Article

Endometrial polyps smaller than 1.5 cm do not affect ICSI outcome

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Abstract

This study aimed to determine whether the presence of endometrial polyps discovered during ovarian stimulation affects the outcomes of intracytoplasmic sperm injection (ICSI) cycles. This retrospective descriptive study was conducted in a private assisted reproductive technology unit. Medical records of ICSI cycles performed between January 2003 and December 2004 were reviewed. Patients were divided into three groups: patients with endometrial polyps discovered during ovarian stimulation (group 1, $n = 15$), patients who underwent hysteroscopic polyp resection prior to their ICSI cycle (group 2, $n = 40$) and patients without polyps (group 3, $n = 956$). Main outcome measures were clinical pregnancy rates and implantation rates. Age of the patients, age of the husbands, body mass index, total amount of gonadotrophins used, length of stimulation, peak oestradiol concentrations, peak endometrial thickness and number of embryos replaced were not significantly different between the groups, nor were the pregnancy and implantation rates. Only one patient (12.5%) from the first group experienced miscarriage within 12 weeks of pregnancy. In conclusion, endometrial polyps discovered during ovarian stimulation do not negatively affect pregnancy and implantation outcomes in ICSI cycles.

Keywords: *endometrial polyp, ICSI, implantation rate, pregnancy rate*

Introduction

Embryo implantation depends mainly on two factors, embryo quality and uterine receptivity. Endometrial thickness, structure and texture are the crucial elements in endometrial receptivity. Structural pathologies destroying the texture of the endometrium may play an important role in both implantation failure and miscarriage. Endometrial polyps (EP) are among the most common cavity lesions that cause uterine texture abnormalities. EP may vary in size from local elevation of the endometrium to a growth filling the endometrial cavity. More than half of the EP encountered in infertile women were found to be <1 cm and only 16% of them were >2 cm (Spiewankiewicz *et al*., 2003). EP have been shown to interfere with fertility in natural conceptions (Valle, 1984; Youfang *et al*., 1992; Varasteh *et al*., 1999) and in intrauterine insemination cycles (IUI) (Perez-Medina *et al*., 2005).

Theories including space-occupying lesion mechanisms (Spiewankiewicz *et al*., 2003) or an increase in glycodelin concentrations (Richlin *et al*., 2002) have been proposed for the pathophysiological association with infertility. The incidental finding of a polyp during ovarian stimulation in an IVF or intracytoplasmic sperm injection (ICSI) cycle is always a dilemma for the assisted reproductive technology clinician; should he or she remove the EP or does he or she cancel the treatment cycle? The clinician may, however, choose to continue with the treatment, ignoring the possible effect of the EP on the pregnancy and implantation outcomes.

It was felt that it would be very useful for the assisted reproduction clinician to know the impact of small EP on assisted reproduction cycles outcomes. It was therefore decided to initiate a retrospective study to investigate the effect of a polyp found during ovarian stimulation on pregnancy and implantation rates in ICSI cycles.

Materials and methods

This retrospective investigation conducted at Antalya IVF received ethics committee approval. Medical records of all ICSI cycles performed in 2003–2004 were reviewed. Three patient groups were constructed. Group I included 15 patients with an EP (<1.5 cm in diameter) discovered during ovarian stimulation for their ICSI cycle. Group II included 40 patients who were diagnosed with EP prior to their treatment cycle. These patients underwent a hysteroscopic polyp resection and ICSI treatments were started in the following cycle. Group III included 956 patients in whom no EP were discovered, prior to and during their ICSI cycle. Frozen embryo replacements were not included in the study.

All patients routinely underwent endovaginal ultrasound examinations and sonohysterographies prior to entering the ICSI treatment programme, to confirm that their uterine cavities were normal. Ovarian stimulation was according to the standard long-course protocol using gonadotrophin-releasing hormone (GnRH) agonist down-regulation. Down-regulation was confirmed by ultrasound, linear endometrium and suppressed ovaries, and by serum oestradiol concentrations (<50 pg/ml). Gonadotrophin stimulation was commenced on the same day and continued until at least two follicles ≥18 mm were detected. Human chorionic gonadotrophin (HCG) (10,000 IU) was administered, followed 35 h later by oocyte retrieval. Up to four cleaving embryos were transferred to the uterine cavity approximately 50 h after oocyte retrieval. Progesterone (50 mg/day in oil) was administered for luteal phase support until the day of the β-HCG assay. Ongoing (clinical) pregnancies were confirmed by ultrasound detection of an intrauterine gestational sac with cardiac activity 3 weeks after embryo transfer.

