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Similar evolution of pain symptoms and quality of life in endometriosis and non-endometriosis patients undergoing assisted reproductive technology (ART)

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ABSTRACT

Introduction: Ten percent of all fertile-aged women suffer from endometriosis, and up to 25% of these women require assisted reproductive technology (ART) to conceive. During ART, the process of controlled ovarian stimulation causes high levels of estrogen, which in theory increases the risk of progression of symptoms related to this estrogen dependent disorder. Owing to several case reports describing worsening of endometriosis during ART we carried out this study in order to investigate if controlled ovarian stimulation during ART aggravates symptoms in women with endometriosis regarding pain and quality of life. **Material and methods:** This prospective cohort study was based on questionnaires containing the Endometriosis Health Profile (EHP-30®) and pain evaluated on the Numerical Rating Scale (NRS). Women below 40 years were recruited and divided into three groups according to their endometriosis and ART status. Questionnaires were administered before and after controlled ovarian stimulation in one ART cycle. Change in EHP-30® and NRS scores from 1st to 2nd questionnaire was analyzed. **Results:** Fifty-two women with endometriosis undergoing ART, 50 not undergoing ART and 52 without endometriosis undergoing ART completed two questionnaires each. Both groups with endometriosis experienced a small increase in quality of life, while women without endometriosis presented a decrease. Pelvic pain worsened among women undergoing ART, but no greater worsening was detected among women with endometriosis compared to women without. **Conclusions:** This study showed no worsening in quality of life and slight worsening in pelvic pain during ART regardless of the endometriosis.

Keywords

Endometriosis, Assisted Reproductive Technology, ART, Quality of Life, Pain, Patient Reported Outcome Measures

Abbreviations

ART, assisted reproductive technology

COS, controlled ovarian stimulation

EHP-30®, Endometriosis Health Profile consisting of 30 items.

IVF, in vitro fertilization

NRS, Numeric Rating Scale

QoL, quality of life

Key Message

This study examined endometriosis symptoms and quality of life during ART. Our results suggest no worsening in these parameters which supports ART as a suitable therapeutic option for women with endometriosis suffering from infertility.

INTRODUCTION

Endometriosis is a common benign gynecological disorder affecting approximately 10% of all fertile women (1). It is characterized by ectopic presence of endometrial glands and stroma (2). Endometriosis differs in location and invasive potential and can be found superficially on the peritoneum, in the ovaries as endometriotic cysts, and as deep infiltrating endometriosis affecting organs close to the pouch of Douglas, such as the rectovaginal septum and the rectosigmoid colon (3). The etiology is still uncertain, but it is well-known that endometriosis is an estrogen dependent disease influenced by hormonal and inflammatory changes (4-9). Symptoms of endometriosis are dysmenorrhea, deep dyspareunia, chronic pelvic pain, and infertility, which affect these women's well-being physically, mentally and socially (10, 11).

Treatment of endometriosis can either be surgical or medical, and choice of treatment is based on the woman's symptoms. Medical hormonal treatment is undesirable for women with endometriosis wishing to conceive due to the contraceptive effects of the hormonal treatments used.

Ten to 25% of women with endometriosis require assisted reproductive technology (ART) to conceive (12). During controlled ovarian stimulation (COS) the estrogen level increases, hence in theory increasing the risk of progression of symptoms related to endometriosis. Anaf et al. identified four cases of rapidly growing sigmoid endometriosis during ovarian stimulation resulting in cessation of ART and bowel surgery (13). Eleven similar cases have occurred in our department since 2007 (14). Moreover, isolated cases with severe worsening of endometriosis during COS have been described (15-18).

The aim of this present study was to investigate if the process of COS during ART aggravates symptoms in women with endometriosis regarding pain and quality of life (QoL).

MATERIAL AND METHODS

This prospective, cohort study was carried out from February 2016 to October 2017. Participants were recruited from the Department of Obstetrics and Gynecology, Aarhus University Hospital, the Fertility Clinic at The Regional Hospital in Horsens, the Fertility Clinic at Aalborg University Hospital, and the private fertility clinic Maigaard Fertilitetsklinik, Aarhus, Denmark. Inclusion criteria were women < 40 years of age receiving COS for in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) with ability to understand and speak Danish. Participants were recruited regardless of previous infertility treatment of any kind. Participants were excluded during the course of the study if they were lost to follow-up, or if egg retrieval was cancelled.

