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Surgery, gonadotropin-releasing hormone agonist downregulation and in vitro fertilisation in women with infertility and endometriomas

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ABSTRACT

INTRODUCTION: The aim of this study was to explore the initial and long-term effects of surgical removal of endometrioma(s) immediately followed by long-term gonadotropin-releasing hormone agonist (GnRHa) treatment on in vitro fertilisation (IVF) in infertile women with ovarian endometrioma(s).

METHODS: This was a single centre retrospective study of infertile women (n = 47) with uni- or bilateral ovarian endometrioma(s) undergoing laparoscopic endometriosis surgery including cystectomy immediately followed by three to six months of GnRHa downregulation and IVF at Rigshospitalet from 2009 to 2012. Results of the first fresh IVF treatment as well as long-term follow-up (2019) were evaluated. Outcome measures were standard IVF parameters including live birth rate (LBR) after the first IVF cycle and cumulative LBR at 6-10-year follow-up.

RESULTS: Positive human choriogonadotropin and clinical pregnancy rates after the first controlled ovarian stimulation were 11/47 (23%) and 7/47 (15%), respectively, and LBR was 7/47 (15%). During the follow-up period, the cumulative LBR by additional assisted reproductive technology (ART) treatment including two cases of oocyte donation (28/47; 60%) and natural conceptions (5/47; 11%) reached 33/47 (70%).

CONCLUSIONS: Surgical removal of endometrioma(s) immediately followed by long-term GnRHa treatment and IVF resulted in a modest initial LBR, possibly due to immoderate suppression of ovarian function. At 6-10-year follow up, LBR corresponded to general results after ART.

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Women with infertility and moderate-severe endometriosis are often treated with in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). These women may also be treated with surgical removal of endometriosis tissue or by medical treatment such as downregulation with gonadotropin-releasing hormone agonist (GnRHa) to relieve symptoms and enhance fertility. The effectiveness of long-term downregulation with GnRHa prior to assisted reproductive technology (ART) treatment was supported by a meta-analysis reporting an increase in clinical pregnancy rate (CPR) in women receiving GnRHa compared to women who did not [1]. Recommendations from the European Society of Human Reproduction and Embryology (ESHRE) are based on results from this meta-analysis, stating that GnRHa may be used for a shorter period prior to ART in order to improve chances of achieving pregnancy [2]. A recent review supports the positive effect of long-term GnRHa on ART in a subset of women [3]. However, the only late study included in the review reported a possible beneficial effect of GnRHa after including cryopreserved embryo transfers only, as pregnancy rates after fresh embryo transfers were diminished [4].

Even though surgical treatment of endometriosis may relieve pain [5], it may also reduce ovarian reserve through unintended removal of viable ovarian tissue. Surgical resection of endometriomas alone does not seem to affect ART outcome compared to conservative treatment [6]. It is therefore generally accepted not to remove endometriomas before ART unless they cause pain, obstruct access to the follicles or have a suspicious sonographic appearance. Whether the presence of endometrioma has a specific impact on reproductive outcome is a matter of ongoing discussion [7, 8]. The ESHRE recommends that clinicians consider operative laparoscopy to increase the chances of natural conception in women with moderate-severe endometriosis, but also recommends counsel regarding the risks of reduced ovarian function after surgery [2].

Administration of long-term GnRHa immediately after surgery might suppress occult microscopic endometriosis [9] and thereby optimise conditions for ART. This study set out to explore pregnancy outcomes of the first fresh IVF cycle in women with moderate-severe endometriosis and at least one endometrioma who suffered from pelvic pain and infertility and were treated with radical laparoscopic surgery immediately followed by long-term GnRHa downregulation and IVF. Cumulative live birth rate (LBR) after ART and natural conceptions at long-term follow-up were also assessed.

METHODS

Design

This was a single-centre retrospective study performed at a national referral centre for endometriosis, Rigshospitalet, Denmark, from 2009 to 2012. In this period, all infertile women undergoing surgery due to endometriosis-related pain and/or large endometriomas

were routinely offered long-term GnRHa and ART, and were therefore candidates for study inclusion. Follow-up was performed in January 2019, 6-10 years after surgery, as part of internal treatment quality assurance. The study included 47 women meeting the following inclusion criteria: I) indication for endometriosis surgery, II) primary or secondary infertility, III) stage III-IV endometriosis according to the Revised American Society for Reproductive Medicine classification of endometriosis [10], IV) radical endometriosis surgery, including stripping of at least one endometrioma, V) histologically confirmed diagnosis, VI) indication for treatment with ART, VII) age 20-39 years and VIII) 18 kg/m^2 < BMI < 35 kg/m^2. Exclusion criteria: I) GnRHa treatment before surgery and II) medical conditions contraindicating participation. No women were excluded due to discontinuation of treatment or loss to follow-up.