During ovarian stimulation, serial transvaginal ultrasound (TvUSG) examinations were carried out using a 7.5 MHz vaginal transducer (Sonoline Sienna; Siemens, Erlangen, Germany). The presence of a polyp was indicated if a hyperechogenic endometrial mass was observed. The diagnosis of a polyp was always verified by a second clinician (**Figure 1**). The measurement of each polyp was done in two planes and the average diameter was recorded. When a polyp of >1.5 cm was detected, a hysteroscopic polyp resection was performed as soon as possible after oocyte retrieval. The embryos from the cycle were frozen and transferred at least 2 months after the resection. When a polyp <1.5 cm was detected, patients were given detailed information, based on published data, to assist them in their decision-making with regards to their options, to proceed to embryo transfer, or to stop the treatment and to freeze all embryos for transfer at a later stage. All patients with a <1.5 cm polyp, however, chose to continue with their treatment cycle to the transfer of embryos. All hysteroscopies to resect a polyp were performed under general anaesthesia using a continuous flow 7 mm operative hysteroscope (Storz, Tuttlingen, Germany). Polyps were resected by loop resectoscope via electrocautery. Group I patients with a negative pregnancy test underwent hysteroscopy in the post-menstrual phase following the ICSI cycle.

Clinical pregnancy rates and implantation rates were the primary study outcomes calculated. In addition demographic factors, patient's age, husband's age, body mass indices (BMI), aetiological reasons of infertility stimulation factors, total amount of gonadotrophins used, length of stimulation, peak oestradiol concentrations, peak endometrial thickness, number of embryos replaced and clinical abortion rates were recorded. Kruskal–Wallis and chi-squared tests were used for the statistical analyses. An alpha value < 0.05 was considered significant.

Results

The demographic, stimulation, and pregnancy factors recorded for the three groups, group I ($n = 15$), group II ($n = 40$) and group III ($n = 956$), were compared. None of the polyps in group I was larger than 1.5 cm, with eight being <1 cm. In group II, the size of the polyps was <1 cm in 23 cases, between 1 and 1.5 cm in 11 cases and >1.5 cm in six cases.

The average demographic factors, age of the patients, age of the husbands and patient BMI were not significantly different (**Table 1**). Aetiological reasons for infertility (**Table 2**) and stimulation factors (**Table 3**) were also not significantly different between the three groups. The average number of gonadotrophin units used for group I was elevated compared with the other two groups. Information on embryo quality has not been included, as it was not available in all cases.

Pregnancy rates and implantation rates for the three groups were also not significantly different (**Table 4**). One of the eight (12.5%) pregnancies from group I and 26 out of the 325 (8.0%) pregnancies from group III experienced first trimester miscarriage.

Six patients in group I who experienced a negative pregnancy test result, and one patient who experienced a chemical abortion, underwent a hysteroscopy. The findings of hysteroscopic examination are recorded in **Table 5**. The hysteroscopic examinations confirmed the ultrasound findings in four (57.1%) of these patients and these were further verified histopatologically.

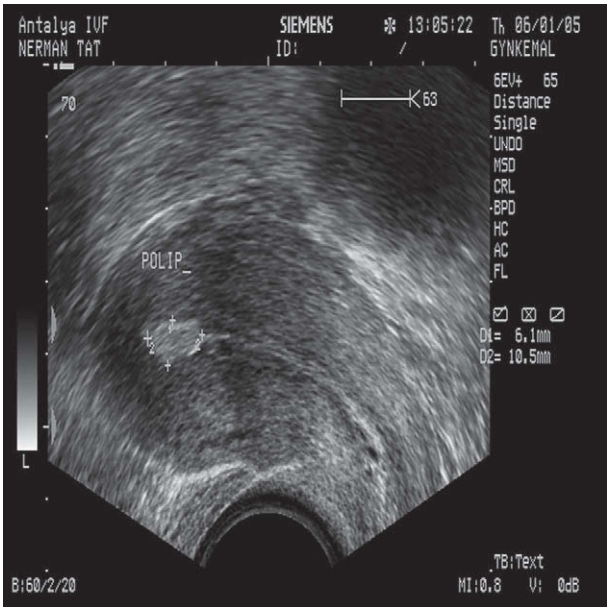

Figure 1. Appearance of endometrial polyp on transvaginal ultrasound.

Table 1. Demographic data for the three patient groups expressed as median (25–75%).

Parameter	*Group I*[a]	*Group II*[a]	*Group III*[a]
No. of patients	15	40	956
Maternal age (years)	34 (29.2–37.7)	31 (28–34)	30 (27–34)
Paternal age (years)	38 (32.5–40)	34 (32–38)	34 (31–38)
Body mass index	26.2 (23.5–30.8)	28 (23–32)	26 (23–29)

Kruskal-Wallis ANOVA showed no statistically significant differences between groups.
[a]For description of the groups, see Materials and methods.

Table 2. Infertility aetiology of the three groups.