One hundred and seventy-seven women were distributed into three groups:

1) Exposed group: Women with peritoneal/ovarian endometriosis or deep infiltrating endometriosis undergoing ART.
2) Reference group 1: Women undergoing ART because of factors other than endometriosis, for example male factor, tubal factor and ovulation disorders.
3) Reference group 2: Women with medically treated endometriosis, with no desire for pregnancy, hence not undergoing ART. Both women with newly diagnosed endometriosis and women with satisfactory response to medical treatment were included.

For the exposed group and reference group 2, diagnosis of endometriosis was confirmed by previous laparoscopy, transvaginal ultrasound scan or magnetic resonance imaging with no time limit retrospectively, or by transvaginal ultrasound at the examination in connection with recruitment. Participants undergoing ART were recruited from the above-mentioned fertility clinics, and reference group 2 was recruited from the endometriosis unit at the Department of Obstetrics and Gynecology, Aarhus University Hospital.

Questionnaires were distributed via e-mail (Supporting Information Appendix S1), and data was administered electronically in REDCap™, which is a secure web application for building and managing online surveys and databases. The participants answered the same questionnaire at all time-points with the exception of baseline characteristics.

The exposed group and reference group 1 received the questionnaire before starting COS and 10 days after egg retrieval. The second questionnaire was administered before knowing the pregnancy test result.

Reference group 2 received the first questionnaire immediately after consultation. In case of changes in the medical treatment, such as oral contraceptives or intrauterine device, the first questionnaire was postponed one month in order to ensure stabilization. The interval between first and second questionnaire was four weeks, corresponding to the gap between two questionnaires in the ART groups.

The questionnaire design was based on recommendations from the Art and Science of Endometriosis meeting (19).

QoL was measured using the validated Danish edition of EHP-30®, where zero indicates the best health status and 100 the worst. Reference group 1 without endometriosis was instructed to answer the questions leaving out of account the phrase "…because of your endometriosis…", as otherwise it could imply missing responses and underreporting of endometriosis like symptoms (20).

Pain symptoms and tiredness were evaluated on the NRS (0 = "no symptom/tiredness" and 10 = "worst symptom/tiredness you can imagine"), as general and worst perception of characteristic endometriosis symptoms; non-menstrual pelvic pain, dyschezia, dyspareunia, and pain during micturition. Wong-Baker FACES® Pain Rating Scale was used as a comparison tool to the NRS in the questionnaire (21).

Qualitative questions were asked relative to non-menstrual pelvic pain and dyspareunia. Frequency of pain symptoms were evaluated on a Likert-type scale (never, rarely, sometimes, often and always). Degree of non-menstrual pelvic pain and dyspareunia was evaluated with questions inspired by the Biberoglu and Behrman score (22). Response categories for the most suitable statement for non-menstrual pelvic pain were "None", "Mild: Some loss in work efficiency", "Moderate: In bed part of the day, occasional loss of work efficiency" and "Severe: In bed one or more days, incapacitation" and for dyspareunia "None", "Mild: Tolerated discomfort" "Moderate: Intercourse painful to the point of causing interdiction" and "Severe: Avoids intercourse because of pain".

Regimen of controlled ovarian stimulation (COS)

No fixed COS protocols were used, as participants were treated individually'. In general, two types of protocols were applicable: 1) Antagonist protocol and 2) long agonist protocol. Purified follicle stimulating hormone or human menopausal gonadotropin was used for COS in both protocols. Gonadotropin releasing hormone (GnRH) was used for down regulation during the long agonist protocol. Pregnancies were diagnosed by serum human chorionic gonadotropin (hCG) > 10 IU/l or a positive urine hCG 14-16 days after oocyte aspiration or embryo transfer depending on which fertility clinic the woman attended.

Statistical analyses

According to a power analysis based on 10 as the smallest relevant difference in EHP-30® score, α=0.05 and power (1-β)=0.90, 48 patients should be recruited per group. Normality assumptions were confirmed using histograms and QQ-plots.

Continuous data on ART cycles were log-transformed where appropriate and described as mean and range or standard deviation, depending if the standard deviations were statistically different between the groups. The two ART groups were compared using t-test or Wilcoxon signed-rank depending on distribution of the data. Categorical data on ART cycles were compared with Chi-squared or Fishers Exact test.

