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Original Article

HYSTEROSCOPY BEFORE IN VITRO FERTILIZATION

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Abstract. *In the last decade, success after in vitro fertilization process (IVF) has remained at a similar rate despite all the improvements implemented in the stimulation protocols and laboratory techniques. Hysteroscopy is a method becoming more widely used with patients after a failed IVF cycle, considering a large incidence of uterus cavum pathological states which have a negative impact on the favorable outcome. Numerous studies have provided different results on the IVF outcome with hysteroscopy performed prior to this treatment in cases with no uterus cavum pathology. The aim of the research was to examine the effect of both diagnostic and surgical hysteroscopy on the outcome of IVF. Hysteroscopy was performed with 74 patients 30 to 50 days prior to IVF and in 33 of them (group I) some pathological state was noticed, which was treated during the same procedure. The control group (group III) included 151 patients who had IVF performed with no prior hysteroscopy. There is no statistically significant difference in the rate of post hysteroscopy implantation between I and II group when compared to the control group (20.62% vs 23.28% vs 17.31%), nor in the rate of clinical pregnancies (45.45% vs 46.34% vs 34.44%). Following the correctional treatment of uterus cavum pathological states, implantation and pregnancy rates remain at a level comparable to hysteroscopically normal medical findings. Statistically significant higher pregnancy rate is present in group I after the first IVF cycle, compared to the next IVF in the same group and in comparison to the next IVF cycle in the control group (60.00% vs 27.91%, $p<0.05$). Hysteroscopy is a simple and safe method allowing nearly identical rate of clinical pregnancies after a surgical treatment of uterus cavum pathological states when compared to the control group, but statistically much higher pregnancy rate if the order of IVF procedure is being compared. In cases of normal ultrasound findings and negative hysteroscopical findings, performing hysteroscopy prior to IVF does not provide significantly better results. Therefore, its routine execution is not recommended.*

Key words: *hysteroscopy, pathological states of the cavum, IVF outcome*.

Introduction

In the last decade, pregnancy rate after IVF has remained almost the same, regardless of a lot of improvements implemented in the stimulation protocols and the progress of the laboratory techniques. That being a major reason, more attention has been paid to the removal of all the pathological states which could possibly have a negative impact on the endometrium receptivity, thus lowering the pregnancy rate after IVF [1,2]. Hysteroscopy is a superior method in uterus cavum visualization enabling a surgical treatment of the pathological changes within the same act. A remarkable progress has been made with the inclusion of cameras, an optical system and a small sized hysteroscope itself, avoiding thus a cervical dilatation, alleviating pain during the intervention and enabling it to be performed in outpatient conditions, without using anesthesia – *office hysteroscopy* [3]. It is widely accepted that hysteroscopy is performed after failed IVF cycles. However, there is still no agreed consensus on a required hysteroscopy prior to IVF cycle, especially in cases of normal cavum ultrasound findings. Numerous studies provide different data on IVF success when hysteroscopy is performed immediately prior to the IVF procedure [4–7].

For all these reasons, the aim of this research was to examine the influence of hysteroscopy on the IVF outcome, both in cases with existing pathological substratum in the uterus cavum and in cases with normal hysteroscopic findings.

Methods

The research was done at the Clinic of Gynecology and Obstetrics of the Clinical Center in Niš, as a prospective study, and it included 225 patients from the National IVF program.

Criteria for inclusion in the research were: less than 40 years of age, FSH < 15 IU/ml, AMH > 0.5, body mass index (BMI) < 30 kg/m², lack of genital infection and favorable karyotype of both partners.

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Criteria for exclusion were: presence of chronic systematic disease, existence of hepatitis C or HIV infection, organic pathology of the ovaries, the cause of immune infertility and azoospermia.

The patients were divided in three groups: group of 33 patients who had hysteroscopy performed prior to IVF, with existing uterus cavum pathology treated within the same procedure; II group of 41 patients, with hysteroscopy prior to IVF but with normal hysteroscopic findings; and the III control group of 151 patients with no hysteroscopy.

Hysteroscopy was performed during oral contraceptive therapy, 30–50 days before IVF. Saline solution was used as a distension medium and a 5mm *Bettocchi office* hysteroscope (Karl Storz GmbH and co, Tuttlingen, Germany) with a 5Fr working channel. The patients were in a lithotomy position all with short termed intravenous anesthesia applied. Vaginoscopic approach was used with no ecarter and no cervix traction. Versapoint and Springle electrode (Johnson) were used in cases of polypectomy, septum resections and smaller myomas. In one case only, with a wider myoma, a bipolar resectoscope was used with a 9mm outer cover. Polyps, myomas and unclear lesions were hystopathologically evaluated.