Parameter	*Group I*[a]	*Group II*[a]	*Group III*[a]
Male factor (%)	3/15(20.0)	15/40(37.5)	273/956(28.5)
Tubal factor (%)	4/15(26.7)	6/40(15.0)	210/956(21.9)
Other female factor (%)	2/15(13.3)	4/40(10.0)	172/956(17.9)
Unexplained (%)	1/15(6.7)	7/40(17.5)	114/956(11.9)
Multifactorial (%)	5/15 (33.3)	8/40 (20.0)	187/956(19.6)

Chi-squared test showed no statistically significant differences between groups.
[a]For description of the groups, see Materials and methods.

Table 3. Stimulation characteristics for the groups expressed as median (25–75%).

Parameter	*Group I*[a]	*Group II*[a]	*Group III*[a]
Duration of stimulation (days)	10 (9–10.7)	9 (9–10)	10 (9–11)
Gonadotrophin units (IU)	3325 (1637–4687)	2537 (1525–3200)	2500 (1075–3600)
Peak oestradiol (pg/ml)	2782 (1055–3403)	2908 (1651–4857)	2564 (1138–4760)
Peak endometrial thickness (mm)	11 (9.5–12)	12 (10–14.1)	11 (10–13)
No. of embryos transferred	3 (2–4)	3 (2–4)	3 (2–4)

Kruskal-Wallis ANOVA showed no statistically significant differences between groups.
[a]For description of the groups, see Materials and methods.

Table 4. Main outcome variables for the three groups of patients.

Parameter	*Group I*[a]	*Group II*[a]	*Group III*[a]
Implantation rate%	26.4	17.6	17.9
Clinical pregnancy/ embryo transfer (%)	8 (53.3)	18 (45.0)	325 (40.1)

*Chi-squared test showed no statistically significant differences between groups.
[a]For description of the groups, see Materials and methods.

Table 5. Hysteroscopy findings of group I patients (n = 15) after intracytoplasmic sperm injection treatment.

Positive βHCG (n = 9)			*Negative–βHCG* (n = 6)	
n	*P outcome*	*HS outcome*	n	*HS outcome*
7	Ongoing	NP	4	EP
1	Clinical abortion	NP (lost to follow-up)	2	Thickened endometrium
1	Chemical abortion	Normal HS	–	–

EP = endometrial polyp, HS = hysteroscopy, NP = not performed, *P* = pregnancy.

Discussion

Uterine cavity defects including fibroids, synechiae and EP have been associated with infertility and recurrent abortion in 5–10 and 15–50% of cases respectively (Vallach, 1972; Stray-Pedersen and Stray-Pedersen, 1984; Seibel, 1990; Fathalla, 1991; Keltz *et al.*, 1997). One of the most common intrauterine lesions encountered during infertility workup are polyps, which are usually as result of the overgrowth of endometrial glands and stroma covered by endometrial epithelium. In more than half of cases the polyp is located in the uterine fundus and presents as a single lesion in more than 80% of cases.

There are very few reports in the literature concerning infertility and EP and the effect of polypectomy on further reproductive outcomes, especially with regard to assisted reproduction treatments. Past studies examining the effect of polyps on natural conception (Valle, 1984; Youfang *et al.*, 1992; Varasteh *et al.*, 1999) have proposed hysteroscopic polypectomy as the optimal therapy for these lesions. The precise mechanism, if any, by which a small, solitary EP restricts normal reproduction ability is not truly known. The primary mechanism has been thought to be the change of the endometrial environment required for embryo implantation. They may act in much the same way as an intrauterine device and cause an inflammatory change in the endometrium, or the presence of a polyp may distort or diminish the volume of the uterine cavity.

In review of their medical records of 21 years, Varasteh *et al.* (1999) reported cumulative pregnancy rates of 78.3% after hysteroscopic polypectomy. They also showed that infertile women post-hysteroscopic polypectomy had a shorter time to pregnancy than those who had normal uterine cavities on hysteroscopy (Varasteh *et al.*, 1999). In the study by Spiewankiewicz *et al.*, (2003), 19 out of 25 infertile patients (76%) in whom polypectomy was performed conceived within a 12-month period. Other studies found lower cumulative pregnancy rates after polypectomy, 23 versus 32% (Valle, 1984; Youfang *et al.*, 1992). In examining the effect of polyps on IUI, Perez-Medina *et al.* (2005), obtained a cumulative pregnancy rate of 64% after hysteroscopic polyp excision, nearly twice that of patients with polyps who underwent diagnostic hysteroscopy only (Perez-Medina *et al.*, 2005). All these findings suggest that polyps do contribute to infertility and that they should be removed. Furthermore, pregnancies after polypectomy are frequently obtained spontaneously while waiting for the treatment (Perez-Medina *et al.*, 2005), suggesting a negative effect of the polyp on implantation.