Change in parameters from 1st to 2nd questionnaire was evaluated as score in 2nd questionnaire minus score in 1st. Hence, a positive change indicates a worsening. Change in EHP-30 score was analyzed using unpaired t-test between the two groups undergoing ART and the two groups with endometriosis separately. For unequal standard deviations Wilcoxon signed-rank test was used. One-way analysis of variance (ANOVA) was performed for comparing continuous, normally distributed variables between all three groups. NRS parameters were described as median with minimum and maximum values and analyzed using the Kruskal Wallis test because of non-normal distribution. Change in degree and frequency of qualitative pain were calculated as categorical outcomes (decline, status quo or increase) and compared between the three groups using Chi squared or Fisher's exact test where appropriate.

Potential confounders were selected a priori based on the scientific literature and evaluated with multiple linear regression. Number of confounders were adjusted to population size. Missing values were excluded from analysis when present. Statistical analyses were performed using Stata 14.2® 2016 (Stata Corp, College Station, TX).

Ethical approval

All women gave written informed consent. The Danish Data Protection Agency approved the study (registration number 2012-58-006), and the study was registered on ClinicalTrials.gov (NCT02762461). Permission to use the Wong-Baker FACES® Pain Rating Scale was given by the Wong-Baker FACES Foundation. No approval from The Central Denmark Region Committees on Health Research Ethics was needed because of the study design (inquiry number 209/2015, 19.10.2015).

RESULTS

Population

During the study period 177 women matched the criteria for the three groups. During the study participants were excluded because of participation refusal, cancelled egg retrieval, spontaneous pregnancy during downregulation or loss to follow up. Ultimately, 154 women were retained for analysis (Figure 1).

The study population was characterized by a mean age of 32.7 years (range 22.0-39.5 years) and mean BMI of 24.5 kg/m^2 (range 17.2-40.3 kg/m^2). Table 1 shows participants' characteristics by groups. Women differed statistically significantly in marital status, smoking and alcohol habits, birth after spontaneous pregnancy, previous infertility treatment (all types) and previous intrauterine insemination. Baseline fertility data concern previous treatments before this study. Median time from 1st to 2nd questionnaire in the exposed group was 40 days (10th/90th percentile 23/66), significantly longer than in reference group 1 (28 days (10th/90th percentile: 21/44)) and 2 (28 days (10th/90th percentile: 28/34.5)) (*P*<.001).

Data on ART cycles (Supporting Information Table S1) showed that women with endometriosis compared to women without endometriosis had significantly lower anti-Müllerian hormone (pmol/l) (14.8 (range:1.6-120.9) vs. 28.1 (range: 13.1-99); *P*<.001), were treated with higher doses of gonadotropin (2594±1172 IU vs. 1844±770 IU; *P*<.001) but stimulated for the same number of days (11.5±2.1 vs. 10.6±2.5; *P*=.062), and were more often treated with agonist protocol (77% (40/52) vs. 27% (14/52); *P*<.001). Ten percent (5/52) of women with endometriosis had embryo transfer cancelled in the exposed group, and 12% (6/52) of women in reference group 1 (*P*=.750). The reasons of infertility in reference group 1 were male factor (48%), tubal factor (13%), ovulatory dysfunction (4%) and other (35%).

Pain

Baseline pain parameters (Table 2) differed between the groups. Moreover, the groups differed in change on the unadjusted parameters tired, general and worst non-menstrual pelvic pain (Table 3). The groups with endometriosis experienced a median change of 0 in tired and general non-menstrual pelvic pain compared to a change of 1 in reference group 1 (*p*=.003 and *P*<.001,

respectively). Regarding worst non-menstrual pelvic pain, the median changes were 1 in the exposed group, 2,5 in reference group 1, and 0 in reference group 2, (P<.001). Adjustment for smoking, marital status and previous infertility treatment on the above-mentioned parameters did not change the results (table 4).

Menstrual pain was not included as the majority of women undergoing ART did not have menstruation, and a bleeding could well be an early miscarriage. Sixteen women with endometriosis undergoing ART had their period within the last four weeks in both questionnaires, and no significant difference in change was found between the groups. Additionally, only 14 women in reference group 2 had their period due to hormonal treatment (data not shown).

Changes in qualitative questions only differed between the groups in non-menstrual pelvic pain both regarding frequency and degree. Regarding degree, 44% of exposed group experienced an increase and 12% a decrease. In reference group 1 52% experienced an increase and 12% a decrease, and in reference group 2 18% had an increase and 20% a decrease (P=.008). Regarding frequency, 50% of exposed group experienced an increase and 23% a decrease, in reference group 1 58% experienced an increase and 8% a decrease, and in reference group 2 26% and 20% experienced an increase and decrease respectively (P=.004).

