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The effects of local endometrial injury made by hysteroscopy on *in vitro* fertilization outcome

Uticaj lokalne endometrijalne povrede načinjene u toku histeroskopije na ishod vantelesne oplodnje

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Abstract

Bacngraund/Aim. Regardless of embryos quality, an appropriate endometrial thickness and a successful embryo transfer (ET)**,** implantation remains a difficulty for a favorable outcome of an *in vitro* fertilization (IVF). Numerous studies with the aim of increasing implantation rate and pregnancy rate suggest local endometrial injury (LEI) prior to the IVF procedure. Hysteroscopy is a method becoming more widely used both with patients after a failed IVF cycle and with patients before the first IVF, considering the large incidence of uterus cavum pathological states which have a negative impact on the favorable outcome. However, there is still no consensus reached over LEI, the way and time of its performing or its impact. The aim of this research was to determine the effect of hysteroscopically made local endometrial lesion on the IVF procedure outcome, both in the first and in the next IVF cycle and also to examine if the new method of LEI provoking using bipolare electrode has a favorable impact on post IVF pregnancy success. **Methods.** Total of 81 patients had hysteroscopy performed 30–50 days prior to IVF, 40 of which had LEI made during hysteroscopy (the LEI group) using bipolar electrode in a way not described in any available literature. Remaning hysteroscopically treated patients (n = 41) had no LEI (the non-LEI group). The control group included 151 patient who had IVF performed with no prior hysteroscopy and LEI. **Results.** The rate of clinical pregnancies after LEI was statistically more significant in comparison to the control group (52.50% *vs* 34.44%, $p < 0.05$) and it meant 2.1 time bigger chance to conceive (OR=2.10; 95% CI: 1.04 – 4.26; $p < 0.05$). We noticed differences in the implantation rate between the LEI group and the non-LEI group on one side and the control group on the other, in favor of the two groups subjected to hysteroscopy (23.89%, 25.47% vs 18.18%, respectively), but they were not of any statistical significance. Not significantly higher rate of pregnancy was present, after the first and the next IVF, both in the LEI and the non-LEI group when compared to the control one. **Conclusion.** New method of LEI provoking by bipolar electrode in the process of hysteroscopy is a simple and safe method allowing higher rate of clinical pregnancies and doubling the probabilty of the positive IVF outcome.

Key words:
infertility; fertilization in vitro; hysteroscopy; iatrogenic disease; uterus; wounds and injuries; pregnancy outcome.

Apstrakt

Uvod/Cilj. Bez obzira na kvalitetne embrione, odgovarajuću debljinu endometrijuma i uspešan embriotransfer (ET), implantacija ostaje problem za povoljan ishod vantelesnog oplođenja (VTO). Histeroskopija je metoda koja se sve više koristi kako kod pacijentkinja nakon neuspešnog ciklusa VTO tako i kod pacijentkinja pre prve VTO, imajući u vidu veliku incidencu patoloških stanja kavuma uterusa koja negativno utiču na povoljan ishod. Brojne studije u cilju povećanja stope implantacije i stope trudnoća predlažu lokalnu endometrijalnu povredu (LEI) pre postupka VTO, međutim, i dalje ne postoji konsensus oko LEI, načina i vremena izvođenja i njenog uticaja. Cilj ovog istraživanja bio je da se utvrdi efekat histeroskopski načinjene lokalne LEI na ishod VTO postupka, kako kod prve VTO tako i kod naredne, a takođe i da se ispita da li novi način izazivanja LEI pomoću bipolarne elektrode ima povoljan uticaj na ostvarivanje trudnoća nakon VTO. **Metode.** Kod 81 pacijentkinje histeroskopija je rađena 30–50 dana pre VTO, od kojih je kod 40 pacijentkinja načinjena LEI u toku histeroskopije bipolarnom elektrodom, (LEI grupa) na način koji nije opisan u dostupnoj literaturi. Kod preostale 41 pacijentkinje nije izvršena LGI (*non* LEI grupa). Kontrolna grupa (II grupa) je obuhvatila 151 pacijentkinju kod koje je rađen VTO bez prethodne histeroskopije i LEI. **Rezultati.** Utvrđena je statistički značajno viša stopa kliničkih trudnoća nakon LEI u odnosu na kontrolnu grupu

