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The effect of endometrial polyps on pregnancy rates in intracytoplasmic sperm injection cycles

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Summary

Objective: The purpose of this study was to determine reproductive results of intracytoplasmic sperm injection (ICSI) for different endometrial polyps subgroup divided according to polyp size and number. *Materials and Methods:* Eighty-three primer infertile patients were retrospectively analyzed. Group A consisted of 36 patients having an endometrial polyp with a diameter ≤ one cm; whereas 47 patients were included in Group B who had a polyp with a diameter > one cm or more than one polyps. All patients underwent a hysteroscopic polypectomy and ICSI treatments were started in the following cycle. *Results:* Pregnancy was achieved in 16 patients (44.4%) in Group A and 23 patients (48.9%) in Group B. The pregnancy ratios did not reveal a statistically significant difference between the two groups. *Conclusion:* The authors concluded that in patients who have undergone hysteroscopic polypectomy before the intracytoplasmic sperm injection (ICSI) cycle, the pregnancy rates do not depend on the diameter of the endometrial polyps.

Key words: Endometrial polyp; Hysteroscopy; ICSI; Pregnancy.

Introduction

Endometrial polyps are frequently encountered during the reproductive period. Their prevalence in women is 24% and this rate further increases with advanced age [1]. Endometrial polyps usually develop as a result of an anomaly in hormonal receptivity, namely the persistence of the receptors for estrogen and the absence/downregulation of the receptors for progesterone. Hormonal disorders such as disovulation/anovulation, luteal insufficiency, and hyperestrogenemia frequently accompany endometrial polyps [2].

Endometrial polyps are easily diagnosed with sonohysterography or office-based hysteroscopy in symptomatic women; they may also be incidentally encountered with transvaginal sonography in asymptomatic women.

Endometrial polyps damage the normal endometrial tissue and play an important role in the implantation failure. Mittal *et al.* [3] have reported that the gland and stroma of the endometrial polyps remained unresponsive to the stimulation by progesterone. This fact seems to cause a defective implantation at the polyp site. In patients diagnosed with an endometrial polyp, the increased plasma concentration of glycodeline was held responsible for the implantation failure [4]. The presence of an endometrial polyp can also affect the implantation and the embryonic development by inducing local inflammatory changes or deteriorating the normal shape of the uterine cavity [5].

It was previously shown that endometrial polyps interfere with fertility during natural conception [6, 7] as well as intrauterine insemination [8]. Their detection during or just before the in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles is more troublesome. In such a case, one of the four different approaches to the endometrial polyp is preferred: 1) cancellation of the cycle followed by polypectomy; 2) removal of the endometrial polyp and embryo freezing with embryo transfer after a few months; 3) negligence of the polyp and completion of the treatment protocol; 4) the utilization of hysteroscopic polypectomy during the ICSI cycle before the oocyte retrieval [9-11]. The abundance of different treatment options may confuse the clinician specialized in assisted reproductive techniques who aims for a better implantation and pregnancy rates overall.

Materials and Methods

In this study all fresh ICSI cycles admitted in Zeynep Kamil Women and Children's Diseases Training and Research Hospital were retrospectively analyzed. All patients with primary infertility were included into the study. Following a complete infertility workup of the couples, the presence of an endometrial polyp remained as the only possible reason of infertility. The design of the study was approved by the local ethics committee and written consent has been taken from each patient.

Prior to the ICSI treatment program, all of the patients underwent transvaginal ultrasonography and sonohysterography exam-

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Table 1. — *Characteristics of the study groups.*

	Group A (n=36)	Group B (n=47)	*p* value
Mean age (years)	34.85±4.17	33.67±4.22	0.208
BMI (kg/m^2)	26.98±6.09	26.87±6.17	0.935
Duration of infertility (years)	3.23±4.12	3.98±4.32	0.512
Duration of stimulation (days)	8.93±1.50	8.34±1.75	0.392
Total gonadotropin dose	2510±800	2416±799	0.403
Number of oocytes retrieved	10.14±6.12	10.1±4.53	0.976
Peak E2 Level (nmol/I)	1068.45± 134.78	1098.57± 133.66	0.313
Endometrial thickness	10.98±2.76	10.89±2.85	0.885

$p < 0.05$ is considered statistically significant.

Table 2. — *Frequency of pregnancy and abortus.*

	Frequency of pregnancy (%)	Frequency of abortus (%)
Group A (n=36)	44.4% (n=16)	8.3% (n=3)
Group B (n=47)	48.9% (n=23)	10.6% (n=5)
p value	0.684	0.724

$p < 0.05$ is considered statistically significant.

Table 3. — *Different categories of delivery mode and live birth rates.*

	Group A (n=36) Frequency (%)	Group B (n=47) Frequency (%)	*p* value
Cesarian delivery	76.9% (n=10)	66.7% (n=12)	0.535
Vaginal delivery	23.1% (n=3)	33.3% (n=6)	
Live birth rate	36.1%	38.3%	0.838

$p < 0.05$ is considered statistically significant.

inations. Sonohysterography was performed with 8F foley catheter and saline infusion. The diameter of each endometrial polyp was calculated as the mean value of three individual measurements. According to the diameter and number of the polyps, patients were divided into two separate groups. Group A consisted of 36 patients having an endometrial polyp with a diameter ≤ one cm; whereas 47 patients were included in Group B who had a polyp with a diameter > one cm or more than one polyps.

