Clinical guidelines

The Nordic clinical guidelines are an aid to doctors treating infertility. They should be viewed as the best recommendations available at the time of writing for principles relating to the examination and treatment of infertile couples. The examinations and treatments discussed should be seen as suggestions from among several alternatives, and not as the only options that can be used.

Each clinical situation, including the condition of the patient and other information, must be assessed individually by the doctor, who should then act based on his or her experience, knowledge, and evaluation. Medical science is constantly developing. New examination and treatment options may therefore arise. Some of these may be internationally recognised, but not yet assessed in relation to the existing guidelines.

Please also refer to guideline number 1: Introduction to clinical guidelines.

10. Endometriosis and infertility

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Reviewer: Ulla Breth Knudsen.

1. Recommendations regarding minimal/mild endometriosis-associated infertility

It is recommended that infertile women with minimal/mild endometriosis confirmed through laparoscopy have as much of the endometriosis as possible resected.	**A**
It is recommended that women after an operation for endometriosis should be referred for intrauterine insemination (IUI) and controlled ovarian stimulation (COS), under the condition that their tubes are normal.	**A**
Younger women may wait for spontaneous conception for e.g. a period of three to six months, but the woman/couple should be informed that there is a higher probability of pregnancy through IUI + COS compared to simply waiting or IUI without ovarian stimulation.	**B**

2. Recommendations regarding moderate/severe endometriosis-associated infertility

Most patients should be referred directly to IVF unless the woman suffer from severe pain, and therefore need an operation.	**D**
Infertile women with moderate to severe endometriosis confirmed by operation should be referred to IVF treatment instead of IUI.	**C**
Young patients with moderate to severe endometriosis may be referred to primary operative treatment, as this may improve the probability of subsequent spontaneous pregnancy, especially for the subgroup of patients with tubal cofactor. If operated on and the couple wants to await spontaneous pregnancy, they should be informed to ask for infertility treatment after 6 month if not pregnant.	**C**
Infertility does not motivate high risk surgery for endometriosis.	**D**
Where endometriosis is found by chance in an infertile woman through laparoscopy, resection of the endometriosis is recommended as far as possible (debulking), while attempting to preserve ovarian tissue. In the case of endometriomas, however, the guidelines below should be followed.	**C**
If there are signs of recurrence following a previous operation, the patient should be referred to IVF rather than new surgical treatment, except where there are additional symptoms which indicate operation.	**B**

Recommendations regarding resection of endometriomas

Women with endometriosis seem to reach menopause earlier than their chronocological age suggest. This may even be aggravated by operations on the ovary, some resulting in POF. The women must be informed of this.	**B**
Surgical removal of endometriomas prior to IVF treatment is only recommended where these are causing pain, or it is believed that resection will make access to the follicles significantly easier.	**C**
The patient should be informed that resection of endometriomas can result in a lower oocyte harvest during subsequent IVF treatment.	**C**
Laparoscopy is recommended in stead of laparotomy for resection of endometriomas, as far as technically possible. Difficult cases should be treated in tertiary referral centers. It is recommended that a *biopsy* always be taken to get a final diagnosis.	**B**

Excision is recommended over ablation for the resection of endometriomas, as far as possible. *Excision* of endometriomas involves opening the cyst, either with or without the use of electrosurgery or a laser. The cyst wall is then excised or 'stripped away' from the ovarian cortex using a combination of scissors (or monopolar hook) and grasping forceps. *Ablation* of endometriomas involves opening and draining or fenestration, followed by the destruction of the cyst wall using either cutting or coagulating current, or a laser.	**A**

3. Recommendations for treatment of endometriosis-associated infertility using medication

Classic, isolated treatment of endometriosis using medication such as OC pills, gestagen or GnRH agonists cannot be recommended as a fertility promoting treatment, and pre or postoperative use of these preparations has not been found to increase the conception rate. However, OC pills can be used to time the commencement of assisted reproduction treatment (primarily in the case of oligomenorrhoea and amenorrhoea), and GnRH agonists may naturally be used in relation to assisted reproduction as discussed below.	**A**

4. Recommendations regarding IVF treatment for cases of endometriosis-associated infertility

Recommendations regarding suppression

Prolonged suppression using GnRH agonist for 3-6 months appears to lead to more oocytes being retrieved, a greater ongoing pregnancy rate and a lower risk of miscarriage compared to normal long and short protocols. However, since six months of suppression is a long time, with many potential side effects, prolonged suppression cannot currently be recommended as routine. Instead suppression for three months and then stimulation treatment could be initiated two weeks after the final Zoladex injection, so that the down-regulation is still in place, and thereby shortening the process.	**A**
The standard long protocol should be followed as a minimum	**C**

During prolonged suppression, patients may also be treated with “add back” in the form of gestagen dominated low-dose oestrogen combinations for women with pronounced side-effects. However, we do not know anything about possible effects on the probability of pregnancy during subsequent IVF treatment. If the endometrium grow during the add back this must be shed prior to stimulation	✓

Recommendations regarding presence of endometriomas

Aspiration of endometriomas in connection with egg retrieval is not recommended, but if aspiration takes place accidentally or to increase access to the follicles, antibiotic prophylaxis should be administrated.	D

Recommendations regarding egg donation

Infertile women with severe endometriosis who are unable to use their own eggs may be suitable for egg donation, as they are ideally suited as recipients. The NFS underlines though, that the procedures is presently illegal in some Nordic country.	C
Women with endometriosis should not be used as egg donors.	C

Definitions

The revised classification recommended by the American Society for Reproductive Medicine (ASRM) is used. Fert Steril 1997;67(5):817-21 [1].

Minimal to mild endometriosis (rAFS I-II).
Moderate to severe endometriosis (rAFS III-IV).
Endometriomas: ovarian endometriosis cysts.

Scope

This guideline contains methods for the treatment of infertile women with endometriosis in connection with fertility treatment:

- Methods for the surgical treatment of endometriosis
- Methods for the surgical treatment of endometriomas
- Recommendations in connection with IVF treatment for endometriosis patients
- Recommendations in connection with egg donation from and to endometriosis patients.