Quality of Life

Baseline EHP-30® scores can be seen in table 2. All modules except for "self image" were significantly higher among the exposed group compared to reference group 1. Only the module "self image" differed between the two endometriosis groups. Regarding change in the five EHP-30® modules, significant differences were found between the exposed group and reference group 1 in all modules except "self image". No statistically significant differences were found between the exposed group and reference group 2 (Table 3). After adjusting for smoking, marital status and previous infertility treatment (table 4) no differences were found between the two endometriosis groups. The two groups undergoing ART differed on all EHP-30® modules compared to reference group 2 after adjustment.

Change in pain or QoL within the groups according to different COS protocols (agonist or antagonist) was evaluated and no systematic differences were found (data not shown).

DISCUSSION

The present study aimed to investigate if COS during ART aggravated symptoms in women with endometriosis regarding pain and QoL. The main finding of this study was that women with endometriosis did not experience worsening in pain and QoL during ART compared to women without endometriosis and women with endometriosis not undergoing ART.

Pain

Both groups undergoing ART experienced an increase in worst non-menstrual pelvic pain. During ART women without endometriosis got tired and increased in general non-menstrual pelvic pain compared to the other groups. A possible explanation is the relation between pain and COS itself or the presence of the ovarian corpus luteum, while women with endometriosis already were used to a higher baseline pain level. Additionally, most women with endometriosis underwent downregulation during the long protocol which is known to reduce endometriosis symptoms. However, the groups only differed maximum 1.5 point on the 0-10 NRS, hence it can be discussed if these changes are clinically relevant. Thus, women with endometriosis do not experience a greater worsening in pain symptoms compared to women undergoing ART for other causes of infertility.

Quality of life

QoL worsened among women without endometriosis, while women with endometriosis experienced a very small improvement. This difference may possibly be ascribed to different approaches to EHP-30® between the groups, and that EHP-30® is not validated for women without endometriosis. For NRS, the changes are not necessarily clinically relevant. Nevertheless, these contradictory changes do not indicate a worsening in QoL among the women with endometriosis undergoing ART.

Our results are in line with those of previous studies suggesting that ART does not increase the risk of endometriosis recurrence. Benaglia et al. (23) did not find any worsening in dysmenorrhea, dyspareunia and chronic pelvic pain during in vitro fertilization. Coccia et al. (2) followed women

with endometriosis comparing recurrence rates if they underwent ART or not. No difference in recurrence rates of endometriosis was found between the groups. Santulli et al. (24) found a comparable or decreased level in pain parameters compared to a reference group. QoL was evaluated at one time-point with the non-endometriosis specific FertiQoL tool, and no significant difference was found compared to women without endometriosis. It is not stated if the great part of women with deep infiltrating endometriosis had undergone prior surgery, hence it is not known if no progression in symptoms was due to prior excision of endometriosis. Contrary to these studies several cases with an uncontrolled design have described severely worsened endometriosis during ART (13, 15, 16, 18, 25, 26) especially concerning bowel endometriosis including 11 cases in our unit (14).

Strengths and limitations

A strength of this study is the two reference groups which allowed us to differentiate between changes in parameters caused by ART and endometriosis individually. Furthermore, the two endometriosis groups made it possible to use the disease specific EHP-30®. It is known that a positive pregnancy test result affects treatment satisfaction (27) as well as QoL (28), and hence the 2nd questionnaire was administered before knowing the result of the pregnancy test. This strength could nonetheless be limited by delayed answering of 2nd questionnaire or early bleedings after embryo transfer indicating a possible, negative pregnancy test result. Data on ART cycles showed that percentages of positive pregnancy tests and embryo transfers did not differ between the two ART groups (data not shown).

Our study included cycle data, which made it possible to correlate the questionnaire parameters to the hypothesis of worsening of endometriosis owing to COS. Despite significantly higher gonadotropin doses among the exposed group, these women did not experience a greater worsening than the reference group.

We consider the questionnaire compliance high, since 87% of women recruited answered both questionnaires, and only 4% (7/177) were lost to follow-up. Multiple linear regression was performed to control for possible confounders and this did not affect the conclusion of the results.

