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Original Research Article

Impact of Intrauterine Masses Diagnosed by Ultrasound During Ovarian Stimulation on Fresh Embryo Transfer Outcomes

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Objective: **to evaluate the impact of intrauterine masses discovered in ultrasound during IVF-ICSI cycle on pregnancy rate and implantation.** ***Study design:*** **Case – control study of all IVF cycles performed in our ART center from 2007 to February 2013. The study group consisted of 39 patients in whom an intrauterine mass was visualized in ultrasound during ovarian stimulation. The control group was composed of 39 age matched patients with normal endometrium. All patients were planned to have fresh embryo transfer. We also analyzed the hysteroscopic findings in patients who failed to be pregnant.** ***Results:*** **The mean size of intrauterine masses was 11.1 ± 5.7 mm (ranging 2-22 mm). Pregnancy rate was significantly lower in the study group (9.1% versus 26.4%, p<0.05). There was no difference regarding implantation rate (6 % versus 10.6%, NS). Among the 17 patients who had a subsequent diagnostic hysteroscopy, 11 were effectively polyps (66%).** ***Conclusion:*** **According to our study, intrauterine masses diagnosed in ultrasound during ovarian stimulation are associated with decreased pregnancy rate.**

Keywords: Implantation, IVF, Polyps, Ultrasound, Hysteroscopy.

INTRODUCTION

In IVF, implantation remains poorly understood. This process requires a high implantation potentiality embryo, a functional endometrium and an effective dialog between those major actors. The dialog involves synchronized mutual reactions. Some pathologic conditions are identified as associated with implantation failure such as poor embryo quality or high level of aneuploidy. Uterine pathologies are also a common cause of implantation failure: intrauterine adhesions, endometritis or decreased endometrial thickness. Endometrial polyps and submucous /intra-cavitary fibroids are a frequent cause of implantation failure in IVF or natural conception.

Hysteroscopy is the reference exam for uterine cavity evaluation. It has also been proved that, even when performing normal hysteroscopy before IVF, it increases pregnancy rate by inducing inflammatory reaction leading to improvement in implantation rate [1]. However, hysteroscopy is still not performed systematically before IVF by all teams, for various reasons such as cost or availability [2]. In contrast, ultrasound, which is less effective in detecting intrauterine abnormalities, is performed systematically before starting ovarian stimulation.

In some cases, despite a normal basal ultrasound exam, intrauterine hyperechogenic masses appear during ovarian stimulation when endometrium becomes thick. These images are generally considered as undiagnosed small polyps or polypoid hyperplasia [3]. This situation raises several concerns about its impact on IVF outcomes and the way to manage it.

MATERIAL AND METHODS

This is a case – control study of all fresh ICSI cycles performed at our IVF center between April 2007 and February 2013. Institutional Review Board approval was not requested for this study, because it is a retrospective analysis and all standard procedures were respected.

We identified all patients, candidates for IVF, in whom intrauterine mass has been detected during ovarian stimulation while the basal ultrasound performed in the first day of cycle was normal (n=39). All patients diagnosed with intrauterine

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masses have continued their IVF cycle and were advised to have an embryo transfer. To constitute a control group, we randomly selected 39, age matched, patients that have attempted an IVF cycle during the same period, with no uterine abnormalities detected on ultrasound during ovarian stimulation.

All patients underwent pituitary desensitization using Leucopride acetate (Decapeptyl, Ipsen®) given daily 0.1mg from the first day of cycle in case of flare-up protocol or from 21th day of the previous cycle in case long agonist protocol. For antagonist cycles, Cetrorelix (Cetrotide 0.25mg, Merck Serono®) was started when E2 was superior to 150 pg/ml. Ovarian stimulation was performed using recombinant FSH (Gonal-F, Merck Serono®) or HMG (Menopur, Ferring®). Ovarian stimulation was monitored according to follicular size and plasma estradiol levels. Ultrasound was performed using Aloka alpha 7(Hitachi ®)

Endometrium thickness was measured and in case of intrauterine lesions, masses were measured and located. When at least three or more follicles reached a diameter of 17 mm, human chorionic gonadotrophin (Ovitrelle, Merck Serono®) was administered. Oocyte pickup was performed 36 h later. ICSI was used in all cases for oocytes fertilization. Embryo transfer was performed 2 or 3 days later and luteal phase support was started using vaginal progesterone 200mg three times a day (Utrogestan, Besins Healthcare®).

A pregnancy test was performed 15 days after embryo transfer, a pregnancy was diagnosed in case of BHCG level > 50mUI/ml. In this case, an ultrasound was performed at 5 GW. If no pregnancy occurred or no embryo was transferred, patients were advised to have a diagnostic hysteroscopy using 2.9-mm, 30° office hysteroscope (Storz, Germany). In case of polyp or fibroid, an operative hysteroscopy under general anesthesia was performed. If a polypoid hyperplasia was diagnosed, a progestin treatment was administrated for 21 days.

Chi-square test was used to compare qualitative variables. Student test was used to compare quantitative variables. A cut off of 0.05 was considered for statistical significance. SPSS software was used for statistic analysis.

