



Endometriosis reduces ovarian response in controlled ovarian hyperstimulation independent of AMH, AFC, and women's age measured by follicular output rate (FORT) and number of oocytes retrieved

Kristin Nicolaus¹ · Dominik Bräuer¹ · Robert Sczesny¹ · Jorge Jimenez-Cruz^{1,2} · Klaus Bühler¹ · Ines Hoppe¹ · Ingo B. Runnebaum¹

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Abstract

Purpose To determine the influence of endometriosis on the ovarian response during controlled ovarian hyperstimulation measured by number of oocytes retrieved and the follicular output rate (FORT).

Methods A retrospective, single center study included 96 women, who underwent ICSI treatments for male factor infertility according to World Health Organisation between 2016 until 2018. A total of 96 patients were included in the study with 205 fresh ICSI cycles. The study group included 26 patients with endometriosis after surgical and medical treatment; the control group included 70 patients without endometriosis. The women with endometriosis underwent 47 and the control group 158 ICSI cycles. Women underwent fresh intracytoplasmic sperm injection cycles after controlled ovarian hyperstimulation following a GnRH-antagonist protocol. The FORT was calculated as the ratio of pre-ovulatory follicle count \times 100/small antral follicle count at baseline.

Results A lower number of retrieved oocytes (5.89 vs. 7.25, $p=0.045$), lower FORT (75.67 vs. 94.63, $p=0.046$), lower number of metaphase II oocytes (4.87 vs. 6.04, $p=0.046$), and lower fertilization rate after intracytoplasmic sperm injection (40.61 vs. 57.76, $p=0.003$) were found in women with endometriosis compared to women without endometriosis. The number of oocytes retrieved was 0.71 lower in the group with endometriosis than in the group without ($p=0.026$). The FORT was 24.55% lower in the group with endometriosis ($p=0.025$).

Conclusions Endometriosis reduces the FORT and the number of metaphase-II oocytes after controlled ovarian hyperstimulation independently of women's age, antral follicle count and anti-Müllerian hormone.

Keywords Endometriosis · Follicular output rate · Ovarian response · Retrieved oocytes · Controlled ovarian hyperstimulation

Introduction

Endometriosis is defined as the presence of endometrial-like tissue outside the uterine cavity. Endometriosis induces a chronic inflammatory reaction, adhesions, and scar tissue [1]. It is one of the most common gynecological disorders occurring in 10–15% of women of reproductive age. Endometriosis occurs more often in infertile women, with a prevalence of 25–40% [2, 3]. However, the mechanism of endometriosis associated with infertility remains incompletely understood. Distorted pelvic anatomy, impaired ovarian function, altered microenvironment, affected endometrial

✉ Ingo B. Runnebaum
direktion-gyn@med.uni-jena.de

¹ Department of Gynecology and Reproductive Medicine, University Women's Hospital Jena, Jena University Hospital, Friedrich-Schiller-University Jena, Am Klinikum 1, 07747 Jena, Germany

² Present Address: Department of Obstetrics and Prenatal Medicine, University Women's Hospital Bonn, Bonn, Germany

receptivity, and embryo quality have been researched as possible implicators [4, 5].

Assisted reproductive technology (ART) is known to be the most effective therapy for infertility associated with endometriosis and endometriosis represents an increasing indication for (ART) [6, 7]. Women's age also shows an increasing trend for using ART, in 2017 women were on average 35.7 years old in Germany [8]. The numerous in vitro fertilization (IVF) stimulation protocols facilitate the application of individually tailored treatments for example in endometriosis and at advanced reproductive age. The success of IVF largely depends on the number and quality of retrieved oocytes following controlled ovarian hyperstimulation (COH).

Various methods of assessing the ovarian reserve have been used in clinical practice, including measurement of baseline follicle stimulating hormone (FSH) levels, number of antral follicle count (AFC) measured by ultrasonography, and estimation of anti-Müllerian hormone (AMH) levels [9–11]. Assessment of ovarian reserve in women with endometriosis undergoing COH has been an important problem as women with endometriosis have a lower ovarian reserve and higher basal FSH level than women without endometriosis [12, 13]. Even mild stages of endometriosis may have negative effects on oocyte development, embryogenesis, or implantation [14–16]. The outcome of IVF in patients with revised classification of the American Society of Reproductive Medicine (rASRM) stage IV endometriosis was significantly lower compared to age-matched patients with tubal-factor infertility. This was a result of higher cycle cancellation rates and lower oocyte yield in the former [17]. Ovarian sensitivity to gonadotropins differs between patients and it plays an important role on ovarian response. An efficient quantitative and qualitative marker for ovarian responsiveness to gonadotropins, especially for low responder, presents the follicular output rate (FORT) [18].