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(52.50% *vs* 34.44%, $p < 0.05$) i 2,1 put veća šansa da se ostvari trudnoća (OR = 2,10; 95% IP: 1,04–4,26; $p < 0.05$). Utvrdili smo razliku u stopi implantacije između LEI i *non* LEI grupa s jedne i kontrolne grupe s druge strane (23,89%, 25,47% *vs* 18,18%, redom), ali bez statističke značajnosti. Bila je prisutna, ali ne značajno viša, stopa trudnoća i nakon prve VTO i nakon sledeće u LEI i *non* LEI grupi u odnosu na kontrolnu grupu. **Zaključak**. LEI načinjena bipolarnom elektrodom u toku histeroskopije je jednostavna i sigurna metoda koja daje višu stopu kliničkih trudnoća i duplira verovatnoću za pozitivan ishod VTO.

Ključne reči:
neplodnost; oplođenje in vitro; histeroskopija; jatrogena bolest; materica; povrede; trudnoća, ishod.

Introduction

Implantation represents a critical phase in *in vitro* fertilization (IVF) cycle. Despite having a good number of oocytes and embryos quality as well as an appropriate thickness of the endometrium, in the last decade, pregnancy rate was the same - about 30%–40% in the IVF cycle.

The idea of performing hysteroscopy prior to every IVF procedure was greatly favored for two reasons: due to high frequency of uterus cavum pathological states (10%–60%) and the influence of hysteroscopy itself on the better IVF outcome [1, 2].

Many studies have tried to show that local endometrial injury (LEI) prior to IVF leads to an inflammatory response causing an increased endometrial receptivity and bigger IVF success rate [3–5]. In the majority of studies, LEI was made on the front or the back of uterus wall [6], using Pippele biopsy catheter [7–9], Novak biopsy catheter [10] or endometrial cell sampler [11]; in smaller number of studies, LEI was made during hysteroscopy using grasping forceps [12, 13] or monopolar electrode [14].

However, there is still no agreement on the necessity of a mechanical endometrial injury (EI), on the way and the timing of its making, neither on whether it is better for the EI to be made by biopsy or during diagnostic hysteroscopy.

For all these reasons, the aim of this study was to determine the influence of LEI on IVF during hysteroscopy and whether provoking an endometrial lesion by using bipolar electrode can favorably influence on the IVF outcome before the first IVF cycle as well as on the next.

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 232 patients from the National IVF program with maximum of 2 IVF cycles on the state's budget.

Criteria for being included in the research were: less than 40 years of age, FSH < 15 IU/mL, anti-Müllerian AMH > 0.5, body mass index (BMI) < 30 kg/m², lack of genital infection and favorable caryotype of both partners.

Criteria for being excluded were: presence of chronic systemic disease, existence of hepatitis C or human immunodeficiency virus (HIV) infection, organic pathology of ovaries, immune sterility cause and azoospermia.

The patients were divided into 3 groups: the group I of 40 patients who had hysteroscopy and LEI performed prior to IVF – the LEI group; the group II of 41 patients, with hysteroscopy prior to IVF but with no LEI – the non-LEI group; and the control group (the group III) of 151 patients with no hysteroscopy nor LEI. All the patients from the groups I and II had a favorable hysteroscopical report.

Hysteroscopy was performed during oral contraceptive therapy, 30–50 days before IVF. Saline solution was used as a distension medium and 5 mm Bettocchi office hysteroscop (Karl Storz GmbH and co, Tuttlingen, Germany) with 5Fr working canal. The patients were in a lithotomyc position with short-term intravenous anesthesia applied. Vaginoscopic approach was used with no cervix traction. LEI was made in a way which was not described in any literature available. It was performed with a springle bipolar electrode (Johnson), fundic, in a transversal direction, 10–15 mm in length, throughout the whole endometrial thickness.