IVF procedure was performed 1–2 months post oral contraceptive therapy. Long and short protocol with GnRH agonists was used. Serial ultrasound checkups during controlled ovary hyperstimulation (COH) were done with a "Shimatzu" ultrasound device, starting with the 6^{th} day of stimulation. On finding 2 or more follicles larger than 18mm, patients got 10000 IU Pregnyl injection, and 34–36 hours afterwards, a transvaginal oocytes pick-up was performed (OPU). Embryo transfer (ET) was done on the 2^{nd}, 3^{rd} or 5^{th} day after the aspiration, monitored by an ultrasound, putting back 3 embryos at the most. "Cook's" catheter was used for the ET. The same therapy was applied for all patients, after ET: Utrogestan 200mg tablets, 3 times a day; Cardiopirin 100mg tablets, once a day; Dexason 0.5mg tabl., once a day. ßHCG from blood was determined for biochemical verification of pregnancy, 15 days post OPU. Clinical pregnancies were verified by transvaginal ultrasound check up, by visualization of the embryo's cardiac activity, 4–5 weeks after ET.

This prospective clinical trial was approved by the Ethics Committee. The treatment of the patients included hysteroscopy and a long and short GnRH agonist protocol. Written informed consent was provided from all the patients participating in the study.

The data were processed by standard descriptive statistical methods (average value, percentage representation). The statistical processing was done among defined groups. Continual variables relative to data distribution were compared using Student's t-test, Pearson's χ^2 test or ANOVA test.

Results

The patients from the examined groups were not significantly different in any of the generally examined parameters (Table 1).

There are also no statistically significant differences among the groups considering: the number of oocytes, conceived embryos, transferred embryos, and the day of embryo transfer as well (Table 2). The long protocol with agonists was most frequently used in the control group when compared to the I group, at a statistical level of significance $p<0.05$. Based on the general parameters and the features of the IVF cycle, homogeneity of the groups is present, which makes further results valid for this research.

Presence of pathological states in the group of patients with hysteroscopy was 44.59% (Table 3), with endometrial polyp as the most common pathological state (63.64%), shown in Graph 1. There is no statistically significant difference in the incidence of uterus cavum pathological states between the first and the next IVF (Table 4).

Although the implantation rate is higher in hysteroscopic groups 1 and 2, compared to the control group (20.62% vs 23.28% vs 17.31%), and the pregnancy rate as well (45.45% vs 46.34% vs 34.44%), there are no significant differences between the groups. There is no statistically important difference neither in the multiple pregnancy rate nor in the rate of biochemical pregnancy, comparing all the three groups (Table 5).

Table 1 General parameters of patients in examined groups

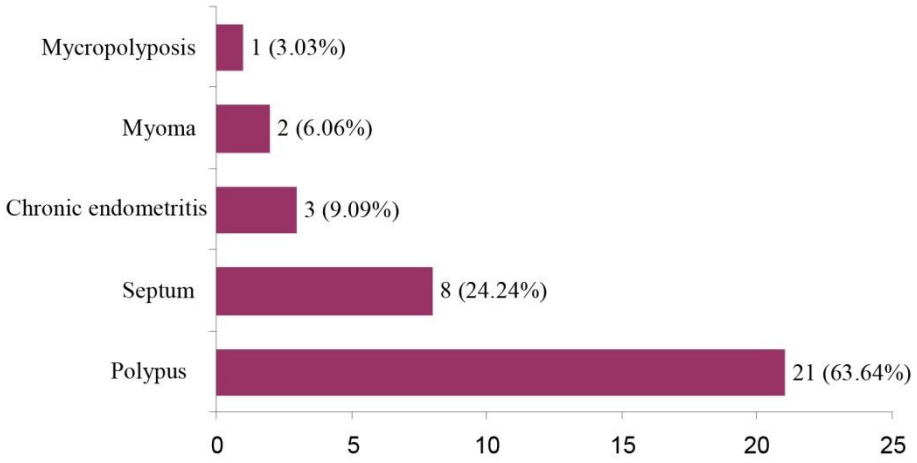
	I group (n = 33)	II group (n = 41)	III – Control group (n = 151)
Age (years)	34.00 ± 2.97 (33.00)	34.00 ± 3.49 (35.00)	33.61 ± 3.65 (34.00)
Patients per age group			
≤30 years	3 (09.09%)	7 (17.07%)	34 (22.52%)
31–35 years	18 (54.55%)	19 (46.34%)	61 (40.40%)
36–40 years	12 (36.36%)	15 (36.59%)	56 (37.09%)
Duration of infertility (years)	7.12 ± 3.53 (6.00)	5.93 ± 2.86 (6.00)	6.38 ± 3.58 (6.00)
FSH (mIU/mL)	6.91 ± 3.10 (6.45)	6.88 ± 2.90 (6.10)	5.93 ± 2.59 (5.50)
AMH (ng/ml)	3.31 ± 3.08 (2.32)	2.92 ± 2.88 (1.84)	3.02 ± 2.47 (2.18)
BMI (kg/m²)	23.85 ± 2.60 (24.00)	23.59 ± 2.96 (23.00)	23.50 ± 2.95 (23.00)