This guideline does not cover:
Sub-classification of endometriosis
Investigation of endometriosis
Treatment of endometriosis/endometriomas in women who are not seeking treatment for infertility.

Background

Endometriosis is an estrogen-dependant chronic inflammatory disorder characterized by implantation and growth of endometrial tissue outside the uterine cavity. It is associated with chronic pelvic pain, dysmenorrhoea, dyspareunia and infertility. It is considered one of the most common gynecological conditions. The prevalence estimates of endometriosis varies from approximately 4% to 18% in largely asymptomatic women undergoing tubal ligation to 50% of teenagers with severe dysmenorrhoea ***(Cramer and Missmer, 2002; Moen, 1987)*** [2-3]. In Norway an estimate of the prevalence of endometriosis in the general population was approximately 2% **(Moen and Schei, 1997)** [4]. In women with infertility, the prevalence is variable, depending on selective use of laparoscopy in infertility investigation and on the bias of variable patient recruitment. Studies show that endometriosis can be found in 30% to 71% of infertile women ***(D'Hooghe, Debrock et al., 2003)*** [5].
The endometriosis tissue exhibits two basic pathologic processes, growth and inflammation, that are responsible for chronic pelvic pain and infertility. Estrogen enhances the growth and invasion of endometriotic tissue, prostaglandins (PGs) and cytokines mediate pain, inflammation and infertility ***(Attar and Bulun, 2006)*** [6]. Contrary to a normal eutopic endometrial cell from women without endometriosis, all the proteins and enzymes required for de novo synthesis of estrogens have been identified in endometriotic stromal cells ***(Noble, Simpson et al., 1996;Tsai, Wu et al., 2001*)** [7-8].
The role of the immune system in endometriosis has been studied extensively, and numerous immune abnormalities have been found. It is, however, not been solved whether immune abnormalities are the cause or result of endometriosis. There are evidence though, suggesting that women with endometriosis have an altered response to progesterone, being essential for endometrial receptivity ***(Young and Lessey, 2010)*** [9].

The effects of endometriosis on fertility and the underlying mechanisms are unclear, but there is general agreement that endometriosis reduces fertility. The presence of endometriosis can theoretically affect fertility in several ways:

* Mechanically:
    - The formation of intra/peritubal and periovarian adhesions.
    - Endometriomas which are so large that the surrounding ovarian tissue has ceased to function.
    - The surgical removal of endometriomas, leading either to oophorectomy or such reduced ovary volume that the number of follicles is reduced compared to the preoperative state.

* Immunological, inflammatory, and endocrinological factors:
    - Reduced ovarian function
    - Luteinized unruptured follicle syndrome (LUF)
    - Impaired fertilization
    - Abnormal tubal milieu and gamete and enbryo transport
    - Defective endometrial receptivity during implantation

Literature review

Prepared based on the DSOG, RCOG and ESHRE guidelines and literature searches in PubMed, the Cochrane library, and the references from the above guidelines.

1. Recommendations regarding minimal/mild endometriosis-associated infertility

Resection versus observation

Marcoux et al. 1997 [10] carried out a multicentre RCT involving 341 infertile women who were found to have minimal/mild endometriosis in connection with a diagnostic laparoscopy. In half of the subjects, as much endometriosis as possible was destroyed or resected, and adhesions were removed. The other half of subjects received no treatment. The spontaneous outcome was then observed for 36 weeks (approximately 9 months). The group which received treatment had a cumulative pregnancy rate of 37.5%, and an ongoing rate of 31%, compared to 22.5% and 18% respectively in the untreated group (cumulative incidence ratio 1.7; 95 % CI 1.2-2.5 (evidence level 1b)). Monthly fecundity was calculated to be 4.7% in the group which received surgical treatment versus 2.4% in the group which only received diagnostic laparoscopy.

Gruppo Italiano (Parazzini *et al.,* 1999) [11] carried out an Italian multicentre RCT involving 51 women who underwent endometriosis resection/ablation, and 45 women who only received diagnostic laparoscopy. They were observed for one year. The cumulative PR was 24% in the first group and 29% in the second group, and the cumulative birth rate was 19.6% and 22.2% (n.s.) respectively. They conclude that their study does *not* support the hypothesis that ablation of endometriosis elements improves fertility.

Jacobson et al., 2010 [12] carried out a systematic Cochrane analysis of the two studies above (Marcoux and Parazzini) and found a significantly higher fecundity rate in the group which underwent surgical treatment compared to the untreated group, OR 1.64; 95 % CI 1.05-2.57 (evidence level 1a). The authors believe that the different results from the two works are partly due to the fact that the Italian study was smaller and had broader inclusion criteria. This meta-analysis supports the view that treating minimal to mild endometriosis is indicated.

Based on the above studies it is estimated that infertile women who undergo surgical resection/ablation for minimal to mild endometriosis achieve an annual cumulative spontaneous birth rate of approximately 20 to 40%.

This is supported by a more recent prospective uncontrolled study in which ***Nardo*** et al., 2006 [13] (n=43) found a cumulative ongoing PR of 23.2% during the first year among infertile women who had undergone laparoscopic treatment using a special device for minimal to mild endometriosis (evidence level 2a).

Infertile women with minimal to mild endometriosis diagnosed using laparoscopy who did NOT have their endometriosis removed were reported by ***Berube*** et al., 1998, [14] to have an annual ongoing pregnancy rate of 18.2% (evidence level 2a).

IUI and COS for cases of minimal/mild endometriosis-associated infertility

Three RCTs together show that the pregnancy rate following COS + IUI is significantly higher than after simply waiting, IUI alone or COS alone.
In an RCT involving a total of 311 cycles among 103 women with surgically treated and untreated mild endometriosis confirmed by laparoscopy as the only infertility factor, ***Tummon IS*** et al., 1997, [15] found that the birth rate was 11% per cycle following hMG + IUI, compared to 2% per cycle under observation, OR 5.6; 95 % CI 1.8-17.4 (evidence level 1b).