Treatment

Intended radical laparoscopic surgery was performed by specialised gynaecologists. After an initial diagnostic evaluation of the abdominal cavity, pelvis adhesions were lysed. The ovaries were mobilised and after antimesenterial incision, surgical stripping of endometriomas was performed by traction and countertraction using atraumatic grasping forceps. Haemostasis was obtained by gentle use of bipolar coagulation. The ovarian incision was left unsutured. Any multiple and bilateral endometriomas were removed. All visible endometriotic tissue was removed.

After surgery, all women were treated with subcutaneous depot GnRHa goserelin 3.6 mg every 28th day from day one post-operatively for 3-6 months. Ovarian stimulation with highly purified human menotropin was initiated 14 days after the last goserelin administration, and an injection of human choriogonadotropin (hCG) was administered when three follicles reached ≥ 17-18 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 35-37 hours after hCG, and oocytes were fertilised by IVF or ICSI.

Endpoints

Study endpoints were characteristics and outcome of the first fresh IVF cycle immediately following combined surgery and long-term GnRHa: number of pre-ovulatory follicles, oocytes retrieved, embryos transferred, presence of non-responding ovary during high-dose gonadotropin stimulation, positive hCG, CPR and LBR. Clinical pregnancy was defined as ultrasonographically confirmed gestational sac(s) at six to seven weeks of gestation. Furthermore, cumulative LBR including pregnancies after ART as well as natural conceptions at follow-up were assessed.

Statistics

Analyses were performed using SPSS version 23. Demographics and baseline characteristics were provided by descriptive summary measures expressed as median and interquartile range or mean and standard deviation for continuous variables and number and percentage for categorical variables.

Ethics

The Danish Data Protection Agency approved the data handling in relation to the first IVF treatment and the first follow-up in 2014 (R. no. 2013-41-1953). The Executive Board of the Juliane Marie Centre at Rigshospitalet, approved the long-term follow-up by early 2019.

Trial registration: not relevant.

RESULTS

Baseline characteristics and surgery parameters are presented in **Table 1** and **Table 2**. On the day of surgery, 26/47 (55%) presented with unilateral and 21/47 (45%) with bilateral endometriomas, and all but one woman had additional peritoneal endometriosis. Thirteen (28%) women had previously been operated for endometrioma. Characteristics of the first fresh IVF cycle immediately following surgery and GnRHa treatment are presented in **Table 3**. Oocytes were successfully retrieved in 43/47 (91%) women, and a minimum of one embryo was transferred in 37/47 (79%). Twelve women (26%) had one non-responding ovary with no mature follicles after stimulation. In all but one of these cases, the woman had recent (9/11) or previous (2/11) surgery on the non-responding side. Three women (6%) developed pre-ovulatory follicle(s) in one ovary that was inaccessible for aspiration. Positive hCG and CPR after the first fresh IVF cycle was 11/47 (23%) and 7/47 (15%), respectively, and LBR was 7/47 (15%). In terms of cumulative LBR, **Table 4** summaries LBR by ART and natural conception at 6-10-year follow-up. We found that 31/47 (66%) women had more than one ART treatment (2-8) including two women receiving oocyte donation. At follow-up, 28 (60%) women had delivered as a result of ART and five (11%) by natural conception producing a cumulative LBR of 33/47 (70%).

TABLE 1 / Baseline characteristics of the 47 women included.

Age at surgery, median (IQR), yrs	33 (29-35)
BMI, median (IQR), kg/m^2	22 (20-24)
Regular menstrual cycles, n (%)	43 (92)
Duration of infertility, median (IQR), mo.s	27 (18-48)
Primary infertility, n (%)	36 (77)
Dysmenorrhea, n (%)	38 (81)
Dyspareunia, n (%)	15 (32)
Cancer antigen 125, preoperatively, median (IQR), kIU/l	48 (27-79)
Previous excision of endometrioma, n (%)	13 (28)

IQR = interquartile range.

TABLE 2 / Intraoperative findings and staging of endometriosis (N = 47).

