



Consensus on current management of endometriosis

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Montpellier 2011 evidence based guideline on the management of endometriosis





Expertos participantes del Consenso:

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Directores / Coordinadores:

Neil Johnson (N.Z.) y Lone Hummelshoj (World Endometriosis Society)

Montpellier 2011 evidence based guideline on the management of endometriosis



Topic

What evidence supports IUI and IVF in the management of endometriosis – related infertility?

Edgardo D. Rolla M.D.

Coordinator – Endometriosis – ALMER

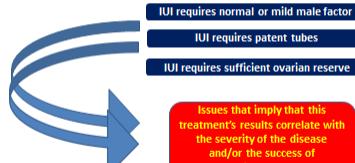
(Asociación Latinoamericana de Medicina Reproductiva)



Topic

The role of IUI in endometriosis associated infertility

To keep in mind:



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Evidence supporting IUI for endo patients

Moderate quality

PRs: Subit, 2011 Am J Rep Inmun → Double IUI improves fertility in Antidiendometrial Antibody(+) endo pts.

Moderate quality

RCCs: Werbrouck, 2006 Fert & Steril → In min/mild endo COH + IUI = effective as in unexpl. infert.

Moderate quality

SysRev: Hughes, 1997 Hum Repr → COH + IUI useful in endo. Endo ↓ ½ PR by COH + IUI
...one key finding of this review is that further studies are urgently needed

PR: Pregnancy rate
RCC: Randomized controlled trial
SysRev: Systematic review

WES 2011 Consensus on Endometriosis

Evidence supporting IUI for endo patients

ESHRE GUIDELINES

Evidence level 1b

High quality

Treatment with intra-uterine insemination (IUI) improves fertility in minimal-mild endometriosis: IUI with ovarian stimulation is effective but the role of unstimulated IUI is uncertain (Tummon et al., 1997).

IUI with or without controlled ovarian hyperstimulation (COH) is associated with a higher pregnancy rate than expectant management (Tummon, 1997). There is no evidence that COH significantly increases the probability of pregnancy compared to IUI alone (RR=1.83 (95% CI: 1.1-22.5) - Nulsen, 1993 - RCT). Systematic review of 31 trials demonstrated superiority of COH + IUI in ovulatory infertility plus endometriosis - Costello 2004 - RCT. Moderate evidence that COH + IUI is better than IUI alone in women with mild-moderate endometriosis (RR=1.31 (95% CI: 1.0-5.6) - Costello 2004 - RCT). Endometriosis reduced by half the effectiveness of IUI in 5214 cycles - Hughes, 1997 - Logistic regression model. Homologous insemination resulted in similar PR as surgically treated endometriosis and unexplained infertility after 6 cycles - Werbrouck, 2006 - Case control study

Significant improvement of PR can be expected with COH/IUI in endometriosis patients despite the negative impact of the disease

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Evidence supporting IUI for endo patients

ASRM Practice Committee - Endometriosis and Infertility

High quality

Treatment of endo patients with COH + IUI is effective

Quick: COH + IUI vs. IUI alone = P^{2.02} = Unadjusted infertile including treated endometriosis - RCT
Full: COH + IUI vs. IUI alone = P<0.001 = Unadjusted infertile including treated endometriosis - RCT
Moderate: COH + IUI vs. IUI alone = P<0.001 = Unadjusted infertile including treated endometriosis - RCT
Table 4
Clomiphene Cb + IUI vs. IUI only better than IUI in subfertile endo patients - Deaton, 1990 - RCT

Treatment of endometriosis in the female partner of an infertile couple raises a number of complex clinical questions that do not have simple answers - 2006

COH: Controlled ovarian hyperstimulation

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Evidence supporting IUI for endo patients

HIGH QUALITY

RCTs: Tummon, 1997 Fert & Steril → Stimulated is effective
...but the role of unstimulated IUI is uncertain

HIGH QUALITY

RCTs: Nulsen, 1993 Obst Gynecol → Stimulated is more effective

HIGH QUALITY

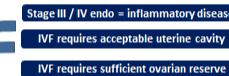
RCTs: Costello, 2004 Au N Z J O Gyn → CC + IUI better
(Syst. Review)
HMG: Human Menopausal Gonadotropin

WES 2011 Consensus on Endometriosis

Topic

The role of IVF in endometriosis associated infertility

To keep in mind:



WES 2011 Consensus on Endometriosis

Evidence supporting IVF for endo patients

ESHRE GUIDELINES

Evidence level 1a

High quality

IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility (Barnhart et al., 2002).

Evidence level 2b

Moderate quality

In vitro fertilization (IVF) is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed

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Evidence supporting IVF for endo patients

ESHRE GUIDELINES

Evidence level 1b

High quality

Treatment with a GnRH agonist for 3-6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However the recommendation is based on only one properly randomized study and called for further research, particularly on the mechanism of action (Sallam et al., 2006).