In addition to the number of oocytes, the maturity of the oocyte plays a decisive role in the success of an ART. The exact evaluation of the metaphase II (MII) oocytes is performed as part of an intracytoplasmic sperm injection (ICSI) treatment. However, studies on endometriosis and ART success usually only consider IVF treatments. Some authors argue that the application of intracytoplasmic sperm injection (ICSI) technology may have a positive effect on endometriosis and fertility [6].

The present study was undertaken to compare ovarian response in COH of women with endometriosis to those without endometriosis to provide further evidence of the influence of endometriosis on ovarian response and maturity of retrieved oocytes.

The FORT Index should be used to assess ovarian response in order to examine this particular low responder collective in more detail and in contrast to current studies,

women of advanced age should not be excluded. Only ICSI treatments should be specifically examined to assess the oocyte maturity.

Materials and methods

Study population and inclusion criteria

All fresh ICSI cycles carried out following controlled ovarian stimulation in the Department of Gynaecology and Reproductive Medicine, Jena University Hospital, and with AMH concentration recorded, were retrospectively identified between January 1st 2016 and June 30th 2018.

The inclusion criteria for this study included the following factors: primary male factor infertility for ICSI indication based on the WHO 2010 criteria; women aged ≤ 43 years; and ovarian hyperstimulation following a GnRH-antagonist protocol. Exclusion criteria included: cycles using frozen sperm samples; mild ovarian stimulation cycles; natural cycles and the existence of ovarian involvement of endometriosis.

Ninety-six women underwent 205 ICSI cycles in this period. Patients with symptoms such as pelvic pain and dysmenorrhea underwent a diagnostic laparoscopy prior to ICSI. Endometriosis was diagnosed in 26 patients by laparoscopy after histological confirmation within the last 12 months. Complete resection of the endometriosis was also performed intraoperatively. Postoperatively, the patients received Dienogest, 2 mg daily per os until assisted reproductive technology (ART) treatment or ART treatment was carried out directly in the following cycles.

Ovarian response to controlled ovarian hyperstimulation was measured by the number of retrieved oocytes and by follicular output rate (FORT). The Follicular Output Rate was calculated as the ratio of pre-ovulatory follicle (16–22 mm in diameter) count on day of human chorionic gonadotropin $\times 100$ /small antral follicle (3–8 mm in diameter) count at baseline:

$$\text{FORT} = \frac{\text{preovulatory follicle count on dhHCG}}{\text{antral follicle count at baseline}} \times 100.$$

Follicles 16–22 mm in diameter were considered for the calculation of FORT on the basis of an investigation by Genro et al. [19]. Serum AMH was measured within 3 months prior to ovarian stimulation. If the surgical therapy of the endometriosis was performed before (no surgery on the ovary, as endometriomas were excluded), the AMH determination was updated before the start of the stimulation. Hormone assaying was performed at the time of oocyte retrieval, and the basic values for FSH were assayed at the time of the basal

antral follicle count. The number of basal antral follicles was counted at day 2 or 3.

Ovarian stimulation protocol

A controlled ovarian hyperstimulation protocol was initiated following lack of confirmation by ultrasound of any naturally growing follicle greater than 10 mm in diameter. Oral contraceptives were not used for cycle initiation.

Ovarian hyperstimulation was commenced on day 2 or 3 of the cycle with daily subcutaneous injections of recombinant human FSH (follitropin α —Gonal F[®], Merck Serono or follitropin β —Puregon[®], MSD) and/or urinary human menopausal gonadotropin (menotropin—Menogon HP[®], Ferring Pharmaceuticals) or mixed recombinant human FSH/luteinising hormone (Pergoveris[®], Merck Serono) with a starting dose of 87.5–250 IE/day. The short protocol with a GnRH-antagonist implied the use of ganirelix (Orgalutran[®], MSD) at a daily dose of 0.25 mg from the sixth day of stimulation until the end of stimulation. Ovarian hyperstimulation was monitored by transvaginal ultrasonographic monitoring of follicular growth and endometrium thickness and by determining serum estradiol and Luteinising hormone levels.

Recombinant human chorionic gonadotropin (Ovitrelle, Merck Serono) was administered subcutaneously in a single 250 μ g dose when a dominant follicle reached a diameter of 16 mm or greater. Ultrasound-guided transvaginal follicle aspiration was performed approximately 35–36 h later under local or general anesthesia.