The IVF procedure was performed 1–2 months after oral contraceptive therapy. A long and short protocol with gonadotropin-releasing hormone (GnRH) agonists was used. Serial ultrasound checkups during controlled ovary hyperstimulation (COH) were done with a Shimadzu ultrasound device, starting on the 6th day of stimulation. On finding 2 or more follicles larger than 18 mm, patients got 10,000 U Pregnyl® injection and a transvaginal oocytes pick-up (OPU) was performed 34–36 hours afterwards. Embryo transfer (ET) was done on the day 2, 3 or 5 after the aspiration, monitored by an ultrasound, putting back a maximum of 3 embryos Cook's catheter was used for the ET. After the ET, the patients underwent the following therapy: tabl Utrogestan® 200 mg, 3 times a day, vaginal application; tabl Cardiopirin® 100 mg, once a day; tabl Dexason® 0.5 mg, once a day. 10–12 days post ET (15 days post OPU), the ß-subunit of human chorionic gonadotropin (ßHCG) from blood was determined for biochemical verification of pregnancy. Clinical pregnancies were verified by transvaginal ultrasound checkup by visualization of the embryo's cardio activity 4–5 weeks after the ET.

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

The data were processed by using 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. Also, a univariate logistic regression analysis was used for determination of important IVF outcome parameters.

Results

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

There were also no statistically significant differences among the groups considering the number of oocytes, conceived embryos, transferred embryos and the day of embryo transfer (Table 2). The long protocol with agonists was most frequently used with all 3 groups of the patients. Based on the general parameters and the features of the IVF cycle, homogeneity of the groups was present making the further results valid for this research.

The implantation rate was higher in the non -LEI group (25.47%) and in the LEI group (23.89%), when compared to the control one (18.18%), but with no statistical significance.

Clinical pregnancy rate was highest in the LEI group; it was significantly higher in comparison to the control group (52.50% *vs* 34.44%, $p < 0.05$). A difference was also noticeable between the LEI and non-LEI group (52.50% *vs* 46.34%), but with no statistical significance. The same was noticed between the non-LEI group and the control one.

There was no statistically significant difference neither in the multiple pregnancy rate nor in the rate of biochemical pregnancy, comparing the 3 groups (Table 2).

The rate of pregnancy was higher after the second IVF in the LEI group, whereas in the non LEI group and the control group, the first IVF showed better results, although with no statistically significant difference (Table 3).

Due to considerably more frequent long protocol with agonists, we compared pregnancy rates in relation to the applied stimulation protocol. Higher rate of pregnancy was present in the LEI group with long protocol than in the control group, and also in the non-LEI group with short protocol; these differences were not statistically significant. This leads to a conclusion that application of a certain protocol cannot seriously influence obtained results (Table 3).

Table 1

General characteristics of patients in the examined groups

Parameters	LEI group (n = 40)	non LEI group (n = 41)	Control group (n = 151)
Age (years)	32.78 ± 4.12 (32.50)	34.00 ± 3.49 (35.00)	33.61 ± 3.65 (34.00)
Patients per age group (years), n (%)			
≤30	14 (35.00)	7 (17.07)	34 (22.52%)
31–35	14 (35.00)	19 (46.34)	61 (40.40%)
36–40	12 (30.00)	15 (36.59)	56 (37.09%)
Duration of infertility (years)	6.20 ± 3.08 (5.00)	5.93 ± 2.86 (6.00)	6.38 ± 3.58 (6.00)
FSH (mU/mL)	5.95 ± 2.10 (5.50)	6.88 ± 2.90 (6.10)	5.93 ± 2.59 (5.50)
AMH (ng/mL)	3.57 ± 2.39 (3.43)	2.92 ± 2.88 (1.84)	3.02 ± 2.47 (2.18)
BMI (kg/m²)	23.28 ± 2.91 (22.50)	23.59 ± 2.96 (23.00)	23.50 ± 2.95 (23.00)

Data are given as absolute numbers (percentages), or mean ± standard deviation (median);
LEI – local endometrial injury; FSH – follicle-stimulating hormone; AMH – anti-Mülleriar hormone;
BMI – body mass index.