Evidence level 1b

High quality

Laparoscopic ovarian cystectomy in patients with unilateral endometriomas between 3 and 6 cm in diameter before IVF/ICSI can decrease ovarian response without improving cycle outcome (Demiro et al., 2006).

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Evidence supporting IVF for endo patients

ESHRE GUIDELINES

Evidence level 2a

Moderate quality

Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF (D'Hooghe et al., 2006).

GCP

Very low quality

Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥ 4 cm in diameter is present to confirm the diagnosis histologically, reduce the risk of infection, improve access to follicles and possibly improve ovarian response. The woman should be counselled regarding the risks of reduced ovarian function after surgery and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.

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Evidence supporting IVF for endo patients

ASRM Practice Committee - Endometriosis and Infertility

High quality

IVF better than EMbut no new and large RCTs to confirm
Salman, 1998 Fert & Steril - 3 months GnRH-agonist vs. no GnRH-agonist PR = 17.3% vs. 13.8% P = 0.13

Long term GnRH agonist suppression improves PR in severe endo

Survey, 2002 Fert & Steril - 3 months GnRH-agonist vs. no GnRH-agonist PR = 17.3% vs. 13.8% P = 0.13

But there is no unanimous strategy consensus

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Evidence supporting IVF for endo patients

HIGH QUALITY

RCTs: Bianchi, 2007 Fert & Steril → Deep endo laparosc. surgery does not improve IVF results
....and more ovulatory drugs required for a smaller total # of oocytes

HIGH QUALITY

RCTs syst. review: Benschop, 2010 Cochrane → Ag. better ov. response vs. ant.
....4 studies - 3212 pts. included
....no reference to live births
Agonists vs. antag = PR
Cystec. or drain + coag = EM
Cystec vs. drain + coag = PR
Cystec vs. drain + coag = NM0
EM: expectant management PR: pregnancy rate NM0: number of mature oocytes

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Topics for discussion

P:

Different stages

Women with histologic confirmation and those without histology sampling
Those previously surgically treated, those not previously surgically treated and both

Women with endometriosis

Deep infiltrating endometriosis

Bowel endometriosis

IUI - who to treat, when, why, how to treat - stimulated, unstimulated, and who

IVF - who, when, why, how and treatment limits including how many cycles

Specifically tailored protocols

Any other intervention

versus no intervention

versus other medical treatment

Role of egg donation and surrogacy

Live birth primary outcome

Pregnancy

Egg quality

Endometrial receptivity

Risks, burden and costs

O:

Topics for discussion

References

- Demiro, 2006 - Fert & Steril - 3 months GnRH-agonist vs. no GnRH-agonist PR = 17.3% vs. 13.8% P = 0.13
- Salman, 1998 - Fert & Steril - 3 months GnRH-agonist vs. no GnRH-agonist PR = 17.3% vs. 13.8% P = 0.13
- Bianchi, 2007 - Fert & Steril - Deep endo laparosc. surgery does not improve IVF results
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EM: expectant management PR: pregnancy rate NM0: number of mature oocytes
- WES 2011 Consensus on Endometriosis

Consensus on current management of endometriosis

Neil P. Johnson and Lone Hummelshoj, for the World Endometriosis Society
Montpellier Consortium, World Endometriosis Society, 89 Southgate Road,
London, Human Reproduction, Vol.0, No.0 pp. 1–17, 2013

Surgery for infertility in women with endometriosis

- (46) Laparoscopic surgical removal of endometriosis improves fertility in stage I and II endometriosis (strong). g
- (47) Although RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially where pain is present (weak). g
- (48) Laparoscopic excision (cystectomy) where possible for endometriomas is preferred to laparoscopic ablation (drainage and coagulation) to enhance fertility (strong). a
- (49) The best surgical approach to deep endometriosis in women with infertility is unclear (weak). g
- (50) Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to have fertility benefit (strong). a

Surgery for infertility in women with endometriosis

- La remoción de las lesiones mejora la fertilidad en los estadios I y II (**alta evidencia**)
- Se recomienda la extirpación de las lesiones, en especial cuando hay dolor (**evidencia débil**)
- Para mejorar la fertilidad se prefiere la quistectomía de los endometriomas (**alta evidencia**)
- No está claro cuál es la mejor táctica frente a la endometriosis profunda para mejorar la fertilidad (**evidencia débil**)
- La terapia médica postlaparoscópica no ha demostrado beneficiar la fertilidad (**alta evidencia**)

Assisted conception for infertility in women with endometriosis

- (51) There is no evidence to support the use of controlled OS alone and insufficient evidence to recommend one agent over another (weak). g
- (52) Intrauterine insemination (IUI) with controlled OS (COS) is effective in improving fertility in minimal and mild endometriosis, but the role of unstimulated IUI is uncertain (strong). g
- (53) Double insemination should be considered for intrauterine insemination (IUI) (weak).
- (54) Although IVF may be less effective for endometriosis than for other causes of infertility, it should be considered for use to improve the success rate above expectant management (strong).