This study also has limitations. Women with endometriosis were included regardless of stage, which caused disease heterogeneity explaining the great variations in the questionnaire parameters. Endometriosis was not staged according to the American Society for Reproductive Medicine stratification as it only includes intra and not extraperitoneal endometriosis. Women in reference group 2 were recruited from a tertiary referral center, why this group may have particularly severe stages of endometriosis. This may explain the higher baseline scores compared to the exposed group observed in all pain parameters and the EHP-30® module "self image". Reasons of infertility in reference group 1 included both male and female factors which may affect the woman's QoL differently (28, 29), additionally subclinical endometriosis cannot be ruled out in this group. The follow-up period was four weeks, hence any symptoms evolving slowly and persisting over time were possibly not detected. Even so, as most side effects associated with COS are generally of short duration, this is most likely a small problem. Baseline data were obtained as COS began and the women already were in another setting than usual. Optimally, baseline data could have been recorded before starting fertility treatment.

CONCLUSION

This study did not show any worsening in endometriosis symptoms, regarding pain or QoL during ART. Hence it provides further support for ART as a suitable therapeutic option for infertile women with endometriosis. However, as we do not know the stage of endometriosis in this study, we cannot rule out that a worsening could be found in women with deep infiltrating endometriosis since most cases of worsening have been described among women with this endometriosis phenotype. Therefore, more research using controlled prospective trials is needed to investigate the long-term effects as well as the effect of ART on deep infiltrating endometriosis.

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References

1. Vigano P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: epidemiology and aetiological factors. Best Pract Res Clin Obstet Gynaecol. 2004;18(2):177-200.
2. Coccia ME, Rizzello F, Gianfranco S. Does Controlled Ovarian Hyperstimulation in Women with a History of Endometriosis Influence Recurrence Rate? J Womens Health. 2010;19(11):2063-9.
3. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril. 2012;98(3):564-71.
4. Malutan AM, Drugan T, Costin N, et al. Pro-inflammatory cytokines for evaluation of inflammatory status in endometriosis. Cent Eur J Immunol. 2015;40(1):96-102.
5. Khan KN, Kitajima M, Inoue T, Fujishita A, Nakashima M, Masuzaki H. 17beta-estradiol and lipopolysaccharide additively promote pelvic inflammation and growth of endometriosis. Reprod Sci. 2015;22(5):585-94.
6. Zhao Y, Chen Y, Kuang Y, et al. Multiple Beneficial Roles of Repressor of Estrogen Receptor Activity (REA) in Suppressing the Progression of Endometriosis. Endocrinology. 2016;157(2):900-12.
7. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364(9447):1789-99.
8. Berkley KJ, Rapkin AJ, Papka RE. The Pains of Endometriosis. Science. 2005;308:1587-9.
9. Bulun SE, Utsunomiya H, Lin Z, et al. Steroidogenic factor-1 and endometriosis. Mol Cell Endocrinol. 2009;300(1-2):104-8.
10. Bianconi L, Hummelshoj L, Coccia ME, et al. Recognizing endometriosis as a social disease: the European Union-encouraged Italian Senate approach. Fertil Steril. 2007;88(5):1285-7.
11. Friedl F, Riedl D, Fessler S, et al. Impact of endometriosis on quality of life, anxiety, and depression: an Austrian perspective. Arch Gynecol Obstet. 2015;292(6):1393-9.
12. Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. Hum Reprod. 2009;24(3):496-501.
13. Anaf V, Nakadi IE, Simon P, et al. Sigmoid endometriosis and ovarian stimulation. Hum Reprod. 2000;15(4):790-4.
14. Seyer-Hansen M, Egekvist A, Forman A, Riiskjaer M. Risk of bowel obstruction during in vitro fertilization treatment of patients with deep infiltrating endometriosis. Acta Obstet Gynecol Scand. 2018;97(1):47-52.