Table 2

***In vitro* fertilization (IVF) cycle features of patients in the examined groups.**

Parameters	LEI group	non-LEI group	Control group
Gonadotropin (U)	2,113.00 ± 792.36 (2012.50)	2,078.66 ± 710.05 (1975.00)	2,019.97 ± 674.64 (1950.00)
Oocytes, n	10.35 ± 8.64 (10.00)	10.73 ± 7.37 (10.00)	9.98 ± 6.58 (8.00)
Embryos, n	5.88 ± 4.50 (5.00)	5.59 ± 3.54 (5.00)	4.89 ± 3.22 (4.00)
Transferred embryos, n	2,82 ± 0.15 (3.00)	2.58 ± 0.41 (3.00)	2.68 ± 0.20 (3.00)
Protocol, patients			
long agonists	33 (82.50)	27 (65.85)	98 (64.90)
short agonists	7 (17.50)	14 (34.15)	53 (35.10)
Endometrial thickness (mm)	10.88 ± 1.67 (11.00)	9.98 ± 1.57 (10.00)	10.02 ± 1.72 (10.00)
First / second IVF	24 (60.00) / 16 (40.00)	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)
2nd	1 (2.50)	4 (9.76)	4 (2.65)
3rd	22 (65.00)	28 (68.29)	96 (63.58)
5th	17 (32.50)	9 (21.95)	51 (33.77)
Implantation rate	23.89% (27/113)	25.47% (27/106)	18.18% (72/396)
Clinical pregnancy rate	52.50% (21/40*c)	46.34% (19/41)	34.44% (52/151)
Biochemical pregnancy rate	10.00% (4/40)	12.20% (5/41)	6.62% (10/151)
Multiple pregnancy rate	23.81% (5/21)	36.84% (7/19)	36.54% (19/52)

Data are given as absolute numbers (percentages), or mean ± standard deviation (median);
LEI – local endometrial injury; ET – embryo transfer; *$p < 0.05$, c – *vs* control group.

Table 3

Succes rate (pregnancy) for first and second *in vitro* fertilization (IVF) and the applied protocol

Parameter	Succes rate (SR)		
	LEI	non-LEI	Control
First VTO [SR = 65 (41.14%)]			
patient, n	24	26	108
pregnancy, n (%)	12 (50)	13 (5)	40 (37.04)
Second IVF [SR = 27 (36.49%)]			
patient, n	16	15	43
pregnancy, n (%)	9 (56.25)	6 (40.00)	12 (27.91)
Long protocol with agonist [SR = 68 (43.04%)]			
patient, n	33	27	98
pregnancy, n (%)	18 (54.55)	12 (44.44)	38 (38.78)
Short protocol with agonist [SR = 24 (32.43%)]			
patient, n	7	14	53
pregnancy, n (%)	3 (42.86)	7 (50.00)	14 (26.42)

LEI – local endometrial injury.

Table 4

Estimation of the influence of important factors on conceiving – results of a univariate logistic regression analysis

Factor	*p*	OR	95% CI for OR boundary	
			Lower	Upper
LEI group	0.0388*	2.10	1.04	4.26
non- LEI group	0.1636	1.64	1.82	3.31
Age (years)	0.0079**	0.91	0.84	0.97
Age group, 36–40 years	0.0321*	0.46	0.23	0.94
Oocytes	0.0280*	1.04	1.00	1.08
Embryos	0.0055**	1.11	1.03	1.19
Endometrial thickness	0.0160*	1.22	1.04	1.43
IVF/ICSI	0.0243*	0.48	0.25	0.91

*** – $p < 0.05$; ** – $p < 0.01$, *** – $p < 0.001$**

OR – odds ratio; CI – confidence interval; LEI – local endometrial injury; IVF – *in vitro* fertilization; ICSI – intra-cytoplasmic sperm injection.