Data are given as absolute numbers (percentages), means ± SD (medians)

Table 2 The IVF cycle features of patients in the examined groups.

	I group	II group	III – Control group
Gonadotropin (IU)	2081.24 ± 804.63 (1850.00)	2078.66 ± 710.05 (1975.00)	2019.97 ± 674.64 (1950.00)
No. of oocytes	9.55 ± 5.08 (9.00)	10.73 ± 7.37 (10.00)	9.98 ± 6.58 (8.00)
No. of embryos	5.73 ± 3.46 (5.00)	5.59 ± 3.54 (5.00)	4.89 ± 3.22 (4.00)
No. of transferred embryos	2.94 ± 0.83 (3.00)	2.58 ± 0.41 (3.00)	2.68 ± 0.20 (3.00)
Protocol			
Long agonists	16 (48.49%)	27 (65.85%)	98 [a*] (64.90%)
Short agonists	17 (51.51%)	14 (34.15%)	53 (35.10%)
Endometrial thickness (mm)	10.23 ± 1.81 (10.00)	9.98 ± 1.57 (10.00)	10.02 ± 1.72 (10.00)
First / second IVF	20 (60.60%) / 13 (39.40%)	26 (63.41%) / 15 (36.59%)	108 (71.52%) / 43 (28.48%)
ET day	3.83 ± 1.03 (3.00)	3.34 ± 0.94 (3.00)	3.65 ± 0.98 (3.00)
2^{nd} day (%)	0 (0.00%)	4 (9.76%)	4 (2.65%)
3^{rd} day (%)	21 (63.64%)	28 (68.29%)	96 (63.58%)
5^{th} day (%)	12 (36.36%)	9 (21.95%)	51 (33.77%)

Data are given as absolute numbers (percentages), means ± SD (medians)
* – p<0.05, a – vs I group



Graph 1. Percentage of presence of pathological findings in I group

Table 3 Presence of pathological findings in the study group

Group	Patient nb	Total %
I + II group	74	100,00%
I group	33	44.59%
II group	41	55.41%

Table 4 Presence of pathological findings in I group related to the first and second IVF

	First IVF n=20		Second IVF n=13	
Polypus	14	70.00%	7	53.85%
Septum	5	25.00%	3	23.08%
Chronic endometritis	1	5.00%	2	15.38%
Myoma	1	5.00%	1	7.69%
Mycropolyposis	0	0.00%	1	7.69%

Table 5 IVF features of patients in the examined groups

	I group		II group		III – Control group	
Implantation rate	20.62%	20 / 97	23.28%	27 / 116	17.31%	72 / 416
Clinical pregnancy rate	45.45%	15 / 33	46.34%	19 / 41	34.44%	52 / 151
Biochemical pregnancy rate	12.12%	4 / 33	12.20%	5 / 41	6.62%	10 / 151
Multiple pregnancy rate	33.33%	5 / 15	36.84%	7 / 19	36.54%	19 / 52

Data are given as absolute numbers (percentages)

Table 6 Pregnancy rate in the examined groups, with first and second IVF cycle compared.

