Ovarian reserve assessment in women with different stages of pelvic endometriosis

Ocena rezerwy jajnikowej u kobiet z endometriozą miednicy mniejszej

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Abstract

Introduction: *Endometriosis is defined as the appearance of ectopic endometrial cells outside the uterine cavity. Ectopic cells demonstrate functional similarity to eutopic cells, but structural and molecular differences are significant and manifest themselves in gene expression of the metalloproteinase genes, integrin or the Bcl-2 gene. Pelvic pain remains to be the main symptom of the disease. Endometriosis may cause dysfunction of the reproductive system and lead to infertility. Pathogenesis of infertility in endometriosis is based on its influence on the hormonal, biochemical and immunological changes in the eutopic endometrium, as well as structural damages of the ovaries and the fallopian tubes.*

Objectives: *The aim of the study was to assess the ovarian reserve in patients with endometriosis.*

Material and methods: *A total of 39 patients (aged 22-34 years) with different stages of endometrial changes were recruited for the study. The number of antral follicles was rated by vaginal ultrasonography and the level of FSH was measured between days 1-3 of the menstrual cycle. The stage of the disease was established after laparoscopy with the rASRM scale.*

Results:*No statistically significant correlation between the number of follicles(AFC), the level of FSH and the stage of endometriosis was found.*

Conclusions: *Evaluation of the number of antral follicles and measurements of the FSH level do not allow to predict the ovarian reserve in women with endometriosis.*

Key words: **endometriosis** / **ovarian reserve** / **FSH** / **infertility** /

Streszczenie

Wstęp: *Endometrioza charakteryzuje się występowanie ektopowego endometrium poza jamą macicy. Jego komórki wykazują funkcjonalne podobieństwo do komórek eutopowego endometrium, jednak wykazują zmiany strukturalne i molekularne dotyczące np. ekspresji genów kodujących metaloproteinazy, integryny, Bcl-2. Schorzenie to obok różnego typu dolegliwości bólowych może powodować poważne zaburzenia w funkcjonowaniu układu rozrodczego i prowadzić do niepłodności. Ograniczenie żeńskiej płodność tłumaczy się wpływem endometriozy na funkcjonowanie układu hormonalnego, immunologicznego, biochemicznymi zmianami w obrębie eutopowego endometrium oraz uszkodzeniem struktury jajowodów i jajników.*

Cel: *Celem pracy jest ocena rezerwy jajnikowej u pacjentek z endometriozą miednicy mniejszej.*

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Materiał i metody: *Do badania zakwalifikowano 39 pacjentek w wieku rozrodczym (22-34 lata), u których na podstawie badania ultrasonograficznego lub objawów klinicznych podejrzewano istnienie endometriozy w miednicy mniejszej. Przed zabiegiem operacyjnym ceniono ultrasonograficznie liczbę pęcherzyków antralnych oraz oznaczono poziom FSH pomiędzy 1 a 3 dniem cyklu. Rozpoznanie i stopnień zaawansowania endometriozy ustalono laparoskopowo. Zastosowano skalę zaawansowania wg rASRM.*

Wyniki: Nie potwierdzono istotnej statystycznie zależności pomiędzy liczbą pęcherzyków antralnych (AFC), poziomem FSH oraz stopniem zaawansowania endometriozy miednicy mniejszej.

Wnioski: *Ocena liczby pęcherzyków antralnych oraz oznaczenie poziomu FSH nie pozwala na prognozowania rezerwy jajnikowej u kobiet z endometriozą miednicy mniejszej.*

Słowa kluczowe: **endometrioza** / **rezerwa jajnikowa** / **FHS** / **niepłodność** /