A univariate logistic regression analysis proved that the age as a continual variable, the age group 36–40, the number of obtained oocytes, the number of conceived embryos, the IVF in relation to intra-cytoplasmic sperm injection (ICSI) and the LEI in relation to the control group, were statistically important predictors of the pregnancy outcome (Table 4).

The LEI group of patients had statistically significant, 2.1 time bigger chance for pregnancy when compared to the control group [odd ratio (OR) = 2.10; 95% confidence interval (CI): 1.04–4.26; $p < 0.05$), but with no statistically significant difference when compared to the non-LEI group of patients. The non-LEI group of patients, in comparison to the control group, had a higher probability of pregnancy (64%), but it was not of statistical significance (OR = 1.64; 95% CI: 0.82–3.31).

Discussion

Mechanical LEI before ovary stimulation for IVF was suggested in order to improve the conditions for implantation in women having inexplicable repeated implantation failure (RIF). It has been shown that mechanical manipulation on the endometrium can improve the receptivity in a way that it modulates the genes expression of factors necessary for the implantation, such as: glycodelin A, laminin alpha 4, integrin alpha 6 and matrix metalloproteinase 1 [2]. Mechanical manipulation or LEI can be provoked by endometrial biopsy or by hysteroscopy. It is assumed that due to the endometrial injury, changes occur in the endometrium, in the immune system and in the gene expression, all of which leads to increased receptivity and formation of an appropriate environment for implantation.

In their study, Gnainsky et al. [4] proved that endometrial biopsy provokes an inflammatory response characteristic for the influx of the macrophage and dendritic cells (DC), together with an increase of proinflammatory cytokines. Proinflammatory cytokines, produced in an injured endometrium, stimulate the secretion of chemokines and cytokines which later recruit the macrophage and DC cells to the implantation spot. These immune cells enforce the inflammatory reaction and provoke a synthesis of molecules in the endometrium which react on their own with a blastocyst, enabling its apposition and adhesion to the uterine wall.

Our research included LEI during hysteroscopy using a bipolar springle electrode, fundic in a transversal line, 10–15 mm in length. We did not find any data in literature saying that LEI was done in that way. The advantage of making an endometrial lesion in this way is that hysteroscopy is be-

coming more and more frequently used method, superior in diagnosing the states of uterus cavum. Due to frequent unexpected pathological results with patients having clear ultrasonography and hysterosalpingography (HSG) and also due to the possibility of making a surgery in a single act with extremely rare complications while performing hysteroscopy, it becomes significantly important as a procedure. Bipolar springle electrode is easy to handle and use. Having a larger circumference than the Twizzle® bipolar electrode, it enables a larger space of effect, there is no bleeding during intervention, there is no electricity overflow towards the tissue as with the monopolar electrode, no thermal effect further than the tissue contact spot, so it could be performed in daily hospital conditions.

Our study showed significantly higher rate of pregnancy with patients who underwent LEI in comparison to the control group (52.50% *vs* 34.44%; $p < 0.05$). We could not reach a statistical significance in comparison to the non- LEI group, possibly due to the sample size, even though there was a difference in favor of the LEI group (52.50% *vs* 46.34%).

In a retrospective study of Kara et al. [7], in which the endometrial injury was made by a biopsy catheter, on the day 21 of the cycle, prior to the IVF procedure, statistically higher rate of pregnancy was obtained in the study group when compared to the control group (43.9% *vs* 21.4%). One more research showed statistically significantly higher rates of implantation, clinical pregnancies and infants born alive in patients who underwent LEI within the cycle, prior to the IVF cycle [15]. The study group had rates of 13.07%, 32.7% and 22.4%, respectively; the rates of the control group were 7.1%, 13.7% and 9.8%, respectively. A pioneer study on 30 patients, in which, hysteroscopically, the endometrial injury was made with a jagged forceps on the *cavum* back wall, in the mid line, 10–15 mm from the *fundus*, showed the pregnancy rate of 100% in the LEI group and 46% in the group with no endometrial injury.