Assisted conception for infertility in women with endometriosis

- No hay evidencia que respalde la simple estimulación ovárica (*evidencia débil*)
- La IIU bajo estímulo ovárico es útil para mejorar la fertilidad en los estadíos mínimos y leves, pero el rol de la misma sin estímulo es incierto (*evidencia fuerte*)
- La IIU doble (en el mismo ciclo) podría ser considerada (*evidencia débil*)
- A pesar de que la FIV puede ser menos efectiva en la endometriosis vs otras causas de infertilidad, se indica para llevar las tasas de embarazo por encima de las del manejo expectante (*evidencia fuerte*)

Adjuncts to assisted conception for infertility in women with endometriosis

- (55) There is insufficient evidence of benefit of gonadotrophin-releasing hormone (GnRH-a) treatment before intrauterine insemination (IUI) (weak). a
- (56) There is insufficient evidence of benefit of laparoscopic surgery prior to IUI/COS (weak). g
- (57) GnRH analogue administered for 3–6 months prior to IVF/ICSI in women with endometriosis increases the clinical pregnancy rate (strong). g
- (58) There is insufficient evidence to support the use of the combined OCP prior to IVF/ICSI (weak). g
- (59) There are no data to compare the approach of pretreatment with the combined OCP versus gonadotrophin-releasing hormone agonists (GnRH-a) (weak). g
- (60) There is no evidence that surgical removal of endometriosis or surgical treatment of endometriomas (by aspiration or cystectomy) improves success rates through IVF (weak). g
- (61) Ovarian response might be reduced in some women who have undergone surgery for endometriomas (weak). a
- (62) Since endometriomas may damage the ovary, and since complications can arise in women with endometriomas undergoing ART, laparoscopic ovarian cystectomy may sometimes be recommended for women with endometriomas larger than 3 cm diameter (weak). a

Adjuncts to assisted conception for infertility in women with endometriosis

- Hay evidencia insuficiente acerca de la utilidad de los análogos de GnRH antes de la IIU (**evidencia débil**)
- Hay evidencia insuficiente acerca del beneficio de la laparoscopía antes de la IIU (**evidencia débil**)
- El uso de análogos de GnRH por 3 a 6 meses antes de la FIV/ICSI aumenta las tasas de embarazo (**alta evidencia**)
- Hay evidencia insuficiente acerca del uso de ACOs antes de la FIV/ICSI (**evidencia débil**)
- No hay datos comparando el pre-tratamiento con ACOs vs análogos de GnRH (**evidencia débil**)

Adjuncts to assisted conception for infertility in women with endometriosis

- No hay evidencia de que el tratamiento de los endometriomas (quistectomía o punción/drenaje) mejore los resultados de la FIV (*evidencia débil*)
- La respuesta ovárica puede estar afectada en algunas mujeres que han sido operadas por endometriomas (*evidencia débil*)
- Debido a que los endometriomas pueden dañar el ovario y porque pueden existir complicaciones en las mujeres que reciben tratamientos de RA, en algunos casos se puede recomendar la quistectomía de los endometriomas cuando los mismos tienen un Ø mayor a los 3 cm (*evidencia débil*)

Medical therapy for infertility in women with endometriosis

- No hay evidencia de que el tratamiento médico beneficie la fertilidad – la supresión de la ovulación puede retrasar el logro del embarazo y por lo tanto no se recomienda (**alta evidencia**)

Emerging therapies for infertility in women with endometriosis

- (64) Lipiodol hysterosalpingogram improves live birth rates in women with endometriosis, but otherwise unexplained infertility, who are attempting natural conception (weak). g
- (65) There is no evidence of fertility benefit from pentoxifylline for women with mild-to-moderate endometriosis (strong). a
- (66) There is no evidence of fertility benefit of TCM over gestrinone or Danazol (weak). g
- (67) There is insufficient evidence of increased pregnancy rates from the use of vitamins (weak). a
- (68) There is insufficient reliable evidence of improved fertility with mifepristone (weak). a
- (69) There is no evidence of impact of rosiglitazone on fertility (weak).

Emerging therapies for infertility in women with endometriosis

- La HSG con LIPIODOL mejora las tasas de embarazo en mujeres con endometriosis como única causa de infertilidad, cuando intentan embarazar naturalmente (*evidencia débil*)
- No hay evidencia de que la PENTOXIFILINA mejore la fertilidad de aquellas mujeres con endometriosis leve a moderada (*alta evidencia*)
- La medicina tradicional china no beneficia la fertilidad por sobre la gestrinona o el danazol (*evidencia débil*)
- Hay evidencia insuficiente acerca de la mejoría en las tasas de embarazo utilizando vitaminas (*evidencia débil*)
- Hay evidencia confiable insuficiente acerca de la mejoría que la MIFEPRISTONA puede tener sobre la fertilidad (*evidencia débil*)
- No hay evidencia del impacto de la ROSIGLITAZONA en la fertilidad (*evidencia débil*)



comencemos ahora la
discusión