Selection of the protocols depended on the age and AMH as well as AFC, body mass index (BMI), and FSH levels.

Statistical analysis

The statistical analysis was performed with SPSS ver. 25 (SPSS Inc., Chicago IL USA). Comparisons of continuous data between the two groups were performed using the non-parametric Mann–Whitney *U* test or the parametric unpaired *t* test based on data distribution. Mean \pm SD are presented for each group to describe the data. Fisher's exact test was applied to compare categorical data between the groups. Absolute and relative frequencies are reported for both groups. The multivariate linear regression analysis was performed in order to investigate independent variables associated with the number of oocytes retrieved and FORT. A *p* value of <0.05 was considered statistically significant.

Ethical approval

This research project was covered by the study approval for data use and clinical studies of the General Ethics Commission, Faculty of Medicine, Jena University Hospital, Germany (no. 2018-1073). An additional ethical

approval from the Ethics Commission of the Faculty of Medicine, Jena University Hospital, Germany, was not required because the analysed data were anonymised. A declaration of consent of the patients is available.

Results

The study included 96 patients who underwent 205 cycles of ICSI. In addition to male factor infertility, female causes of infertility included an advanced age of >35 years ($n=62$, 30.3%), tubal infertility ($n=19$, 9.3%), and endometriosis ($n=47$, 22.9%). Sixty-two (30.2%) women were older than 35 years, and 33 (16.1%) were older than 38 years.

Patients with endometriosis ($n=26$) underwent 47 cycles (group I) and patients without endometriosis ($n=70$) underwent 150 cycles (group II). Stages of endometriosis in all cycles included: 12.2% ($n=25$) with rASRM I + II, 8.3% ($n=17$) with rASRM III + IV, and 6.3% ($n=13$) with deep infiltrated endometriosis.

There was no significant difference in age, age at menarche, average menstrual cycle length, BMI, duration of infertility, or type of infertility between group I and group II. There was also no significant difference in serum AMH level, basal FSH level, Thyroid-stimulating hormone level, and AFC (Table 1).

There was no significant difference in the duration of stimulation, starting dose of gonadotropins, total recombinant FSH dose, and mean serum estradiol level on the day of follicle aspiration as well as pre-ovulatory follicle count (16–22 mm) (Table 2). However, the FORT (75.67 vs. 94.63, $p=0.046$), number of oocytes retrieved (5.89 vs. 7.25, $p=0.045$), number of metaphase II oocytes (4.87 vs. 6.04, $p=0.046$), and the fertilization rate (40.61 vs. 57.76, $p=0.003$) were significantly lower in group I than group II (Table 2). The cancellation rate was similar in both groups (7.5% vs. 5.7%, $p=0.16$).

Comparing patients with endometriosis stage I/II to those with stage III/IV (as classified by ASRM) there was no significant difference in the number of retrieved oocytes (5.8 vs. 6.1, $p=0.81$), metaphase-II oocytes (4.8 vs. 4.7, $p=0.91$), and FORT (76.3% vs. 72.3%, $p=0.89$).

As shown in Tables 3 and 4, multivariate linear regression analysis demonstrated that the number of retrieved oocytes, FORT and endometriosis was not associated with covariates as women's age, AFC, and AMH. The number of oocytes retrieved was on average 0.7 lower in the endometriosis group than in the group without endometriosis ($p=0.026$). FORT was on average 24.6% lower in the endometriosis group compared to the control group ($p=0.025$).

Table 1 Clinical characteristics of women with endometriosis (group I) and women without endometriosis (group II) undergoing ICSI

	Group I (endometriosis)	Group II (no endometriosis)	<i>p</i> value
No. of cycles	47	158	
<i>Age (years)</i>			
Mean	33.04 ± 4.4	32.96 ± 4.3	0.918
Median	33	33	0.318
Age ≤ 35 years	33	110	0.938
Average menstrual cycle length (days)	29.85 ± 9.7	30.34 ± 13.2	0.813
Age at menarche	12.74 ± 1.3	12.48 ± 1.44	0.25
BMI (kg/m ²)	23.22 ± 4.6	24.29 ± 4.7	0.169
Duration of infertility (months)	44.06 ± 31.8	34.87 ± 24.5	0.07
Type of infertility			0.388
Primary	41	128	
Secondary	6	30	
<i>AMH (ng/ml)</i>			
Mean	2.33 ± 1.6	2.79 ± 2.2	0.180
Median	1.7	2.24	0.068
Basal FSH (IU/l)	6.74 ± 2.3	6.39 ± 2.9	0.395
Thyroid stimulating hormone (mU/l)	1.58 ± 0.7	1.73 ± 0.8	0.237
<i>AFC</i>			
Mean	11.80 ± 5.1	10.90 ± 5.6	0.319
Median	10.00	9.50	0.313