In an RCT (n=57), ***Nulsen JC*** et al., 1993, [16] compared hMG + IUI with IUI and found a significant increase in PR following hMG + IUI (19 % vs. 0 %) (evidence level 1b).

Werbrouck E et al Fert Steril,86,566-571, 2006 [17]. The data from this Leuven study suggest that when minimal and mild endometrios endometriosis is surgically removed prior to COS / IUI the results are at the same level as in patients with unexplained infertility versus earlier studies from ***Omland AK*** et al 1998 [18] and ***Nuojua-Huttunen S*** et al 1999 [19].

IVF and ICSI for cases of minimal/mild endometriosis

Opoien HK et al. RBMOnline 2011[20]. This study shows that women with ASRM Stage I and II endometriosis undergoing IVF / ICSI have significantly shorter time to pregnancy and higher live birth rate if all visual endometriosis is completely eliminated at the time of diagnostic surgery.

Conclusion

Infertile women with minimal or mild endometriosis should undergo resection or destruction of their endometriosis in connection with laparoscopy. Referral to COS+IUI is then recommended.

The attempt may be made to achieve spontaneous pregnancy for 3-6 months where there is normal tubal patency, depending on the woman's age and any other fertility reducing factors. The number of IUI treatments should also depend on these factors. Please also refer to guideline number 11 on IUI-H.

Presumably no more than three IUI treatments should be carried out before IVF is offered, see ***Werbrouck*** et al 2006 [17] and ***Dmowski et al.***, 2002, [21] below.

2. Recommendations regarding moderate/severe endometriosis-associated infertility

Surgical treatment for moderate to severe endometriosis

No RCTs were found which investigate the effects of surgery on the spontaneous conception rate for cases of moderate to severe endometriosis. The spontaneous conception rate among infertile women with moderate to severe endometriosis is reported as low, approaching zero, when these women are observed during operation (***Adamson GD*** et al., 1997 [22]; ***Olive DL*** et al., 1985 [23]). Several retrospective reviews report a somewhat higher conception rate following surgery.

Vercellini P et al, 2006 [24] calculated the cumulative pregnancy rate to be 47% after 36 months (n = 537) among infertile women who had undergone their first conservative surgical (laparoscopic) procedure. No significant difference in the pregnancy rate was found between the various degrees of endometriosis (51% grade I, 49% grade II, 46% grade III, 44% grade IV; log rank test, $X^2_3 = 1.5$, P = 0.68). Among the 222 women/couples for whom there were no other fertility reducing factors apart from endometriosis, a cumulative pregnancy rate after three years observation time of 51% was found (55 % grade I, 49 % grade II, 48 % grade III, 50 % grade IV; log rank test, $X^2_3 = 1.75$, P = 0.62). None of the women received IVF treatment during the observation period, but it is not clear from the article whether some of the women were treated using COS and/or IUI during the observation period (evidence level 3).

In a retrospective analysis of the spontaneous pregnancy rate among 237 women who underwent an operation for pelvic endometriosis, with or without endometriomas, ***Fujishita A*** et al., 2002 [25] found that only tubal factors were predictive for the cumulative pregnancy rate. The observation time was 3-118 months, with an average of 26 months, and the following cumulative pregnancy

rates were reported: 51 % (47/93) in stage I, 49 % (17/35) in stage II, 53 % (28/38) in stage III and 35 % (13/37) in stage IV.

IVF versus observation

Kodama et al., 1996 [26] carried out a retrospective study of IVF treatment versus observation following diagnosis of endometriosis through laparoscopy: 60 patients received IVF treatment within six months of their operation, and 58 patients were simply observed during the same period. The cumulative pregnancy rate 36 months postoperative was 62% in the IVF group compared to 43% in the control group (not significant). When age was taken into account, a significantly higher cumulative pregnancy rate was found following IVF treatment among patients over 32 years of age (52 % versus 29 %). A relatively large difference in the pregnancy rate was also found between the two groups among patients with grade III and IV endometriosis (52% following IVF versus 27% after observation). However, this difference was not significant.

IVF versus IUI treatment

In a retrospective work, ***Dmowski*** et al., 2002 [21] calculated the cumulative cycle-specific fecundity rate following IVF and IUI treatment. The cumulative rate following 1-3 IVF treatments was significantly higher (73%) than following six IUI cycles (41%). Patients were evenly distributed with respect to the degree of endometriosis, apart from grade IV, where significantly more patients primarily received IVF treatment. A total of 648 IUI cycles were involved, and 139 IVF cycles, along with 98 IVF cycles among women who had not become pregnant following IUI. The sub-classification had significance for the results of IUI, such that the pregnancy rate was 10% in the first IUI cycle among women with grade IV endometriosis, and 0% hereafter. The results of IVF treatment were comparable for grade II, III and IV.

Reoperation versus direct IVF treatment

In a retrospective study, ***Pagidas*** et al., 1996 [27] compared women with grade III and IV endometriosis in order to calculate the cumulative pregnancy rate following reoperation for endometriosis (n=18) and direct IVF treatment without reoperation (n=23). The cumulative pregnancy rate following reoperation after 3, 7 and 9 months was 5%, 18% and 24%, respectively, while the rate following one IVF treatment was 33%, and 70% following two treatments. These figures were comparable with the results following IVF treatment among women with infertility due to tubal factors.

Conclusion

It has not been possible to find definitive evidence to show that surgical excision of the moderate/severe endometriosis group increases the postoperative spontaneous pregnancy rate, and it is not possible to conclude that operation of moderate/severe endometriosis increases the chance of pregnancy following IVF treatment.
IVF offers a higher probability of pregnancy than observation, and infertile women with moderate to severe endometriosis confirmed by operation should be referred to IVF treatment instead of IUI;

If there are signs of recurrence following a previous operation, the patient should also be referred to IVF rather than new surgical treatment, except where there are symptoms which indicate surgery.