Introduction

Endometriosis is a chronic disease which affects a steadily increasing number of women of childbearing age. The disease is characterized by the occurrence ofectopic endometrialcells outside the uterine cavity. Although the formation of endometriosis remains to be fully elucidated, numerous authors [1-5] accept the theory that eutopic endometrial cells penetrate the abdominal cavity through the fallopian tubes (the transplantation theory, Sampson 1927 [1]. In that cavity, a series of biochemical, genetic and immunological changes occur, enabling cell adhesion to the peritoneum and their subsequent growth by inhibiting apoptotic processes through, among others, the Bcl-2 gene [2, 3]. Modulation of E-cadherin expression and the increase of mitotic processes of the eutopic endometrial cells additionally facilitate the growth of the cells and increase their invasiveness. However, recent findings have undermined the transplantation theory by suggesting *de novo* formation of endometriotic foci [5]. Depending on the location and the clinical stage, endometriosis may negatively influence the homeostasis of an organism, especially fertility. The issue of fertility disorders is tackled here on many levels: structural damages in the ovarian endometriosis (damaged ovarian cortex, reduced number of antral follicles [6, 7], post-inflammatory adhesions), and functional/hormonal disorders including ovulatory dysfunctions[8]. Fertility analysis comprises of extensive evaluation of the ovarian reserve, i.e. hormonal tests and ultrasonographic assessment of the ovaries [9, 10].

Measurement of FSH (F ollicle Stimulating Hormone) levels is of key importance in patients under 35 years of age with anovulatory cycles and in patients with diagnosed endometriosis preparing for ART (Assisted Reproductive Technology) [11, 12]. Numerous studies showed that FSH in blood serum corresponds with response to ovulation stimulations [13, 14, 15, 16].

In a study by Erdem et al., elevated levels of FSH in the early follicular phase were indicated in women poorly responding to stimulation [13, 14]. Additional AFC (Antral Follicle Count) measurements significantly increase the possibility of predicting response to stimulation in infertile women, since the number of follicles of 2-10 mm in diameter is directly proportional to the ability of responding to hormonal stimulation [13, 14, 17]. A high number of antral follicles in the ovary increases the chances for live birth [18, 19, 20] and conception in general [21]. Some authors suggest that AFC measurements are of the same prognostic value as hormonal and biochemical evaluation in patients preparing for IVF [22].

AMH (anti-Müllerian hormone) measurements, vastly applied and recognized as the basis for hormonal diagnosis of infertility, have not been clearly confirmed in tests on the reserve assessment in patients with endometriosis [23]. FSH receptor expression disorders have been revealed in patients with endometriosis who underwent IVF as compared to women without the ovarian infertility factor [12].

Objectives

The aim of the study was to assess the influence of endometriosis on the ovarian reserve in patients prepared for laparoscopic treatment atthe Department of Gynecology and Oncology, Krakow University Hospital. The study included 39 women (aged between 22-34 years), who were attempting to conceive. The subjects were divided into subgroups depending on the endometriosis stage according to the rASRM scale (American Society for Reproductive Medicine revised Classification of Endometriosis).

Material and methods

The study was conducted in a group of patients, aged 22-34 (n-39), with ovarian endometriosis, qualified for a laparoscopic removal of endometrial lesions at the Gynecology and Oncology Clinic, Krakow, between 2011-2012.

Before the surgery all patients had undergone assessment of the ovarian reserve. The Bioethics Committee of the Jagiellonian University Medical College approved of the study. The exclusion criteria were: history of laparotomy and/or inflammation in the small pelvis, oral contraceptive use and pregnancy.

All patients underwent a vaginal ultrasonography examination with volumetric intravaginal transducer 2D/3D/4D 5-9 MHz of Voluson E6 apparatus in order to confirm the presence and estimate the size of the endometrial cysts, as well as to measure AFC. A 3D SonoAVC (Automated Volume Calculation) technology of GE Healthcare Voluson E6 BT12 apparatus and program 4D view 10.5 were used for the assessment of the antral follicles. The basal levels of FSH on days1-3 of the cycle were also established.

The patients were divided into groups corresponding to the severity of the disease: stages I and II (n-5), stage III(n-25) and IV (n-8). Qualification to the above mentioned severity groups occurred during the laparoscopic procedure.

Patient characteristics:

Statistical analysis

The normality of quantitative data distribution was evaluated on the basis of skewness parameters and the results of the Kolmogorov–Smirnov distribution normality test. In order to compare qualitative variables, a chi-squared test was used. In cases when the expected count was ≤ 5 at least in one group, Fisher's exact test was applied. In all analyses the significance level of $\alpha=0.05$ was adopted. The calculations were done with MS Excel Sheet and statistical suit SPSS Statistics 17.0.