Data are presented as median, mean ± standard deviation, analysed using the Fisher exact test

Table 2 Parameters of ovarian stimulation of women with endometriosis (group I) and without endometriosis (group II) undergoing ICSI

	Group I (endometriosis)	Group II (no endometriosis)	<i>p</i> value
Starting dose of recomb. FSH (IE)	171.54 ± 56.1	174.44 ± 45.2	0.746
Total dosage of recomb. FSH (IE)	1757.71 ± 583.0	1965.58 ± 1827.2	0.444
Duration of stimulation (day)	10.1 ± 2.3	10.19 ± 2.2	0.805
Pre-ovulatory follicle (16–22 mm) count	7.97 ± 5.4	8.70 ± 5.8	0.448
FORT (%)	75.67	94.63	0.046
Mean serum estradiol level on day of follicle aspiration (pmol/l)	3772.88 ± 2993.6	3334.67 ± 2349.1	0.295
Number of oocytes retrieved	5.89	7.25	0.045
Number of metaphase II oocytes	4.87	6.04	0.046
Fertilization rate %	40.61	57.76	0.003

p value < 0.05 in bold

Data are presented as mean ± standard deviation or as percentage, analysed using the Fisher exact test

Discussion

The influence of endometriosis on the outcome of assisted reproductive technology is controversial. The success of IVF largely depends on the number and quality of oocytes retrieved following COH. Assessment of ovarian reserve in women with endometriosis undergoing COH is an important problem as women with endometriosis have a lower ovarian reserve and a higher rate of cycle cancellation than women without endometriosis [20]. A reduced ovarian

response to gonadotropins, lower oocyte yield, and poor clinical pregnancy rate per cycle have all been described as well [17].

The our study was undertaken to compare ovarian response in COH of women with endometriosis to those without endometriosis. The FORT Index should be used to assess ovarian response in order to examine this particular low responder collective in more detail and in contrast to current studies, women of advanced age should not be excluded.

Table 3 Multivariate linear regression analysis of factors potentially associated with the number of oocytes retrieved

	<i>B</i>	SE	<i>p</i> value
Age	−0.271	0.031	0.390
Endometriosis (yes vs. no)	0.714	0.318	0.026
BMI (kg/m ²)	−0.006	0.031	0.842
AMH (ng/ml)	0.076	0.074	0.304
FSH (IU/l)	−0.054	0.051	0.291
AFC	−0.033	0.031	0.286
Pre-ovulatory follicle (16–22 mm) count	0.775	0.024	<0.001

p value <0.05 in bold

Linear regression parameters: *B* is the estimated regression coefficient, SE the standard error of the coefficient

Table 4 Multivariate linear regression analysis of factors potentially associated with FORT

	<i>B</i>	SE	<i>p</i> value
Age	−2.089	1.058	0.050
Endometriosis (yes vs. no)	24.554	10.860	0.025
BMI (kg/m ²)	−2.974	0.983	0.003
AMH (ng/ml)	−5.212	2.245	0.021
FSH (IU/l)	0.480	1.675	0.775

p value <0.05 in bold

Linear regression parameters: *B* is the estimated regression coefficient, SE the standard error of the coefficient

In the present study patients with endometriosis demonstrated similar levels of AMH, basal FSH, and AFC prior to COH as patients without endometriosis. Thirty percent of women in the present study were older than 35 years, and 16.1% were older than 38 years. Most studies only included women up to the age of 38 years. But the advanced women's age represents an increasing indication in the ART treatment. Advanced age and endometriosis are risk factors for the failure of oocyte retrieval in infertile patients undergoing IVF treatment [21]. Gonadotropin stimulation was similar for the endometriosis group and for those without with regard to starting dose, duration of stimulation, and total dosage of rFSH.

However the number of oocytes retrieved was significantly lower for patients with endometriosis than for those without endometriosis (5.89 vs. 7.25, $p=0.045$). This result is in agreement with previous studies. Dong et al. [22] found that patients with endometriosis responded worse to ovarian stimulation than patients with tubal factors. The group reported longer duration, higher dosage of gonadotropins and a lower number of retrieved oocytes. Barnhart et al. [23] reported a significantly lower number of oocytes retrieved, lower fertilization rate, lower implantation rate, and lower

pregnancy rates in women with endometriosis compared to women with tubal factor who underwent IVF.