Resection of endometriomas prior to IVF treatment

New literature suggest that women with endometriosis reached menopause earlier than other (around 6 years earlier), especially with operations for bilateral endometriomas (***Cocccio ME*** et al,

2011 [28]; ***Yasui*** et al, 2011[29]; ***Pokoradi*** et al, 2011 [30]) Primary Ovarian Failure (POF) were found in 16.3% of women operated for endometriosis (***Coccio ME*** et al, 2011 [28]). This should be taken in to account for when to start infertility treatment and in the discussion with the woman on her probability of a successful treatment.

Tsoumpou et al. 2008 [31]. This meta-analysis compared surgery vs. no treatment of endometrioma and found no significant difference in clinical pregnancy rate between the treated and the untreated groups.

Hirokawa W et al. 2011 [32]. The rate of decline in the serum AMH levels showed a significant correlation to the revised American Society for Reproductive Medicine (rASRM) score (P = 0.003), but not age, cyst diameter, blood loss during the operation or the number of follicles removed.

Demirol et al., 2006 [33] conducted an RCT in which women with unilateral endometrioma(s) who had not previously undergone an ovarian operation were randomly assigned to conservative ovarian surgery (cystectomy) three months prior to ICSI treatment, or directly to ICSI treatment. No difference was found in the fertilisation rate (86 % vs. 88 %), implantation rate (16.5 % vs. 18.5 %), or ongoing pregnancy rate (34 % vs. 38 %) in connection with IVF/ICSI treatment, between the two groups. The number of days of stimulation and the total rFSH dose was significantly greater, whereas the number of aspirated oocytes was significantly lower, in the group which underwent surgery (evidence level 1a). (Unfortunately the article does not report whether any endometriosis outside the ovaries was removed during surgery, so it is not possible to draw general conclusions regarding whether complete surgery in cases of moderate to severe endometriosis might improve the chance of pregnancy in subsequent IVF/ICSI).

Garcia-Velasco *et al*., 2004 [34] carried out a retrospective matched case-control study involving 189 women with endometriomas. The women had never previously undergone an ovarian operation. 56 women received direct IVF treatment, while 133 underwent endometrioma resection first. The operative method is described as excision of the cyst, including electrocoagulation where necessary if it was not possible to completely remove the cyst wall – precisely as recommended. GnRH agonist treatment was not given postoperatively. However, all were treated according to the long protocol during IVF treatment. During subsequent IVF/ICSI treatment, lower serum oestradiol and higher total FSH dosage was found on hCG day among the patients who underwent operation. There were no significant differences in the number of aspirated oocytes or high quality embryos, the fertilisation or implantation rates, or the ongoing pregnancy rate. The size and number of endometriomas was not reported (evidence level 2a).

Tinkanen & Kujansuu, 2000 [35], retrospective case-control study: 45 patients had minor endometriomas during IVF treatment, 36 of these involved recurrence following previous operation. 55 patients had previously undergone an operation to remove endometriomas without recurrence. No negative impact on the IVF outcome was found among patients who had confirmed ovarian endometriomas (on the contrary, there were more embryos and a higher pregnancy rate among the women with endometriomas) (evidence level 2a).

Ragni et al., 2005 [36]: prospective study of 38 women who underwent endometriosis cyst resection within one ovary, and then received IVF treatment. The responses from the two ovaries in the same patient were compared. 60% fewer follicles, 53% fewer oocytes, 55% fewer embryos and 52% fewer embryos of high quality were found in the operated ovary. There was no significant difference in the fertilisation rate (evidence level 2a).

Aspiration of endometriomas prior to IVF treatment

Pabuccu et al., *2004* [37] carried out a prospective study of 125 patients with endometriomas, and 46 with tubal factor infertility. Group 1 consisted of 41 patients who had not undergone a previous

operation and who underwent endometrioma aspiration at the commencement of stimulation treatment. Group 2 was made up of 40 women who did not have their endometriomas aspirated. Group 3 consisted of 44 women who had all undergone endometrioma resection and had no visible endometriomas in connection with COH. Group 4 represented the control group of women with tubal factors. All patients underwent IVF (with ICSI). No differences in the implantation or clinical pregnancy rates were found between any of the groups. There were fewer mature follicles and fewer metaphase II oocytes among patients who had undergone endometrioma resection or had not had their endometriomas aspirated, compared to the tubal factor group.
All women with endometriomas had fewer metaphase II oocytes compared to the tubal factor group (evidence level 2a).

Laparoscopy versus laparotomy

In a small RCT, ***Mais et al.,*** 1996 [38] found that there was less postoperative pain, lower consumption of analgesics, shorter hospital stays, and a shorter reconvalescence time among women who underwent laparoscopic myomectomy, as opposed to laparotomy. However, no studies are available which compare laparoscopic and laparotomic endometrioma removal so, so the recommendation of laparoscopic surgery has been extrapolated from the above (evidence A therefore becomes B/C).

Excision versus ablation of endometriomas

Hart, *2006* [39]: The effects of ablation versus excision of endometriosis cysts on the risk of recurrence, recurrence of pain, and on subsequent fertility, were investigated in a Cochrane review. Two RCTs were found, both dealing with laparoscopic surgery, which compared excision versus ablation of endometriomas (***Beretta*** 1998 [40]; ***Alborzi*** 2004 [41]). Both studies found a greater incidence of recurrence of abdominal pain, greater recurrence of endometriomas, fewer spontaneous pregnancies, and a greater need for later reoperation among patients who had undergone ablation as opposed to excision of the cysts (observation time 1-2 years). Subsequent ovarian function and the outcomes of any fertility treatment were not investigated.

Conclusion

There is no evidence that the removal of endometriomas prior to IVF treatment increases the implantation or ongoing pregnancy rates.
Women who are experiencing pain and/or have growing endometriomas may be recommended for operation.
If an operation is chosen, it appears to be well supported that endometrioma should be excised, including the entire cyst wall, as opposed to opening and drainage, and that the operation should be performed laparoscopically to reduce the risk of endometriosis cysts recurring, reduce the risk of pain recurring, and increase the chance of subsequent spontaneous pregnancy.