Most polyps are asymptomatic during ovarian stimulation and are discovered incidentally. The diagnosis can be done either indirectly by TvUSG, sonohysterography or directly by hysteroscopy. In spontaneous and induced cycles the sonographic appearance of the endometrium varies according to its phases of development and the reproductive hormone concentrations. Although TvUSG has been reported to be an accurate method to detect EP (Kupfer *et al.*, 1994), it is often difficult to distinguish between a true polyp and a polypoid endometrium, especially after ovulation induction, which causes a thickened late-proliferative endometrium (Lass *et al.*, 1999). Hysteroscopy therefore remains the best method for the diagnosis (Brown *et al.*, 2000; Spiewankiewicz *et al.*, 2003).

As the qualitative description of endometrium by ultrasound is biased by personal interpretation, in this study a second

operator confirmed the diagnosis to minimize the probability of misinterpretation. The post-treatment hysteroscopy findings suggest that some of the lesions diagnosed as EP during COH are in reality temporary focal hyperechogenic images compatible with EP instead of true polyps. Hence, the term 'polyp-like image' is proposed for this clinical finding, unless the diagnosis is confirmed either by hysteroscopy or histopathology. The overall incidence of polyps in the ICSI series was 1.48%. Lass *et al*. (1999) reported similar incidence (1.4%) in their IVF cycles. Seven patients from group I, with a polyp identified by endovaginal ultrasound examinations and sonohysterographies prior to entering the ICSI treatment programme, had their polyps evaluated by hysteroscopy and histopathology. Only four (57.1%) of these patients had their polyp diagnosis confirmed.

Limited data are available in the literature about the effects of polyps in assisted reproduction programmes and in particular for ICSI cycles (Hereter *et al*., 1998; Lass *et al*., 1999). In the study of Lass *et al*. (1999), 83 women with polyps <2 cm in diameter were divided into two groups before oocyte retrieval. Forty-nine women completed the standard IVF–embryo transfer treatment and 34 women underwent hysteroscopy and polypectomy immediately after oocyte retrieval. The latter group's embryos were cryopreserved and transferred in a subsequent cycle. They found that the pregnancy rate of the first group was similar to the overall pregnancy rate for their clinic over the same period of time. The miscarriage rate tended to be higher but the difference was not statistically significant. Similarly, Hereter *et al*. (1998), in their series of 33 patients with an EP compared with 280 without an EP, found no difference between the groups with respect to implantation and abortion in IVF cycles (Hereter *et al*., 1998). In the present study, with a possible true polyp rate of 57.1% in the polyp group, no difference was observed in the pregnancy and implantation rates between the groups. Neither was there a difference in the miscarriage rate; one of the eight (12.5%) pregnancies from group I and 26 (8.0%) of the 325 pregnancies from group III experienced first trimester miscarriage.

Notwithstanding the limitations of this study, retrospective design, ethical constraints, means of first diagnosis and sample size, it is likely that polyps of <1.5 mm will not require treatment prior to an assisted reproduction treatment procedure. The data regarding group II patients also suggest that there is no difference in pregnancy and implantation rates when polyps are diagnosed and addressed surgically prior to COH; the size of EP were >1.5 cm in six cases in group II, and there are no literature data on the effect of EP> 1.5 cm. Regarding the pregnancy rates of group I and group II, the power of the present study is low (0.18) due to small sample size. To reach a power of 0.80 assuming the same pregnancy rates, the number of subjects should be 230 in each group. However, the low incidence of de-novo polyp formation during COH makes it difficult to collect a larger series of patients.

When a polyp is encountered prior to an ICSI or IVF cycle, it may be clinically unethical to randomize patients. Lass *et al*. (1999) performed their randomization prior to oocyte retrieval, which may be more acceptable. Relying on TvUSG as the only means of diagnosis during COH may also result in misrepresentation of groups and their outcomes. The effect of the use of more invasive modalities such as sonohysterography, hysteroscopy or histopathology during COH is uncertain. Recently, Batioglu and Kaymak (2005) treated six IVF patients by hysteroscopic polypectomy preceding oocyte retrieval and in three cases pregnancy was achieved. Their trial suggests the possibility that hysteroscopic polypectomy during COH may be a harmless procedure, but their series is too small to be conclusive.

This study presents the first data on the impact of endometrial polyp-like images on the outcome of ICSI cycles. It is concluded that polyp-like images <1.5 cm which are encountered during ovarian stimulation do not have any negative effects on pregnancy rates and implantation rates in ICSI cycles. Cancellation of the embryo transfer is unnecessary and completion of the cycle should be the appropriate approach for these cases. Larger studies are needed to further clarify the effects of true polyps and polyp-like images. The impact of polyps larger than 1.5 cm in diameter, on assisted reproduction outcomes does warrant further investigation.

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