted reproduction treatment improves outcomes.
De Ziegler et al. Fertil Steril 2010;94:2796-9

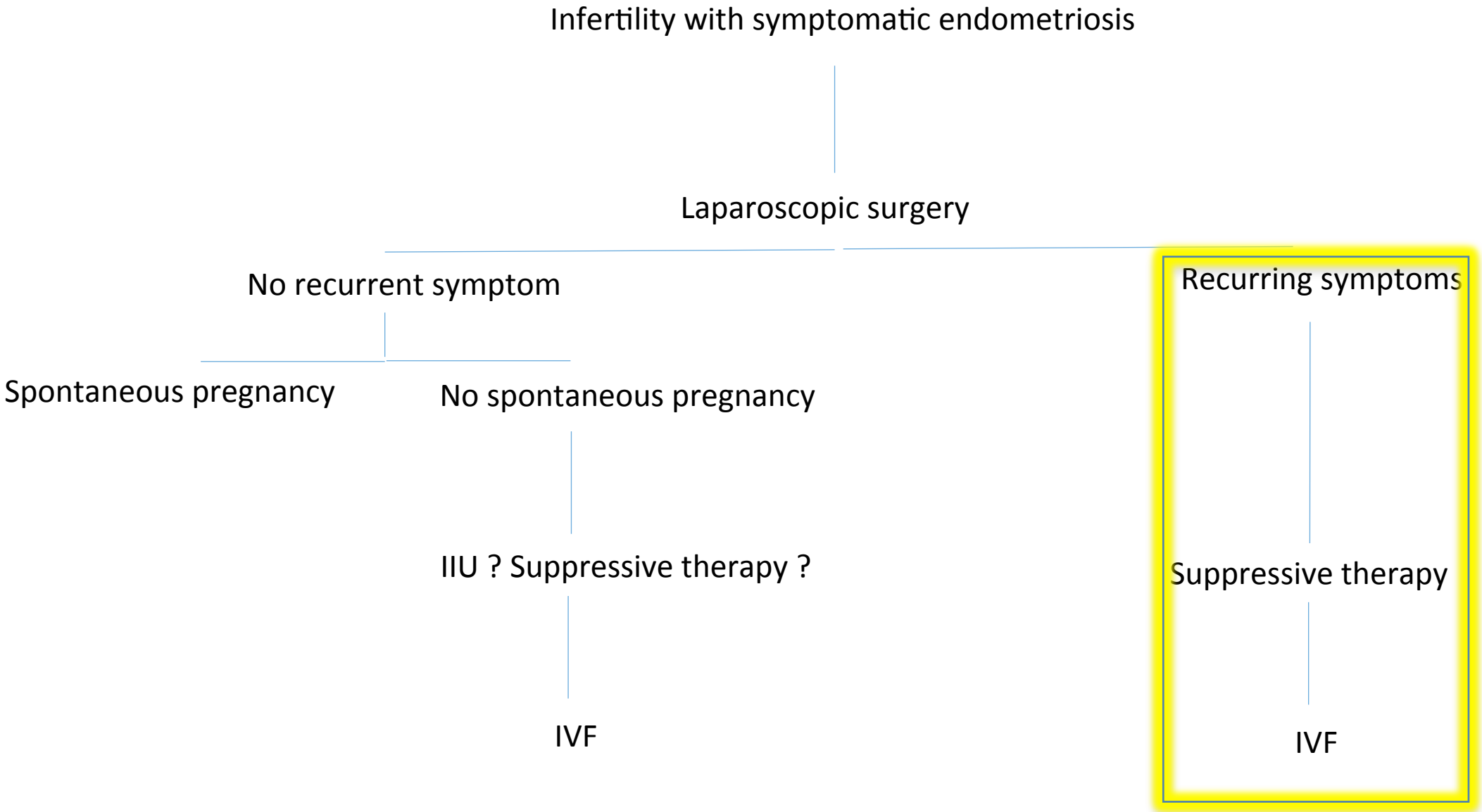
Group 1: œstro-progestatives 6 to 8 weeks

Group 2: no œstro-progestative

	Group 1				Group 2				
		Endometriosis				Endometriosis			
	Controls	I–II	III–IV	OMA	Controls	I–II	III–IV	OMA	*P* value
No. of patients	426	27	58	29	83	89	52	31	
Age	34.7 ± 4.4	35.8 ± 2.7	33.4 ± 3.6	33.4 ± 4.1	35.6 ± 3.9	35.8 ± 3.9	34.9 ± 3.6	35.0 ± 3.6	E: .05 O: .06
Baseline FSH	6.7 ± 2.1	6.1 ± 2.2	6.8 ± 2.0	6.8 ± 2.1	7.8 ± 3.3	7.0± 2.9	9.1 ± 5.6	9.3 ± 6.7	E: .04 O: .66
AMH	3.7 ± 3.5	2.9 ± 1.5	2.9 ± 1.9	3.0 ± 2.0	3.3 ± 2.9	3.0 ± 1.8	2.6 ± 1.7	2.5 ± 1.6	E: 1.00
Clinical PR									E: .47 O: .29
<37 y	42.0	55.0	39.6	40.9	39.7	29.7	23.8	12.0	
>38 y	16.7	28.6	33.3	50.0	18.5	8.0	10.0	16.7	
Total	35.0	48.1	37.9	41.4	32.5[a]	23.6	21.2	12.9[b]	

Unsolved questions

- In patients with asymptomatic endometriosis ?
- In unexplained infertility patients with stage I-II endometriosis ?
- If IIU is to be proposed ?
- For embryo transfer after cryopreservation ?
- In poor responders ?
- In non endometriosis patients ?


Infertility with symptomatic endometriosis
Laparoscopic surgery
No recurrent symptom
Recurring symptoms
Spontaneous pregnancy
No spontaneous pregnancy
IIU ? Suppressive therapy ?
Suppressive therapy
IVF
IVF

Conclusions

- Evidence based-medicine : Ultra-long protocol (with substitutive therapy) is clearly the « best protocol » for IVF in severe endometriosis patients
  - Better pregnancy rates
  - Better life comfort

- Many more studies need to be done in order to
  - Understand why better pregnancy rates
  - If it would be applicable to other patients
  - If it would be applicable to any embryo transfer