Unilateral endometrioma, n (%)	
Single endometrioma	19 (73)
Multiple endometrioma	7 (27)
Subtotal	26 (55)
Bilateral endometrioma, n (%)	21 (45)
Diameter of excised endometrioma, median (IQR), mm	
Largest	40 (30-60)
Total diameter[a]	85 (59-100)
rAFS	
Score, median (IQR)	58 (38-86)
Endometriosis stage, n (%):	
Moderate	12 (25)
Severe	35 (75)
Additional endometriosis, n (%)	46 (98)
Peritoneal lesions	46 (98)
Bladder- or intestinal lesions	4 (9)

rAFS = The Revised American Society for Reproductive Medicine classification of endometriosis.
a) The sum of diameters when more than one endometrioma was present.

TABLE 3 / Assisted reproductive technology outcome after the first fresh in vitro fertilisation cycle following combined surgery and long-term gonadotropin-releasing hormone agonist treatment (N = 47).

Duration of treatment with GnRHa, median (IQR), mo.s	4 (3-6)
Duration of stimulation, median (IQR), days	11 (10-13)
Total dose of HP-HMG, median (IQR), IU	2,700 (2,250-3,250)
Cycles converted to IUI, n (%)[a]	4 (9)
Patients with oocyte retrieval, n (%)	43 (91)
Follicles for aspiration, median (IQR), n	6 (3-8)
Oocytes retrieved, median (IQR), n	4 (3-8)
Embryos, median (IQR), n	2 (1-3)
Patients with embryo transfer, n (%)	37 (79)
Embryos transferred, median (IQR) [mean ± SD], patients (%)	1 (1-2) [1.42 ± 0.55], 16 (34)
Patients with embryos cryopreserved	
Non-responding ovary, n (%)[b]	12 (26)
Contralateral surgery, n/N	3/12
Ipsilateral surgery, n/N	3/12
Bilateral surgery, n/N	6/12
Positive hCG, n (%)	11 (23)
Clinical pregnancies, n/N (%)	7 (15)
Live births per 1st	
Started stimulation, n (%)	7 (15)
Embryo transfer, n/N (%)	7/37 (19)

GnRHa = gonadotropin-releasing hormone agonist; hCG; human choriogonadotropin; HP-HMG = highly purified human menotropin; IUI = intrauterine insemination; SD = standard deviation.
a) ≥ 1 patent tube and < 3 follicles.
b) There were no cases with bilateral non-responding ovaries.

TABEL 4 / Live birth rate by assisted reproductive technology or natural conception per cycle at 6-10-year follow-up.

	ART cycles, n				
	1	2	3	⟩3	total
Women, n	47	31[a]	25	15	47
Live birth after ART, n (%)					
Fresh ART	7 (15)	4 (13)	8 (32)	3 (20)	22 (47)
Frozen ART	3 (6)	1 (3)	-	-	4 (9)
Oocyte donation	-	-	-	2 (13)	2 (4)
Natural conceptions[b], n (%)	1 (2)	1 (3)	2 (8)	1 (7)	5 (11)
Cumulative live birth rate, n (%)	11 (23)	17 (36)	27 (57)	33 (70)	33 (70)

ART = assisted reproductive technology.
a) 5 women were excluded due to missing data on number of ART cycles undergone, 0 of these women had given birth at follow-up.
b) Natural conception after the 1st, 2nd, 3rd or higher number ART cycle.

Discussion

The main finding of this study was that infertile women with endometrioma(s) and moderate-severe endometriosis undergoing intended radical laparoscopic surgery immediately followed by long-term GnRHa downregulation and IVF had a modest LBR after the first fresh cycle (15%). However, the cumulative LBR after 6-10 years was 70%, indicating that immediate post-operative GnRH downregulation may not be efficient with regards to the first fresh cycle, but that appropriate ART cycles subsequently provide a good prognosis.

The cumulative LBR of our study is in line with the results of a large Danish national cohort study reporting a cumulative LBR of 80% after five years in women aged 35 years or younger initiating treatment with ART regardless of cause of infertility [11]. A summary report from the Society for Assisted Reproductive Technology demonstrated similar results for women with endometriosis-associated infertility (61-82%) [12].