3. Recommendations for treatment of endometriosis-associated infertility using medication

Medication as a fertility promoting treatment

Hughes E et al., 2003 [42] carried out a Cochrane analysis investigating the significance of ovulation suppression using medication for subsequent pregnancy. Six RCTs were analysed involving a total of seven different treatments comparing ovulation suppressing medication with placebo or no treatment. The study found an odds ratio for pregnancy following ovulation suppression versus placebo or no treatment of 0.74 (95 % CI 0.48-1.15). These results were independent of which suppression medication was used. There was therefore no significant advantage from this form of treatment. Danazol® was most frequently used. A comparison of the

results following GnRH agonist treatment and Danazol® gave the same result: no significant difference. Side-effects were not taken into account (evidence level 1a).

In another Cochrane review, ***Yap C*** et al., 2004 [43] came to the same conclusion. No difference was found in subsequent pregnancy rates among patients who received preoperative or postoperative hormonal suppression. Postoperative suppression, compared to surgical treatment alone, had no influence on the pregnancy rate, but significantly reduced the rate of recurrence (evidence level 1a).

Conclusion

Classic, isolated treatment of endometriosis using medication such as POP pills, gestagen or GnRH agonists cannot be recommended as a fertility promoting treatment, and pre or postoperative use of these preparations has not been found to increase the spontaneous conception rate.
However, POP pills can be used to time the commencement of assisted reproduction treatment (primarily in the case of oligomenorrhoea and amenorrhoea), and GnRH agonists may naturally be used in relation to assisted reproduction as discussed below.

4. Recommendations regarding IVF treatment for cases of endometriosis-associated infertility

The effect of the presence of endometriosis on IVF results

Barnhart et al., 2002 [44] carried out a meta-analysis based on 22 works involving 2377 IVF cycles among women with endometriosis, and 4383 cycles among women without endometriosis. They found that significantly fewer oocytes were harvested among endometriosis patients, and the more severe the endometriosis, the fewer oocytes were aspirated.
Pregnancy and implantation rates were similarly reduced and correlated to the degree of endometriosis. The probability of pregnancy was found to be one third lower among women with endometriosis, compared to women without endometriosis.
None of the studies involved were randomised and controlled! Since the work was a meta-analysis, it is classified as evidence level 1a (cf. the ESHRE guidelines).
No conclusion regarding whether treatment of endometriosis prior to IVF improves the IVF results can be drawn from this work.
Opoien HK et al. 2011 [20]: This study shows that women with ASRM Stage I and II endometriosis undergoing IVF / ICSI have both higher implantation rate and live birth rate if all visual endometriosis is completely eliminated at the time of diagnostic surgery.

Diaz et al., 2000 [45] and ***Simon*** et al., 1994 [46] found no evidence that implantation and pregnancy rates are affected.
The hypotheses that the endometrium is affected is not supported either by ***Hickman*** et al., 2002 [47], based on implantation and pregnancy rates, or ***Matalliotakis*** et al., 2007 [48], who found the same implantation and pregnancy rate among patients previously operated on for endometriosis as among patients with tubal factors (retrospective case-control study). However, endometriosis patients had more cancelled treatments, required a higher FSH dose, and had fewer eggs. There was no difference in the number of embryos transferred.The above work might therefore suggest that endometriosis does not directly impact on the receptivity of the endometrium, but more specifically on the oocyte quality.

Pre-treatment using GnRH agonist prior to IVF treatment

Sallam et al. 2006 [49] carried out a Cochrane analysis to determine the effect of suppression for 3-6 months prior to IVF treatment, versus conventional IVF treatment, among women with endometriosis.
Three RCTs involving a total of 165 women were included in the analysis. The clinical pregnancy rate (n = 165) and live birth rate (n = 67) were significantly higher in the group which underwent 3-6 months of suppression; OR 4.28. 95 % CI 2.0-9.15 and OR 9.19. 95 % CI 1.08-78.22. The miscarriage rate could not be calculated with certainty due to major differences in the material in the three works (evidence level 1a).
The study did not investigate the side-effects of the long period of suppression, or its effects on later pregnancy outcomes and children.

Marcus & Edwards, 1994 [50] carried out a non-randomised investigation of prolonged, long or short treatment using GnRH among women with endometriosis grade III or IV. Group 1 consisted of 69 women who were treated under the short or long protocol and stimulated using 225 IE hMG until HCG day. Group 2 consisted of 15 patients who received prolonged suppression using Zoladex® every fourth week for 2-7 months, followed by stimulation using hMG 225 IE until hCG day, as well as 20 patients from group 1 who wanted to undergo prolonged treatment following negative hCG.
Results: Prolonged suppression led to no reduction in endometrioma size, a significantly greater consumption of hMG, significantly more fertilised oocytes, a significantly higher pregnancy rate, and significantly more gemelli pregnancies.

Chakravarty et al.2002 [51] presented similar results at the Eighth World Congress on Endometriosis. In this study, women with moderate to severe endometriosis were randomly assigned to suppression for either 6 months, or 2-3 weeks, prior to stimulation. In addition to significantly more aspirated oocytes, the study found a significantly higher cumulative pregnancy rate (52 % vs. 27 %, $p < 0.05$) and significantly lower cumulative miscarriage rate (12 % vs. 33 %) following three IVF treatments, in the group which underwent suppression for six months (evidence level 1a).
A review by ***Zikopoulos*** et al. 2004 [52] concludes on the basis of four retrospective studies from 1989 to 1995 that the pregnancy rate following 2-3 weeks of suppression using GnRH agonist was better than direct ovarian stimulation in connection with IVF treatment in endometriosis patients. However, since all the studies were carried out prior to the GnRH antagonist era, the conclusion must be treated with caution, and cannot be ascribed to the short protocol for the use of GnRH antagonist.

GnRH antagonist treatment for endometriosis patients

Pabuccu et al. 2007 [53] have published an RCT in which 246 endometriosis patients (grade I-II (n=98), patients who have undergone previous endometrioma resection (n=81), and patients with existing endometriomas (n=67)) were randomly assigned to either the standard long GnRH agonist protocol or the standard short GnRH antagonist protocol. ICSI was used as the fertilisation method. The implantation and ongoing pregnancy rates were numerically higher in the agonist group (but not significant). The number of metaphase II oocytes and embryos were significantly higher in the agonist group.
No other works have been published to date which investigate agonist treatment in connection with endometriosis.