All patients underwent a hysteroscopic polypectomy and ICSI treatments were started in the following cycle. The endometrial polyps were removed under general anesthesia with a ten-mm monopolar cutting loop resectescope. The pathological examination confirmed the diagnosis of endometrial polyp in each patient. Frozen embryo transfers were excluded from the study.

Starting from the 21st day of the spontaneous menstrual cycle, all of the patients received standard GnRH agonist (leuprolid acetate) treatment. On the third day of the resulting withdrawal bleeding, recombinant FSH treatment was started. Recombinant FSH doses were titrated according to the E2 levels and the standard criteria for follicular maturation on ultrasonographic examination and 250 mcg recombinant hCG (r-HCG) was administered when at least three of the follicles had reached a diameter of 17 mm. The oocytes were retrieved 36 hours later under intravenous sedation anesthesia and transvaginal ultrasound guidance. Oocytes were inseminated four to six hours after retrieval by ICSI using fresh ejaculates. Prior to the transfer, the overall quality of the embryo was evaluated; thereafter each patient received two embryos between the third to fifth days of oocyte retrieval via a soft catheter under the guidance of transabdominal sonography.

On the day of oocyte retrieval, the luteal phase support was started as a daily vaginal application of 90 mg progesterone. On the 12th day following the embryo transfer, a serum b-hCG level of 20 IU/L was recognized as biochemical pregnancy; the presence of the gestational sac in ultrasonographic examination six weeks following the embryo transfer was regarded as clinical pregnancy.

Total dose of gonadotropins, peak E2 level, number of oocytes retrieved, endometrial thickness on the day of hCG injection, clinical pregnancy rates and clinical abortion rates were compared between the two groups. The statistical analysis of the data was performed with independent Student *t*-test and chi-square test. The values are presented as mean ± SD if not stated otherwise.

Results

A total of 83 patients were included in the study; Group A consisted of 36 patients having an endometrial polyp with a diameter ≤ one cm; whereas 47 patients were included in Group B who had a polyp with a diameter > one cm or more than one polyps. According to various parameters including average age, body mass index (BMI), duration of infertility, required total gonadotropin dosage, number of retrieved oocytes, peak E2 level, and endometrial thickness on the day of hCG application, the comparison of the two groups did not reveal a statistically significant difference ($p > 0.05$) (Table 1).

Pregnancy was achieved in 16 patients (44.4%) in Group A and 23 patients (48.9%) in Group B. The pregnancy ratios did not reveal a statistically significant difference between the two groups ($p = 0.684$) (Table 2). On the other hand, abortion has occurred in three patients (8.3%) in Group A and five patients (%10.6) in Group B; the comparison of these findings revealed no statistically significant difference between the groups ($p = 0.724$) (Table 2). The analysis of the pregnant women also showed that in Group A, ten patients (76.9%) had undergone cesarian section and three patient gave birth through normal vaginal delivery. In Group B, 12 women (66.7%) gave birth by caesarian section and six women (33.3%) by normal vaginal delivery. The comparison of the living birth rates and the delivery methods revealed no statistically significant difference between the two groups ($p = 0.53$) (Table 3).

Discussion

Asymptomatic endometrial polyps are often incidentally detected during the treatment cycles of assisted reproductive technology. Polyps are either composed of immature endometrium that is unresponsive to progesterone and responsive to the growth stimulus of estrogen (the most common type) or they can be also composed of a functional endometrium which can respond to the ovarian hormones just like endometrium [12]. Endometrial polyp is the most

commonly encountered pathological finding during a hysteroscopic evaluation that is performed before the IVF intervention.

In a study by Fatemi *et al.* the prevalence of endometrial polyp was reported as 6% in a group of 678 patients waiting for IVF/ICSI who had a normal transvaginal ultrasonography and no sign of an intrauterine pathology [13].

During the therapy cycles with assisted reproductive technology, the achievement of a successful embryonic implantation is a rather complex process. The most important factors in this respect are the overall quality of the embryo and the endometrial receptivity [14]. Moreover, the diameter, amount, and location of the polyps may also have an impact on the reproductive results.

If the ultrasonographic examination before the IVF or cryo-embryo transfer indicates a suspicious presence of a polyp, a thorough investigation is warranted, followed by appropriate treatment directed at the polyps. On the other hand, polyps smaller than 20 mm and incidental polyps encountered in patients receiving gonadotropin stimulation during IVF have to be treated with a different approach. In such a case ovarian stimulation can be sustained and fresh embryo transfer can be accomplished. Following the cryopreservation of all embryos and removal of the polyp, embryo transfer can be completed; as a rare alternative, the cycle is cancelled and polypectomy is planned [15].