Patients characteristics:

Mean number of antral follicles: right ovary	10.49
Median	11.00
Standard deviation	6.585
Mean number of antral follicles: left ovary	9.15
Median	9.0
Standard deviation	6.761

FSH level	
Mean	7.8495
Median	6.4000
Standard deviation	4.35540
Minimum	2.73
Maximum	22.77

Stage of endometriosis progression				
	Frequency	Percent	Valid percent	Cumulative percent
first/second stage	5	12.8	12.8	12.8
third stage	26	66.7	66.7	79.5
fourth stage	8	20.5	20.5	100.0
Total:	39	100.0	100.0	

BMI		
N	Valid	39
	Lack of data	0
Mean	21.2201	
Median	21.2953	
Standard deviation	2.16529	
Skewness	0.764	
Standard error skewness	0.378	
Minimum	17.65	
Maximum	27.92	

Age	
Mean	28.74
Median	29.00
Standard deviation	3.552
Minimum	22
Maximum	34

Left ovary lesion diameter [mm]		
N	Valid	24
	Lack of data	15
Mean	41.92	
Median	40.00	
Standard deviation	14.631	
Skewness	0.030	
Standard error skewness	0.472	
Minimum	15	
Maximum	70	

Right ovary lesion diameter [mm]		
N	Valid	21
	Lack of data	18
Mean	37.52	
Median	37.00	
Standard deviation	13.556	
Skewness	0.035	
Standard error skewness	0.501	
Minimum	18	
Maximum	60	

Results

No statistically significant correlation between the ovarian reserve (evaluated with FSH and AFC) and the stage of endometriosis progression ($p>0.05$) was revealed in the investigated groups of patients (n-39) (Tables I and II).

Both, the changes in the number of antral follicles in the ovaries and the oscillations of FSH levels did not vary in relation to the stage of endometriosis progression (Table III).

The results suggest an equivocal influence of ovarian endometriosis on the reserve preservation in patients with this disorder. Most likely, damages of the ovarian cortex by endometriomas are not the sole and most crucial factor affecting the ovarian reserve.

Discussion

Our results suggest that factors other than just damage of the ovarian cortex by endometriomas influence the ovarian reserve. Undoubtedly, additional biochemical and immunological processes in patients with endometriosis may have a decisive influence on their fertility [24]. Possible methods of ovarian reserve assessment constitute another issue. Numerous reports demonstrate the usefulness of assessing the antral follicle count (AFC), AMH and FSH levels, especially in case of endometriosis. However, most analyses are based on observations of patients prepared for the ART procedures. Not many studies are based on observation of patients who conceived spontaneously, what seems to be the best indicator of the preserved ovarian reserve. Moreover, recent reports about a reduced number of successful in vitro implantations of embryos from oocytes of patients with endometriosis into healthy subjects have suggested the existence

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Table I. Analysis of the relation between the progression stage of endometriosis and AFC of the right ovary. Cross tabulation of the number of antral follicles in the right ovary and the stage of endometriosis progression.

| | | | Stage of endometriosis progression | | | Total |
			first/ second stage	third stage	fourth stage	
antral follicle count: right ovary	<=5	count	0	9	1	10
		% of antral follicle count: right ovary	0.0%	90.0%	10.0%	100.0%
		% of endometriosis stage of progression	0.0%	34.6%	12.5%	25.6%
	>5	count	5	17	7	29
		% of antral follicle count: right ovary	17.2%	58.6%	24.1%	100.0%
		% of endometriosis stage of progression	100.0%	65.4%	87.5%	74.4%
Total		count	5	26	8	39
		% of antral follicle count: right ovary	12.8%	66.7%	20.5%	100.0%
		% of endometriosis stage of progression	100.0%	100.0%	100.0%	100.0%

Chi-squared test

	Value	Df	Asymptotic 2-sided significance
Pearson's chi-squared test	3.547[a]	2	**0.170**
Likelihood ratio	4.833	2	0.089
Linear correlation test	0.021	1	0.884
No. of valid observations	39		