Conclusion

Prolonged suppression using GnRH agonist for 3-6 months appears to lead to more oocytes being retrieved and a greater ongoing pregnancy rate compared to normal long and short protocols.

However, since six months of suppression is a long time, with more potential side effects, and since relatively few patients were involved in the meta-analysis based on RCTs [35], it seems acceptable to attempt IVF/ICSI treatment under the standard long protocol before possibly attempting prolonged suppression (3-6 months).
Patients may also be treated with “add back” in the form of gestagen dominated low-dose oestrogen combinations for women who experience pronounced side-effects during prolonged suppression (***Zupi** et al.* 2004 [54], **DSOG** guidelines). However, we do not know anything about possible effects on the probability of pregnancy during subsequent IVF treatment, and any growth/development of the endometrium must be shed prior to stimulation using exogenous gonadotropin.

It has not been clarified whether the effect of prolonged suppression can only be seen among endometriosis patients, or is a general effect across all fertility patients.

Endometriosis and egg donation

Diaz et al., 2000 [45] carried out a matched case-control study involving 58 recipients, 25 of whom had grade III or IV endometriosis verified by laparoscopy, while the rest had been declared free of endometriosis following laparoscopy. Eggs from the same donor (without endometriosis) were donated to patients from both groups. No difference was found in the implantation or ongoing pregnancy rates in the two groups (evidence level 2a).

Simon et al., 1994 [46] carried out a retrospective analysis of results following egg donation. The analysis compared the results for recipients with either tubal factors or endometriosis, and found no differences in the implantation or pregnancy rates between the two groups. However, a significantly lower implantation rate was found among recipients who had received eggs from endometriosis patients, compared to donors from all other groups (evidence level 3).

Conclusion

Infertile women with severe endometriosis who are unable to use their own eggs are ideally suited as recipients for treatment using egg donation [45].
Women with severe endometriosis should possibly not be used as egg donors [46].

Use of steroids in connection with fertility treatment

In a Cochrane review involving 13 RCTs (1759 couples), ***Boomsma CM*** et al., 2007 [55] concluded that the pregnancy rate was not significantly improved through the use of glucocorticoid supplements around the time of implantation in connection with IVF/ICSI treatment (OR 1.16; 95 % CI 0.94-1.44). However, a subgroup analysis of the 650 women treated with IVF and not ICSI (six RCTs) found a higher pregnancy rate (just significant) among women treated with glucocorticoids (OR 1.50; 95 % CI 1.05-2.13). Women with endometriosis were excluded from this Cochrane review.

It has only been possible to find a single article covering glucocorticoid supplements for women with and without endometriosis – see below (this article is also included in the above review, but only women without endometriosis were included):
Kim CH et al., 1997 [56]: A randomised controlled study of 42 women with endometriosis + tubal factors, and 87 women who only had tubal factors, who were randomly assigned to IVF treatment, with or without glucocorticoid treatment. The study found a significantly higher pregnancy rate in the group with endometriosis and tubal factors which received the steroid in connection with IVF treatment, compared to the group without steroid treatment. However, 38% of the women with endometriosis + tubal factors were found to have autoantibodies (antinuclear antibodies, lupus anticoagulants, anticardiolipin, rheumatoid factors), and a sub-analysis of endometriosis patients

without autoantibodies found no significant difference in the clinical pregnancy rate. There was no difference in the results for the group with tubal factors alone.

Conclusion

It is therefore still unclear whether there is indication for treating endometriosis patients with steroids prior to or during IVF treatment.

Future considerations

Classification system

Adamson and Pasta**,** 2010 [57] have just introduced a new and validated classification system for endometriosis: "Endometriosis fertility index", EFI. This is a clinical tool that predicts pregnancy rates in patient after endometriosis surgical staging who attempt non-IVF conceptions.

Aromatase inhibitors and endometriosis

The aromatase enzyme is expressed in several different types of cells in the human body, including ovarian granulosa cells, in the syncytiotrophoblast and in Leydig cells in the testes, as well as in skin fibroblasts etc.
Aromatase is active in the last stage of oestradiol synthesis in connection with the conversion of androgen to oestradiol and oestrone. Transcription of the aromatase gene is carefully regulated.
Endometriosis tissue expresses the aromatase enzyme, and it is therefore assumed that local oestrogen synthesis takes place in the actual endometriosis tissue – independent of the steroidal synthesis in the ovaries and adrenal glands to some extent. It is further assumed to be beneficial to inhibit this in situ synthesis using aromatase inhibitors. These have been described very thoroughly by ***Attar & Bulun****,* 2006 [58].
Pharmacological types are available in the form of Anastrazole (Arimidex®), Exemestane (Aromasin®) and Letrozole (Femar®), which have been developed to treat oestrogen dependent mamma tumours among postmenopausal women. This is also the sole indication for the use of these type of medicines in Norway, as stated by the producers.
Aromatase inhibitors inhibit production of oestrogen in the brain, ovaries, endometriosis, and peripheral tissue (fat tissue and skin), thereby stimulating FSH. In premenopausal women this can lead to stimulation of follicle growth in the ovaries.

To date, aromatase inhibitors have only been used experimentally for stimulation treatment in women with unexplained infertility (***Barosso*** *et al*., 2006, [59]). Mitwally et al. have written a number of articles on aromatase inhibitors and stimulation treatment. None of these appear to include women with endometriosis.
Several works discuss treating women with endometriosis with aromatase inhibitors in combination with GnRH analogues, progesterone or POP pills. The studies have been carried out with a focus on analgesic treatment, and the results to date look promising.
In a systematic review and metaanalysis on the use of letrozole in assisted reproduction it was concluded that letrozole is as effective as other methods of ovulation induction. However, further RCT are warranted to define more clearly the effect and safety of letrozole in human reproduction (***Requena*** *et al 2008*) [60]. The effects on children born to such patients are unknown and the reports conflicting (***Tulandi T*** et al) [61-62].
More research is therefore needed before we will know whether aromatase inhibitors should play a role in the treatment of infertile endometriosis patients.