15. Renier M, Verheyden B, Termote L. An unusual coincidence of endometriosis and ovarian stimulation. Eur J Obstet Gynecol Reprod Biol. 2005;63:187-9.
16. Roman H, Puscasiu L, Lempicki M, et al. Colorectal Endometriosis Responsible for Bowel Occlusion or Subocclusion in Women With Pregnancy Intention: Is the Policy of Primary in Vitro Fertilization Always Safe? J Minim Invasive Gynecol 2015;22(6):1059-67.
17. Setubal A, Sidiropoulou Z, Torgal M, Casal E, Lourenco C, Koninckx P. Bowel complications of deep endometriosis during pregnancy or in vitro fertilization. Fertil Steril. 2014;101(2):442-6.
18. Jun SH, Lathi RB. Pelvic pain after gonadotropin administration as a potential sign of endometriosis. Fertil Steril. 2007;88(4):986-7.
19. Vincent K, Kennedy S, Stratton P. Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials. Report from the Art and Science of Endometriosis meeting. Fertil Steril. 2010;93(1):62-7.
20. van de Burgt TJ, Hendriks JC, Kluivers KB. Quality of life in endometriosis: evaluation of the Dutch-version Endometriosis Health Profile-30 (EHP-30). Fertil Steril. 2011;95(5):1863-5.
21. Garra G, Singer AJ, Taira BR, et al. Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients. Acad Emerg Med. 2010;17(1):50-4.
22. Biberoglu K, Behrman S. Dosage aspects of danazol therapy in endometriosis: Short-term and long-term effectiveness. Am J Obstet Gynecol. 1981;139(6):645-54.
23. Benaglia L, Somigliana E, Santi G, Scarduelli C, Ragni G, Fedele L. IVF and endometriosis-related symptom progression: insights from a prospective study. Hum Reprod. 2011;26(9):2368-72.
24. Santulli P, Bourdon M, Presse M, et al. Endometriosis-related infertility: assisted reproductive technology has no adverse impact on pain or quality-of-life scores. Fertil Steril. 2016;105:978-987.e4.
25. Govaerts I, Devreker F, Delbaere A, Revelard P, Englert Y. Short-term medical complications of 1500 oocyte retrievals for in vitro fertilization and embryo transfer. Eur J Obstet Gynecol Reprod Biol. 1997;77:239-43.
26. Egekvist A, Marinovskij E, Forman A, Kesmodel U, Riiskjær M, Seyer-Hansen M. Conservative approach to rectosigmoid endometriosis: a historical cohort study. Acta Obstet Gynecol Scand. 2017;96(6):745-750.

27. van der Houwen LE, Schreurs AM, Schats R, Lambalk CB, Hompes PG, Mijatovic V. Patient satisfaction concerning assisted reproductive technology treatments in moderate to severe endometriosis. Gynecol Endocrinol. 2014;30(11):798-803.
28. Heredia M, Tenias JM, Rocio R, Amparo F, Calleja MA, Valenzuela JC. Quality of life and predictive factors in patients undergoing assisted reproduction techniques. Eur J Obstet Gynecol Reprod Biol. 2013;167(2):176-80.
29. Rashidi B, Montazeri A, Ramezanzadeh F, Shariat M, Abedinia N, Ashrafi M. Health-related quality of life in infertile couples receiving IVF or ICSI treatment. BMC Health Serv Res. 2008;8:186.

Supporting Information legends:

Appendix S1. Questionnaire.

Table S1: Data on ART cycles

Legend

Figure 1: Flowchart of recruitment

Table 1: Baseline characteristics

	+Endo[a]/+ART N = 52	-Endo/+ART N = 52	+Endo/-ART N = 50
Age (years), mean (SD[a])	32.4 (3.5)	33.1 (4.0)	32.7 (4.9)
BMI (kg/m^2), mean (SD)	25.0 (4.9)	23.8 (4.1)	24.6 (3.9)
Alcohol (Danish units/week[b])			
0, n (%)	23 (44)	14 (27)	23 (46)
1-7, n (%)	29 (56)	38 (73)	25 (50)
8-14, n (%)	0 (0)	0 (0)	2 (4)
Smoking habits			
Smoker, n (%)	0 (0)	2 (4)	9 (18)
Former smoker, n (%)	19 (37)	13 (25)	12 (24)
Non-smoker, n (%)	33 (63)	37 (71)	29 (58)
Number of cigarettes, mean (range)	- -	12.5 (5-20)	8.7 (1-20)
Marital status			
Married or cohabiting, n (%)	49 (94)	50 (96)	37 (74)
Single or living alone, n (%)	3 (6)	2 (4)	13 (26)
Baseline fertility data			
Patients with spontaneous pregnancy, n (%)	11 (21)	11 (21)	16 (32)
Patients who have given birth after spontaneous pregnancy, n (%)	2 (4)	6 (12)	12 (24)
Previous infertility treatment, n (%)	32 (62)	39 (75)	21 (42)
Previous IUI, n (%)	19 (37)	26 (50)	5 (10)
Previous IVF, n (%)	22 (42)	30 (58)	18 (36)
Patients who got pregnant owing to IUI/IVF, n (% of those who underwent IUI/IVF)	15 (29)	25 (64)	14 (67)
Patients who gave birth to child after IUI/IVF, n (% of those who underwent IUI/IVF)	10 (19)	19 (49)	12 (57)
Education			
No vocational education, n (%)	3 (6)	2 (4)	4 (8
Skilled or higher education <3 years, n (%)	12 (23)	16 (31)	16 (32)
Higher education 3-4 years, n (%)	30 (58)	19 (37)	24 (48)
Higher education >4 years, n (%)	7 (13)	15 (29)	6 (12)
Occupation			
Employed, n (%)	42 (81)	47 (90)	38 (76)
Not currently employed, n (%)	2 (4)	3 (6)	8 (16)
Student, n (%)	8 (15)	2 (4)	4 (8)