In several studies the effect of endometrial polyps on the pregnancy rates was investigated in patients subject to IVF, intrauterine insemination (IUI) and spontaneous pregnancy cycle. These studies have yielded different results. In a randomized controlled study (n=215), a statistically significant increase in pregnancy rates was reported in patients who had undergone hysteroscopic polypectomy and intrauterine insemination with gonadotropin dependent ovarian hyperstimulation (63% *vs.* 28%, $p < 0.001$) [8]. Additionally, several non-randomized studies have demonstrated an increase in spontaneous pregnancy rates following hysteroscopic polypectomy in women with polyp and infertility due to an unknown cause [5, 6, 16].

HOXA10 and HOXA11 are known as the molecular markers of the endometrial receptivity. Rackow *et al.* conducted a study and investigated the endometrial polyps which were hysteroscopically diagnosed with help of HOXA10 and HOXA11 and the effects of these polyps on endometrium. In uteruses carrying endometrial polyps, an increase in HOXA10 and HOXA11 mRNA levels have been documented, which could have disturbed the implantation process. These findings have suggested a molecular mechanism that is responsible for the decrease in pregnancy rates among the women with endometrial polyps. Therefore Rackow *et al.* primarily evaluated the uterine cavity in infertile women; if an endometrial polyp was detected, they suggested the application of hysteroscopic polypectomy before the infertility treatment in order to increase the fertility [17].

In a study conducted by Stamatellos *et al.* [18], the effect of endometrial polyp diameter on pregnancy rates was investigated in spontaneous cycles. The patients were divided into two groups: those patients with an endometrial polyp diameter equal or below one cm constituted the first group and patients with a diameter above one cm or with multiple endometrial polyps comprised the second group. In both groups patients were followed up for three to 18 months after the hysteroscopic polypectomy procedure and the rates of spontaneous pregnancy, term pregnancy, and spontaneous abortion were analyzed. Following the procedure the rates of spontaneous pregnancy and term pregnancy demonstrated an increase; in the group of patients with a small polyp, the rates were calculated as 67.6% and 58.8%, respectively. In the other group with a greater polyp or multiple polyps, the rates were 57.1% and 51%, respectively. The comparison of both groups for the rates of spontaneous pregnancy and live birth following polypectomy revealed no statistically significant difference. The total rate of spontaneous abortion in the first trimester was identified as 6% (five patients) and no significant difference was found between the groups. The present study differed from this research in that the clinical pregnancy and live birth rates following the polypectomy procedure were analyzed during ICSI cycles and not during spontaneous cycle. In the present study the clinical pregnancy rate and the live birth rate were found as 44.4% and 36.1%, respectively, in Group A and as 48.9% and 38.2%, respectively in Group B. Similar to the findings of Stamellos *et al.* the present authors also found no significant difference in clinical pregnancy and live birth rates between the two groups.

In another study by Lass *et al.* [19] patients with endometrial polyps encountered during transvaginal ultrasonographic examination in IVF cycle were evaluated. They reported that endometrial polyps with a diameter smaller than two cm do not decrease the implantation or pregnancy rates but increase the abortion rates. Therefore they suggested the application of embryonic cryo-preservation upon detection of an endometrial polyp during IVF cycle. In the present study the authors analyzed whether polyp diameter was related to the pregnancy results in patients in whom they have detected endometrial polyp and performed hysteroscopic polyp resection prior to the ICSI cycle. In the present study the diameter of the endometrial polyp (> one cm *vs.* < one cm) or its multiplicity had no significant influence on the rates of clinical pregnancy. The rates of abortion also did not demonstrate a statistically significant difference between the groups.

In a study conducted by Preutthipan *et al.* [20] 190 patients underwent hysteroscopy and women diagnosed with an endometrial polyp were divided into two groups according to the size of the polyp diameter (≤ 2.5 cm *vs.* > 2.5 cm). Following the polypectomy procedure, cumulative pregnancy rates were analyzed. The pregnancy rates did not show a statistically significant difference between the groups. In

this study clinical pregnancy rates were evaluated in spontaneous cycles, in this respect it differs from the present study.

In another study led by Işıkoğlu *et al.* [21], patients receiving ICSI has been divided into three groups: patients with a polyp diameter ≤ 1.5cm detected during ovarian stimulation, patients without polyp detection, and patients who have undergone hysteroscopic polypectomy. In each group pregnancy and implantation rates were evaluated. The comparison of the groups for pregnancy and implantation rates has revealed no statistically significant difference. In the same study the authors were convinced that endometrial polyps with a diameter ≤ 1.5cm did not have a significant influence on the pregnancy and implantation rates during ICSI. Upon the analysis of various data in the literature, it can be concluded that in patients prepared for IVF or ICSI, polyps, independent from their size and amount, do not have a negative effect on the pregnancy rates; nevertheless it seems that the increase in polyp size has a positive correlation with the rise in the rate of early pregnancy loses.

In conclusion, various approaches exist for the management of patients with endometrial polyps undergoing ICSI cycles. In the present study the authors applied hysterescopic polypectomy before the ICSI cycle and observed that in these patients the reproductive results did not depend on the diameter of the endometrial polyps. However more randomized controlled trials are needed which will further enlighten the influence of the hysteroscopic polypectomy before the ICSI cycle on pregnancy outcomes.

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