Larger RCTs are sorely needed which investigate endometriosis and infertility treatment. These guidelines should ideally be much more strongly based on such studies, but this has not been possible. The vast majority of studies are retrospective case-control studies with poorly defined scope.

References

1. *American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817-21.*

2. *Cramer DW and Missmer SA (2002) The epidemiology of endometriosis. Ann N Y Acad Sci, 955, 11-22.*

3. *Moen MH (1987) Endometriosis in women at interval sterilization. Acta Obstet Gynecol Scand, 66, 451-454.*

4. *Moen MH and Schei B (1997) Epidemiology of endometriosis in a Norwegian county. Acta Obstet Gynecol Scand, 76, 559-562.*

5. *D'Hooghe TM, Debrock S, Hill JA, and Meuleman C (2003) Endometriosis and subfertility: is the relationship resolved? Semin Reprod Med, 21, 243-254.*

6. *Attar E and Bulun SE (2006) Aromatase and other steroidogenic genes in endometriosis: translational aspects. Hum Reprod Update, 12, 49-56.*

7. *Noble LS, Simpson ER, Johns A, and Bulun SE (1996) Aromatase expression in endometriosis. J Clin Endocrinol Metab, 81, 174-179.*

8. *Tsai SJ, Wu MH, Lin CC, Sun HS, and Chen HM (2001) Regulation of steroidogenic acute regulatory protein expression and progesterone production in endometriotic stromal cells. J Clin Endocrinol Metab, 86, 5765-5773.*

9. *Young SL and Lessey BA (2010) Progesterone function in human endometrium: clinical perspectives. Semin Reprod Med, 28, 5-16*

10. *Marcoux S, Maheux R and Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997;337:217-22.*

11. *Parazzini F. Ablation of lesions or no treatment in mininimal-mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per la Studio dell'Endometriosis. Human Reprod 1999;14:1332-4.*

12. *Jacobson TZ, Barlow DH, Koninckx PR, Olive D and Farquhar C. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database of Systematic Reviews 2002;(4):CD001398.*
Update in: Cochrane Database Syst Rev. 2010;(1):CD001398

13. *Nardo LG, Moustafa M and Beynon DW. Reproductive outcome after laparoscopic treatment of minimal and mild endometriosis using Helica Thermal Coagulator. Eur J Obstet Gynecol Reprod Biol 2006;126:264-7.*

14. *Berube S, Marcoux S, Langevin M and Maheux R. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. The Canadian Collaborative Group on Endometriosis. Fertil Steril 1998;69:1034-41.*

15. *Tummon IS, Asher LJ, Martin JS and Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril 1997;68,8-12.*

16. *Nulsen JC, Walsh S, Dumez S and Metzger DA. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility.Obstet Gynecol 1993;82:780-6.*

17. *Werbroucke E, Spiessens C, Meuleman C, D'Hooge T. No difference in cycle pregnancy rate in cumulative live-birth rate between women with surgically treted minimal to mild endometriosis and women with unexplained infertility after controlled ovarian stimulation and intrauterine insemination. Fertil Steril 2006; 86: 566-71.*

18. *Omland AK et al 1998, "Artificial insemination by husband in unexplained infertility compared with infertility associated with peritoneal endometriosis", Hum.Reprod., vol. 13, no. 9, pp. 2602-2605.*

19. *Nuojua-Huttunen S et al 1999, Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome, Hum.Reprod., vol. 14, no. 3, pp. 698-703.)*

20. *Opøien HK et al 2011.Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent assisted reproduction treatment. Reprod Biomed Online 23(3):389-95*

21. *Dmowski W P, Pry M, Ding J and Rana N. Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation-intrauterine insemination or in vitro fertilization-embryo transfer. Fertil Steril 2002;68:750-6.*

22. *Adamson GD, Hurd SJ, Pasta DJ and Rodriguez BD. Laparoscopic endometriosis treatment: is it better? Fertil Steril 1993;59,35-44.*

23. *Olive DL, Stohs GF, Metzger DA and Franklin RR. Expectant management and hydrotubations in the treatment of endometriosis-associated infertility. Fertil Steril 1985;44:35-41.*

24. *Vercellini P, Fedele L, Aimi G, De Giorgi O, Consonni D and Crosignani PG. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. Human Reprod 2006;21:2679-85.*

25. *Fujishita A, Khan KN, Masuzaki H and Ishimaru T. Influence of pelvic endometriosis and ovarian endometrioma on fertility. Gynecol Obstet Invest 2002;53(Suppl 1):40-5.*

26. *Kodama H, Fukuda J, Karube H, Matsui T, Shimzu Y and Tanaka T. Benefit of in vitro fertilization treatment for endometriosis-associated infertility. Fertil Steril 1996;66:974-79.*

27. *Pagidas K, Falcone T, Hemmings R and Miron P. Comparison of reoperation for moderate (stage III) and severe (stage IV) endometriosis-related infertility with in vitro fertilization-embryo transfer. Fertil Steril 1996;65:791-5.*

28. *Coccia ME, Rizzello F, Mariani G, Bulletti C, Palagiano A, Scarselli G. Ovarian surgery for bilateral endometriomas influences age at menopause.Hum Reprod. 2011 Nov;26(11):3000-7. Epub 2011 Aug 24.*

29. *Yasui T, Hayashi K, Mizunuma H, Kubota T, Aso T, Matsumura Y, Lee JS, Suzuki S Association of endometriosis-related infertility with age at menopause. Maturitas. 2011 Jul;69(3):279-83. Epub 2011 May 24.*

30. *Pokoradi AJ, Iversen L, Hannaford PC Factors associated with age of onset and type of menopause in a cohort of UK women. Am J Obstet Gynecol. 2011 Jul;205(1):34.e1-13. Epub 2011 Feb 27.*