[a]SD = Standard deviation. [b]One Danish unit equals 12 g of pure alcohol. Endo, endometriosis; ART, assisted reproductive technology; IUI, intrauterine insemination; IVF, in vitro fertilization.

Table 2: Baseline Numerical Rating Scale (NRS) and Endometriosis Health Profile (EHP-30®) scores

	+Endo/+ART N = 52		**-Endo/+ART** N = 52			**+Endo/-ART** N = 50		
NRS parameters[a]	Median	Range	Median	Range		Median	Range	*P*-value[a]
Tired[b]	5	(0-10)	4	(0-10)		7	(3-10)	<.001
Pain								
General pelvic pain	2	(0-10)	0	(0-5)		3	(0-10)	<.001
Worst pelvic pain	2	(0-10)	0	(0-7)		4.5	(0-10)	<.001
General pain during defecation	2	(0-9)	0	(0-5)		3	(0-10)	<.001
Worst pain during defecation	3	(0-9)	0	(0-8)		4	(0-10)	<.001
General pain during urination	0	(0-5)	0	(0-5)		1	(0-9)	<.001
Worst pain during urination	0	(0-6)	0	(0-6)		1	(0-10)	<.001
General pain during sexual intercourse	1	(0-6)	1	(0-4)		1.5	(0-10)	.037
Worst pain during sexual intercourse	2	(0-8)	1	(0-6)		2.5	(0-10)	.017
EHP-30[c]					*P*-value[c]			*P*-value[d]
EHP-30 module								
Pain	17	(0-72.7)	0	(0-65.9)	<.001	20.5	(0-77.5)	.345
Control and powerlessness	22.9	(0-100)	0	(0-62.5)	<.001	41.7	(0-100)	.105
Social support	21.9	(0-93.8)	0	(0-93.8)	<.001	43.8	(0-100)	.105
Emotional well-being	25	(0-70.8)	12.5	(0-79.2)	.006	27.1	(0-87.5)	.211
Self image	12.5	(0-91.7)	8.3	(0-75)	.300	41.7	(0-91.7)	.001

[a] All three groups compared with Kruskal Wallis test.

[b] 1 missing in group +endo/+ART

[c] EHP-30® score is a 0-100 scale; 0 indicating the best health status through to 100 indicating worst. According to the different instructions to EHP-30®, the -Endo/+ART and the +Endo/-ART groups, were compared individually with the +Endo/+ART group using the Wilcoxon rank-rum test.
Endo, endometriosis; ART, assisted reproductive technology.

Table 3a: Change in pain parameters from 1st to 2nd questionnaire

	+Endo/+ART N = 52		**-Endo/+ART** N = 52		**+Endo/-ART** N = 50		
Changes in parametres	Median	Range	Median	Range	Median	Range	P-value[a]
Tired[b]	0	((-6)-8)	1	((-6)-6)	0	((-10)-2)	.003
General non-menstrual pelvic pain	0	((-6)-9)	1	((-4)-8)	0	((-7)-4)	<.001
Worst non-menstrual pelvic pain	1	((-7)-10)	2,5	((-5)-8)	0	((-9)-4)	<.001
General pain during defecation	0	((-6)-8)	0	((-5)-5)	0	((-3)-5)	.606
Worst pain during defecation	0	((-6)-8)	0	((-8)-7)	0	((-7)-5)	.426
Generel pain during urination	0	((-1)-9)	0	((-1)-5)	0	((-7)-5)	.040
Worst pain during urination	0	((-2)-9)	0	((-1)-6)	0	((-6)-4)	.023
Sexual intercourse during the last four weeks in both questionnaires (N)	*31*		*33*		*22*		
General pain during sexual intercourse	0	((-5)-4)	0	((-3)-6)	0	((-6)-4)	.123
Worst pain during sexual intercourse	0	((-4)-4)	0	((-6)-4)	0	((-2)-7)	.084

[a]All three groups compared with Kruskal Wallis test.