To our knowledge, only one other group, Sõritsa et al [13] has investigated the effect of laparoscopic surgery immediately followed by long-term GnRHa downregulation from day one post-operatively and IVF on pregnancy outcome in women with moderate-severe endometriosis. The general characteristics of our populations were comparable in terms of age, BMI and regularity of menstruation. Duration of infertility was longer in Sõritsa's cohort, whereas the rate of primary infertility was lower. The prevalence of endometrioma(s) was 32/58 (55%) compared to 47/47 (100%) in our study. After an average of 1.4 IVF treatments, Sõritsa et al reported an LBR (52%) markedly above the LBR (15%) after the first fresh cycle found in our study. Sõritsa did not report data specifically from the first cycle. The differences in LBR may partly be explained by a lower prevalence of endometrioma in Sõritsa's cohort. In a retrospective cohort study, Ophøien et al found a

significantly lower CPR and LBR in women with endometrioma than in women without endometrioma [8]. In contrast, a recent systematic review reported no negative impact on ART of either the presence or the removal of endometrioma on LBR [7]. It was recently suggested that long-term GnRHa prior to ART may negatively affect the outcome of the first fresh cycle [4]. Long-term GnRHa treatment causes a profound suppression of serum luteinizing hormone (LH) levels, which may affect theca cell androgen synthesis and thereby follicular health [14, 15], as androgens play an important physiological role in follicle development at all stages [16]. To compensate for LH suppression, we stimulated women with highly purified human menotropin in order to add LH activity.

The modest immediate LBR after fresh transfer found in our study may, in part, be explained by the phenomenon of post-operative recovery begetting non-responding ovaries. We saw a non-responding ovary in one fourth of the IVF cycles immediately following treatment, predominantly on the ipsilateral side as cyst resection. Only one woman had a non-responding ovary without having had recent or previous surgery on that side. Ovarian recovery after surgery is commonly assessed by post-operative measurements of anti-Müllerian hormone. Evaluation of serum levels over time indicates a persistent reduction in anti-Müllerian hormone after excision of endometriomas [17], raising concern that surgery may cause permanent damage to the ovarian reserve. Also, the risk of unintentional removal of ovarian stroma in laparoscopic cystectomy for endometriomas compared with dermoid cysts has been reported to be significantly higher in the former [18]. However, a recent meta-analysis comparing surgery versus no treatment of ovarian endometrioma found no differences between groups in pregnancy outcome after ART [6]. In our case, the primary purpose of surgery was not to increase the chances of achieving pregnancy but to relieve endometriosis-associated pain as is current clinical practice [2, 5].

To our knowledge, the evidence of a positive effect of long-term GnRHa before ART for endometriosis-associated infertility has been described in one meta-analysis [1] and one review [19] based on few heterogenic studies of older date, varying quality and outcome measures, only. It should therefore be emphasised that robust evidence in favour of long-term GnRHa downregulation before ART is lacking. As described below, this study too suffers from a number of limitations. However, our data imply a hampering effect of long-term downregulation with GnRHa immediately after surgery on the first fresh IVF cycle, although a reasonable cumulative LBR seems to be maintained. This is in line with the results of a recent study proposing that the short-term negative effect on implantation by long-term administration of GnRHa may be outbalanced by a positive long-term effect [4]. Taking this into account, treatment with oral contraceptive pills, gestagen or even no medical treatment in a period post-operatively before ART could be therapeutic alternatives. Prospective randomised studies on the subject are highly needed. Furthermore, surgical intervention studies with longer periods of follow-up to determine I) the extent of post-operative damage on ovarian tissue following cystectomy, and establish II) whether the damage is transient or

permanent are highly warranted.

Limitations to this study include the retrospective design with its inherited risk of bias, the modest size of the study population, the length of the study period and the lack of a control group. The sample size of the study was limited by several factors, including the rare occurrence of women with stage 3-4 endometriosis and a wish for long-term GnRHa downregulation before IVF. For a deeper understanding of the impact of GnRHa on IVF outcomes, a control group not receiving GnRHa prior to IVF would have been highly desirable. Selection bias was minimised by offering all women the same treatment strategy and by including all women accepting to receive this treatment during the four years of inclusion in the present study. The strengths of this study are that all surgical procedures were performed in a single surgical team at one of the two national referral centres for endometriotic surgery in Denmark.

CONCLUSIONS

We found that infertile women with endometrioma(s) treated with radical surgery and long-term GnRHa downregulation immediately prior to IVF had a modest LBR after the first cycle. This may be the result of immoderate suppression of ovarian function or reduced ovarian function due to surgery. However, 6-10 years after surgery, 70% of the women had delivered, corresponding to general results after ART.

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