	First VTO			Second VTO		
Group	Patient nb/	Pregnancy nb	% pregnancy	Patient nb/	Pregnancy nb	% pregnancy
I group	20	12*cd	60.00%	13	3	23.08%
II group	26	13	50.00%	15	6	40.00%
III–Control group	108	40	37.04%	43	12	27.91%
Total	158	65	41.14%	74	27	36.49%

Data are given as absolute numbers (percentages)
* – $p<0.05$, c – vs control, d – vs second IVF

Significantly higher pregnancy rate is present in I group after the first IVF cycle in comparison to the second IVF in the same group (60.00% vs 23.08%, $p<0.05$), and also between the first IVF cycle in I group compared to the second IVF in the control group (60.00%vs 27.91%, $p<0.05$) (Table 6).

After hysteroscopic polypectomy, highest pregnancy rate was achieved in comparison to uterus cavum pathological states. However, a number of patients did not allow statistical verification (Table 7).

Table 7 Pregnancy rate in relation to the pathological findings

Hysteroscopic findings	Patient nb/	Pregnancy nb	% pregnancy
Polypus	21 /	12	57.14%
Septum	8 /	3	37.50%
Myoma	2 /	0	0.00%
Chronic endometritis	3 /	1	33.33%
Mycropolyposis	1 /	0	0.00%

Discussion

Regardless of the quality of embryos, an appropriate endometrial thickness and a successful embryo transfer (ET), unsuccessful implantation remains a major cause of IVF method failure. Repetitive implantation failure (RIF) is defined as no conception after two or more alternate transfers of one or more adequate quality embryos. All uterus cavum pathological states have a negative impact on the implantation rate. Their diagnostics is one of the primary goals before entering the IVF cycle.

Our research showed cavum pathology incidence of 44.59% with the largest presence of endometrial polyps, in nearly 2/3 of the cases (63.64%). Fatemi [1] found the frequency of only 11% of uterus pathology, whereas Cenksoy [8] discovered pathological states in 44.9% of the patients. In those two studies, endometrial polyp was the most common, but still in a smaller percentage than in our research, 6- 19.7%. In his journal article, Kodaman [9] discovers a post IVF conceiving benefit from hysteroscopic polypectomy, explaining that an endometrial injury during the intervention is a reason of increased endometrial receptivity. Polyp treatment options are: cancellation of the cycle and polypectomy, polypectomy and freezing of embryos with ET after a few months' period, or ignoring the polyps and continuation of the cycle [10].

Even though the implantation and pregnancy rates after cavum pathology treatment are higher than in the control group, our research did not lead to any statistically significant differences. Comparing the IVF outcomes in the first group of patients with clear hysteroscopic findings, similar percentage can be seen. That is in accordance with numerous studies proving the benefit of performing hysteroscopy prior to IVF with patients having pathological substratum and specifying better IVF results after polypectomy, myomectomy or septum uterus resection [7,11,12].

The influence of hysteroscopy itself on the IVF outcome has been considered for quite a long time, advocating hysteroscopy prior to every IVF cycle. In favor of that, many projects discuss the impact of local endometrial injury during hysteroscopy which brings about endometrial inflammation, thus increasing the endometrial receptivity [13].

In their meta-analyses, Pundir and El-Toukhy found the proof of the hysteroscopy benefit prior to the first IVF cycle, proving a higher pregnancy rate with women who underwent hysteroscopy procedure [4]. One more research with 480 patients also showed higher pregnancy rates when hysteroscopy was performed before the first IVF [14]. Our study did not provide information about hysteroscopy itself influencing statistically better IVF outcome results. Pregnancy rate in II group is statistically not different from the pregnancy rates neither in I group nor in the control group (46.34% vs 45.45% vs 34.44%).

Latest randomized multicentral studies showed that if the ultrasonography result is normal, there is no increased pregnancy rate after hysteroscopy. They also showed that there is no significant difference even if hysteroscopy is being performed after repetitive failed IVF cycles, unless there are pathological changes in the uterus cavum [5,6].

Conclusion

Hysteroscopy is a safe method enabling reliable diagnostics of all uterus cavum pathological states which have a negative impact on the IVF outcome. It allows a simultaneous surgical treatment of the pathological changes within the same procedure and it gives a similar IVF outcome as with patients who have clear cavum

findings. In case of normal ultrasonography findings, there are no statistically better results in the IVF procedure after hysteroscopy. Therefore, routine hysteroscopy prior to the first IVF is not recommended, as well as after repetitive implantation failures.

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