31. *Tsoumpou I, Kyrgiou M, Gelbaya TA and Nardo LG. The effect of surgical treatment for endometrioma on in vitro fertilization ou-comes: a systematic review and meta-analysis. Fertil Steril 2008; 92:75-87.*

32. *Hirokawa W, Iwase A, Goto M, Takikawa S, Nagatomo Y, Nakahara T, Bayasula B, Nakamura T, Manabe S, Kikkawa F. The post-operative decline in serum anti-Mullerian hormone correlates with the bilaterality and severity of endometriosis Hum Reprod. 2011 Apr;26(4):904-10. Epub 2011 Feb 2*

33. *Demirol A, Guven S, Baykal C and Girgan T. Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study. Reprod Biomed Online 2006;12:639-43.*

34. *Garcia-Velasco JA, Mahutte NG, Corona J, Zuniga V, Giles J, Arici A and Pellicer A. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. Fertil Steril 2004;81:1194-7.*

35. *Tinkanen H and Kujansuu E. In vitro fertilization in patients with ovarian endometriomas. Acta Obstet Gynecol Scand 2000;79:119-22.*

36. *Ragni G, Somigliana E, Benedetti F, Paffoni A, Vegetti W, Restelli L and Crosignani PG. Damage to ovarian reserve associated with laparoscopic excision of endometriomas: A quantitative rather than a qualitative injury. Am J Obstet Gynecol 2005;193:1908-14.*

37. *Pabuccu R, Onaloan G, Goktolga U, Kucuk T, Orhon E and Ceyhan T. Aspiration of ovarian endometriomas before intracytoplasmic sperm injektion. Fertil Steril 2004;82:705-11.*

38. *Mais V, Ajossa S, Guerriero S, Mascia M, Solla E and Melis GB. Laparoscopic versus abdominal myomectomy: a prospective, randomized trial to evaluate benefits in early outcome. Am J Obstet Gynecol 1996;174:654-8.*

39. *Hart RJ, Hickey M, Maouris P, Buckett W and Garry R. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database of Systematic Reviews 2006;(3):CD004992.*

40. *Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E and Bolis P. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. Fertil Steril 1998;70:1176-80.*

41. *Alborzi S, Momtahan M, Parsanezhad ME, Dehbashi S, Zolghadri J and Alborzi S. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. Fertil Steril 2004;82:1633-37.*

42. *Hughes E, Fedorkow D, Collins J and Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database of Systematic Reviews 2003;(3):CD000155.*

43. *Yap C, Furness S and Farquhar C. Pre and post operative medical therapy for endometriosis surgery. Cochrane Database of Systematic Reviews 2004;(3):CD003678.*

44. *Barnhart K, Dunsmoor-Su R and Coutifaris C. Effect of endometriosis on in vitro fertilisation. Fertil Steril 2002;77;1148-55.*

45. *Diaz I, Navarro J, Blasco L, Simon C, Pellicer A and Remohi J. Impact of stage III-IV endometriosis on recipients of sibling oocytes: matched case-control study. Fertil Steril 2000;74(1):31-4.*

46. *Simon C, Gutierrez A, Vidal A, de los Santos MJ, Tarin JJ, Remohi J and Pellicer A. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation.*Hum Reprod 1994;9:725-9.

47. *Hickman TN , Impact of endometriosis on implantation. Data from the Wilford Hall Medical Center IVF-ET Program. J Reprod Med 2002; 47: 801-8.*

48. *Matalliotakis IM, et al. Women with advanced-staged endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. Fertil Steril, 2007, in press.*

49. *Sallam HN, Garcia-Velasco JA, Dias S and Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database of Systematic Reviews 2006;(1):CD004635*

50. *Marcus SF and Edwards RG. High rates of pregnancy after long-term down-regulation of women with severe endometriosis. Am J Obstet Gynecol 1994;171:812-7.*

51. *Chakravarty BN, Goswami SK and Kabir SN. Effect of long GnRH-agonist hormonal suppression on IVF-ET treatment in stage-III (moderate) or stage-IV (severe) grades of endometriosis-associated infertility. Fertil Steril 2002;77(Suppl 1):S13.*

52. *Zikopoulos K, Kolibianakis EM and Devroey P. Ovarian stimulation for in vitro fertilization in patients with endometriosis. Acta Obstet Gynecol Scand 2004;83:651-5.*

53. *Pabuccu R, Onalan G and Kaya C. GnRH agonist and antagonist protocols for stage I-II endometriosis and endometrioma in in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril 2007 in press.*

54. *Zupi E, Marconi D, Sbracia M, Zullo F, De Vivo B, Exacustos C and Sorrenti G. Add-back therapy in the treatment of endometriosis-associated pain. Fertil Steril 2004;82:1303-8.*

55. *Boomsma C, Keay S and Macklon N. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. Cochrane Database of Systematic Reviews. 2007;(1):CD005996.*

56. *Kim CH, Chae HD, Kang BM, Chang YS and Mok JE. The immunotherapy during in vitro fertilization and embryo transfer cycles in infertile patients with endometriosis. J Obstet Gynaecol Res 1997;23:463-70.*

57. *Adamson GD and Pasta DJ Endometriosis fertility index: the new, validated endometriosis staging system.2010 FertilSteril. Oct;94(5):1609-15.*

58. *Attar E and Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? Fertil Steril 2006;85:1307-18.*

59. *Barosso G, Menocal G, Felix H, Rojas-Ruiz JC, Arslan M and Oehninger S. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial. Fertil Steril 2006;*86:1428-31.

60. *Requena A, Herrero J, Landeras J, Navarro E, Neyro JL, Salvador C, Tur R, Callejo J, Checa MA, Farre M, Espinos JJ, Fábreque F and Graña-Bacia M Use of letrozole in assisted reproduction: a systematic review and meta-analysis. Hum Reprod Upd 2008; 14:571-82.*

61. *Tulandi T et al Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate.Fertility and Sterility 2006; 85:1761-5.*

62. *Tulandi T et al: Limiting access to letrozole--is it justified?Fertil Steril 2007; 88:779-80.*