The number of oocytes retrieved in similar stimulation protocols is dependent on the ovarian reserve. This can be measured by for example the antral follicle count. The final number of pre-ovulatory follicles obtained at COH however, does not truly reflect the sensitivity of the antral follicle to FSH, as this is greatly influenced by the number of small antral follicles available before treatment. This number of antral follicles differs between patients. Women with polycystic ovary syndrome for example have a higher AFC than women without polycystic ovary syndrome or patients after an excision of ovarian tissue. To accommodate this, FORT was defined by Genro et al. [19]. FORT is an efficient quantitative and qualitative marker for ovarian responsiveness to gonadotropins, especially for low responder [18]. Patients with endometriosis showed a significantly lower FORT than patients without endometriosis (75.67 vs. 94.63, $p=0.046$). In the multivariate regression analysis, we showed that endometriosis was negatively associated with FORT (−0.154, $p=0.025$) and the number of oocytes retrieved (−0.061, $p=0.026$). Although patients with endometriosis showed a similar AMH to the control group in our study, they responded significantly worse to gonadotropin stimulation (with the same stimulation duration and dose) by developing a lower final number of pre-ovulatory follicles and obtaining fewer oocytes. Patients with endometriosis have a disturbed FSH sensitivity at the antral follicles and therefore show less response to COH despite the same reserve.

In addition to the number of oocytes retrieved, their quality and maturity are also important for ART success. In the present study, the maturity of oocytes was examined as we performed ICSI due to primary male factor infertility. We observed that the group with endometriosis had a significantly lower number of metaphase-II oocytes than the group without endometriosis (4.87 vs. 6.04, $p=0.046$). There is evidence suggesting that impaired oocyte quality may be responsible for endometriosis-associated infertility [24]. Ashrafi et al. observed in a prospective cohort study a significantly lower number of metaphase-II oocytes in women with endometriomas as compared with a control group [25]. The quality of the embryos obtained and clinical pregnancy rates were comparable.

With regards to the endometriosis stage-related ovarian response, there were no differences in the number of oocytes retrieved, metaphase-II oocytes, and FORT between rASRM stage I and II to III and IV. Safdarian et al. showed that patients with stage III and IV endometriosis had less oocytes than controls (7.27 vs. 9.44, $p=0.001$) [26].

Also, the fertilization rate was significantly lower in the group with endometriosis (40.61 vs. 57.76, $p=0.003$). This result is similar to that described by Senapati and Harb et al. [27, 28]. They both showed a significant decrease in

fertilization rate, number of embryos obtained, and number of day 3 high-quality embryos on patients with moderate endometriosis. Even mild stages of endometriosis may have negative effects on oocyte development, embryogenesis or implantation [13–15]. Despite poorer ovarian response, reduced fertilization rate, and impaired implantation in moderate and severe cases, patients with endometriosis obtain comparable IVF/ICSI success rates to patients with infertility due to tubal factors. The combination of aggressive COH and efficient surgery before ART appeared crucial for IVF/ICSI success [20].

The data were comparable however this study has several limitations that need to be addressed. First, the retrospective and monocentric case–control design has inherent biases which cannot be excluded in this study (mainly selection bias). Another limitation of the study is the fact that not all patients in the control group underwent laparoscopy. Therefore, we cannot definitively confirm the absence of endometriosis. Only women with dysmenorrhea and pelvic pain received a laparoscopic investigation. Also, women underwent laparoscopy in the past due to ovarian cysts or appendectomy for example but no endometriosis was reported.

Conclusions

Women with endometriosis produced significantly lower numbers of oocytes, a lower follicular output rate and lower metaphase-II oocytes independently of AMH, AFC and women's age.

Although ART procedures have been successful for infertile women with endometriosis, poor results can still be expected. In summary, compared with women who do not have endometriosis, the current study showed that patients with endometriosis responded worse to ovarian hyperstimulation as indicated by lower number of oocytes retrieved and lower FORT index, which is an efficient quantitative and qualitative marker for ovarian responsiveness to gonadotropins, especially for low responder. In addition, patients over the age of 38 were included to reflect the current ART treatment population and the response markers are independently of women's age. The special consideration of ICSI treatments allowed an additional detailed assessment of oocyte maturation.

In conclusion our study provided accurate information regarding ovarian response in COH and ART success for women with endometriosis. Our results could be used in clinical practice to inform and counsel couples before ART, especially for patients with advanced age.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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