Unlike the former research, another study did not prove the benefit of LEI in the IVF procedure [8]. Rates of implantation, biochemical and clinical pregnancies in the experimental group were 4.9%, 18.2% and 12.1%, respectively; in the control group, they were 6.71%, 19.5% and 17.1%, respectively, without a statistically significant difference. Werner et al. [11] also stated that there was no improvement in the pregnancy rate with 39 patients who underwent a single endometrial biopsy within the cycle, prior to ET euploid frozen embryos, when compared to the control group (43.6% *vs* 55.0%; $p = 0.13$). One more study demonstrated no significant difference in ongoing pregnancy rates, implantation rates, clinical pregnancy rates and multiple pregnancy rates on 300 unselected subfertile women scheduled for IVF/ICSI treatment [8].

Karimzade et al. [16] discovered that LEI, on the day of oocytes pick-up in the IVF cycle, had a negative effect on the endometrial receptivity, causing triple lower rates of implantation and pregnancy in the experimental group in comparison to the control one.

Three latest studies which compared hysteroscopical groups with and without endometrial lesion, produced opposing results. Seval et al. [14] stated significantly higher rates of implantation and rates of pregnancy with the LEI groups, before IVF whereas El-Khayat et al. [13] and Shokeir et al. [12], examining the natural cycle and cycles with artificial insemination, did not find any justification to perform endometrial lesions.

The IVF success is decreasing with every following attempt. Therefore, pregnancy rates after the second and each following IVF cycle are significantly different from the first IVF, in each and every study. Our research also showed that the pregnancy rate after the second IVF in the LEI group was higher than after the first one, unlike in the non-LEI group in which there was only an insignificant difference in favor of the first IVF cycle. An interesting fact is that the pregnancy rate after the second IVF in the non- LEI group was higher than the pregnancy rate after the first IVF in the control group.

Statistical significance in pregnancy rate was also confirmed by a univariate logistic regression analysis, which pointed to the fact that patients had 2.1 time bigger chance of conceiving if LEI was done prior to the IVF cycle (OR = 2.10; 95% CI: 1.04–4.26; $p < 0.05$).

However, unlike other researches, we did not found a statistical significance in the implantation rate among the groups, although there was a difference between the groups I and II on one side and the control group on the other, in favor of the two first groups (23.89%, 25.47% *vs* 18.18%, respectively). The hysteroscopy itself definitely brings about a mild inflammatory response in the endometrium, leading in that way to an increase of implantation and clinical pregnancy rates which supports the idea of hysteroscopy being necessary even prior to the first IVF cycle and not only in cases of RIF with IVF program patients.

Result Limitation of this research is the smaller number of patients in the LEI and non- LEI group, which can make an impact on insufficient significance of one part of the results. To verify the method of making an endometrial lesion, a new group of patients should be introduced, to whom LEI would be performed using the usual procedure, i.e. with a biopsy catheter, which would enable comparison of effects of using different methods for making lesions.

Regardless of all the thorough research so far, no consensus has been reached on the use of hysteroscopy or endometrial biopsy, on the method of making a hysteroscopical injury, on a single or multiple biopsy or even on the intervention length in relation to the cycle stage.

Considering the frequency of unexpected pathological reports of the *cavum*, including prior the first IVF and after every failed IVF process, hysteroscopy should have an advantage over the biopsy catheter, bearing in mind the possibility of performing a surgical treatment on the changes detected in the diagnostic hysteroscopy. A major issue arouses: whether endometrial injury during hysteroscopy should be limited, i.e. to women with RIF or it could be applied to all the women participating in the IVF procedure, with no *cavum* pathology.

Conclusion

LEI made by a bipolar spingle electrode, fundic, in a transversal direction, in the process of hysteroscopical examination within the cycle prior to IVF, significantly increases the rate of clinical pregnancies and doubles the chance of conceiving post IVF. The increase of pregnancy rates can be seen with the first IVF cycle, but as well as with the next cycle, bringing about a dropping number of IVF attempts and also a shorter time needed for conceiving. LEI made by hysteroscopy represents a simple and safe method which can be performed even in outpatient conditions. It is necessary to conduct further research on a larger sample to verify the obtained results.

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