[b]1 missing in group +endo/+ART

Endo , endometriosis; ART, assisted reproductive technology.

Table 3b: Change in Endometriosis Health Profile (EHP-30®) parameters from 1st to 2nd questionnaire

	+Endo/+ART N = 52		**-Endo/+ART** N = 52			**+Endo/-ART** N = 50		
EHP-30[a]	Mean	SDb[b]	Mean	SD	*P*-value[c]	Mean	SD	*P*-value[d]
EHP-30 module								
Pain	-4.2	24.8	6.9	23.4	.020	-1,9	18.6	.675
Control and powerlessness	-7.6	26.8	7.9	20.6	.001	-3.5	15.1	.230
Social support	-5.4	22.7	4.1	19.3	.024	-6.5	15.9	.932
Emotional well-being	-5.5	17.6	3.1	15.8	.010	-5	13.9	.867
Self image	2.4	20.6	4.3	20.1	.631	-2.5	16.2	.185

[a]EHP-30® score is a 0-100 scale; 0 indicating the best health status through to 100 indicating worst health status, hence a positive change indicates worsening and a negative change an improvement in health-related quality of life. According to the different instructions to EHP-30®, the two endometriosis groups, and the two ART groups were compared individually with Wilcoxon rank-rum test. [b] SD = Standard deviation.
[c]Wilcoxon signed-rank test (due to different standard deviations) comparing +Endo/+ART and -Endo/+ART.
[d]Wilcoxon signed-rank test (due to different standard deviations) comparing +Endo/+ART and +Endo/-ART.
Endo , endometriosis; ART, assisted reproductive technology.

Table 4: Multivariate analysis for change parameters. All three groups were compared in the same multiple linear regression, with reference group 2 (+endometriosis/-ART) as the reference group.

	+Endo/+ART N = 52			**-Endo[a]/+ART** N = 52			**+Endo/-ART** N = 50
NRS parameters	Crude[a]	Adjusted[a,b]		Crude[a]	Adjusted[a,b]		
Tired[c]	1.3	1.7	(0.6 to 2.8)	1.7	2.1	(1.0 to 3.2)	ref
Pain parameters:							
General pelvic pain	1.4	1.7	(0.6 to 2.8)	2.2	2.3	(1.2 to 3.4)	ref
Worst pelvic pain	1.7	2.0	(0.7 to 3.2)	2.9	3.0	(1.7 to 4.3)	ref
General pain during defecation	0.3	0.6	(-0.2 to 1.5)	0.3	0.7	(-0.2 to 1.5)	ref
Worst pain during defecation	0.3	0.7	(-0.4 to 1.8)	0.4	0.8	(-0.3 to 1.9)	ref
Generel pain during urination	1.1	1.5	(0.8 to 2.2)	0.6	1.0	(0.3 to 1.7)	ref
Worst pain during urination	1.4	1.8	(1.0 to 2.7)	1.0	1.4	(0.6 to 2.3)	ref
Generel pain during sexual intercourse[d]	-0.5	-0.4	(-1.4 to 0.7)	0.3	0.6	(-0.4 to 1.6)	ref
Worst pain during sexual intercourse[d]	-0.8	-0.6	(-1.6 to 0.5)	0.0	0.2	(-0.8 to 1.3)	ref
EHP-30 parameters							
EHP-30 modules:							
Pain	-0.7	0.9	(-8.2 to 10.0)	10.4	10.9	(1.8 to 20.1)	ref
Control and powerlessness	-5.7	-3.6	(-13.0 to 5.7)	9.8	10.4	(1.0 to 19.9)	ref
Social support	1.1	3.0	(-5.2 to 11.2)	10.6	12.4	(4.1 to 20.7)	ref
Emotional well-being	-5.2	-0.8	(-7.5 to 6.0)	8.1	8.1	(1.3 to 14.9)	ref
Self image	4.9	6.4	(-1.6 to 14.5)	6.8	8.2	(0.1 to 16.4)	ref

[a] Data presented estimated change (95% confidence interval).

[b] Adjusted for marital status, smoking (smoker, former smoker and non-smoker), previous infertility treatment.

[c] 1 missing in group +Endo/+ART in the parameter tired

[d] N = 31 in group +Endo/+ART, N = 33 in group -Endo/+ART and N = 22 in group +Endo/-ART

Endo , endometriosis; ART, assisted reproductive technology; NRS, Numeric Rating Scale; EHP-30®, Endometriosis Health Profile consisting of 30 items.