No statistically significant difference was revealed between the stage of endometriosis progression and categorized antral follicle count in the right ovary ($p>=0.05$)

Table II. Analysis of the relation between the progression stage of endometriosis and AFC of the left ovary. Cross tabulation of the number of the antral follicles in the left ovary and the stage of endometriosis progression.

| | | | Stage of endometriosis progression | | | Total |
			first/ second stage	third stage	fourth stage	
antral follicle count: left ovary	<=5	count	1	11	1	13
		% of antral follicle count: left ovary	7.7%	84.6%	7.7%	100.0%
		% of endometriosis stage of progression	20.0%	42.3%	12.5%	33.3%
	>5	count	4	15	7	26
		% of antral follicle count: left ovary	15.4%	57.7%	26.9%	100.0%
		% of endometriosis stage of progression	80.0%	57.7%	87.5%	66.7%
Total		count	5	5	26	8
		% of antral follicle count: left ovary	12.8%	12.8%	66.7%	20.5%
		% of endometriosis stage of progression	100.0%	100.0%	100.0%	100.0%

Chi-squared test

	Value	Df	Asymptotic 2-sided significance
Pearson's chi-squared test	2.905[a]	2	**0.234**
Likelihood ratio	3.190	2	0.203
Linear correlation test	0.343	1	0.558
No. of valid observations	39		

No statistically significant difference was revealed between the stage of endometriosis progression and categorized antral follicle count in the left ovary ($p>=0.05$)

Table III. Analysis of the relation between the progression stage of endometriosis and FSH level. Cross tabulation of the level category of FSH and the stage of endometriosis progression.

| | | | Stage of endometriosis progression | | | Total |
			first/ second stage	third stage	fourth stage	
Level category of FSH	<=5	count	0	2	0	2
		% of level category of FSH	0.0%	100.0%	0.0%	100.0%
		% of endometriosis stage of progression	0.0%	7.7%	0.0%	5.1%
	>5	count	5	20	4	29
		% of level category of FSH	17.2%	69.0%	13.8%	100.0%
		% of endometriosis stage of progression	100.0%	76.9%	50.0%	74.4%
	>10	count	0	4	4	8
		% of level category of FSH	0.0%	50.0%	50.0%	100.0%
		% of endometriosis stage of progression	0.0%	15.4%	50.0%	20.5%
Total		count	5	26	8	39
		% of antral follicle count: left ovary	12.8%	66.7%	20.5%	100.0%
		% of endometriosis stage of progression	100.0%	100.0%	100.0%	100.0%

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Chi-squared test

	Value	Df	Asymptotic 2-sided significance
Pearson's chi-squared test	6.853[a]	4	**0.144**
Likelihood ratio	7.592	4	0.108
Linear correlation test	4.105	1	0.043
No. of valid observations	39		

No statistically significant difference was revealed between the stage of endometriosis progression and categorized FSH level (p>=0.05)

of some factors hindering conception other than those resulting from ovarian cortex damage and ovarian reserve diminishment [25]. Our nearly completed study about ovarian reserve assessment in patients with endometriosis who underwent surgical treatment will certainly bring new results concerning ovarian reserve preservation after laparoscopic treatment. The obtained results will provide new arguments for the ongoing debate about the best methods of conquering this dysfunction and effective ways of diagnosing infertility in patients with endometriosis.

Conclusions

Fertility predictions ought to be formulated with caution while assessing the ovarian reserve in patients with confirmed endometriosis. It seems expedient to apply additional biochemical and immunological methods which, together with hormonal (FSH, AMH) and ultrasonographic (AFC) test results, will provide information about the reproductive potential of patients and help plan a proper treatment.

Oświadczenie autorów

1. Ewa Posadzka – autor koncepcji i założeń pracy, przygotowanie manuskryptu i piśmiennictwa – autor zgłaszający i odpowiedzialny za manuskrypt.
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4. Agnieszka Nocuń – autor analizy i interpretacji wyników, przygotowanie, korekta i akceptacja ostatecznego kształtu manuskryptu.

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