RESULTS

Study and control groups were similar regarding demographic characteristics. In the study group, 7 (17.9%) patients had history of previous polyp resection while no patients in the control group reported such previous surgery (the difference is not significant) (table1).

There was no difference regarding ovarian stimulation outcomes between two groups. Pregnancy rate was significantly lower in the study group (9.1% versus 26.4%, $p<0.05$). Implantation rate was lower in the study group, but this was not significant (6 % versus 10.6%, NS) (table2).

The size of the intrauterine masses was determined in 27 patients. The mean size of polyps was 11,1 ± 5.7 mm (ranging 2-22 mm). In 13 cases (53%), intrauterine masses were equal or superior to 10 mm. There was no significant difference regarding pregnancy rate between patients with intrauterine mass ≥ 1 cm and < 1 cm (14% versus 7% respectively, NS).

Seventeen (47 %) of the 36 patients who failed to conceive had diagnostic hysteroscopy in our unit. Among them, only 11 were found to have polyps (66%). In 4 cases, the exam was normal (23.5%) (Table 3).

DISCUSSION

Discovering an intrauterine hyperechogenic mass in ultrasound during ovarian stimulation while basal exam is normal raise two questions: what is the histological nature of these findings? What is their impact on IVF outcome?

Intrauterine hyperechogenic masses are generally diagnosed as polyps. Although polyps are commonly considered as associated with poor implantation and pregnancy rate, this has not been confirmed by different authors.

Three previous studies have studied the impact of intrauterine masses discovred during ovarian stimulation. Lass reported 83 cases of suspected polyps on ultrasound during ovarian stimulation. In this study, authors advised their patients to choose between (i) proceeding with the IVF cycle to embryo replacement or (ii) proceeding to oocyte recovery, hysteroscopy and polypectomy in the same procedure, followed by insemination of the oocytes and freezing and, then, subsequent transfer. They reported similar pregnancy rate in the two protocols. In addition, no difference was found when they compared those groups to pregnancy and implantation rate in the general population during the same year[3].

Isikoglu have published a study about 15 patients in whom polyps were suspected on ultrasound during ovarian stimulation. The author compared their IVF outcomes to a group of patients that had had a polypectomy prior to ovarian stimulation and to another group of patient without any intrauterine pathologies. No difference was found regarding pregnancy and implantation rate between the three groups[4].

Recently, Tiras have published a large retrospective study about 128 cases of diagnosed polyps during IVF cycle. No difference have been found regarding pregnancy and implantation rate compared to patients with polypectomy prior IVF cycle or patients with normal uterine cavity[5].

In contrast with these publications, our results showed that the pregnancy rate is significantly lower in patients having abnormal endometrium on ultrasound during ovarian stimulation.

Surprisingly, no miscarriage occurred in the study group and no difference has been demonstrated regarding pregnancy loss. This is probably due to the small number of occurred pregnancy.

To our knowledge, our study is the first to demonstrate a potential negative impact of the appearance of intrauterine masses during ovarian stimulation on pregnancy rate in IVF.

Conclusions have to be taken with caution. The discordance with the other studies may be due to a heterogeneity regarding inclusion criteria, especially regarding polyp size.

Indeed, Lass have excluded all cases where masses were superior to 2 cm (cycles were cancelled and patients referred to surgery [3]. Isikoglu, also, have excluded all cases where intrauterine masses were superior to 1.5 cm and proceeded to an embryo freezing [4]. Tiras, even if he did not apply a cut off, reported a maximum size of 14 mm[4]. In our study the mean size was 11,1 ± 5.7 mm with 53% of intrauterine masses being superior to 10 mm with a maximum of 22 mm. However, despite a decreased pregnancy rate in patients having an intrauterine mass > 1 cm, we failed to demonstrate any impact of size, probably due to the small sample.

Another possible bias is the real nature of such images visualized before oocyte retrieval. In almost all reported studies, the authors have considered the discovered images on ultrasound as polyps. Tiras have confirmed the diagnosis of polyp in all cases that had a subsequent hysteroscopy[5].

Table 1: Demographic characteristics of patients.

	Study group N = 39	Control Group N = 39	p
Age (years)	36,91±4,53	35,18±4,52	NS
Basal FSH (mUI/ml)	7,22±3,60	8,01±3,77	NS
Cycle Rank	1,6±0,93	1,36±0,74	NS
History of polyps	17.9%	0%	NS
Previous IVF failure	13.9%	16.7%	NS

Table 2: In vitro fertilization outcomes

	Study group N = 39	Control Group N = 39	p
Protocols			
Long	53.8%	63.2%	
Short	38.5%	36.8%	NS
Antagonist	7.7%	0%	
E2 level hCG day (pg/ml)	2084,19 ± 1667	1655,2 ± 1011,1	NS
Endometrium thickness (mm)	10,4 ± 2,56	10,5 ± 2,7	NS
Retreived oocyte	4,73±3,36	4,05±2,42	NS
Number of transferred embryos	1,83±0,77	1,89±0 ,63	NS
Patient with Embryo Transfer (%)	33(84.6%)	34(87.2%)	NS
Clinical pregnancy Rate per transfer (%)	3/33(9.1 %)	9/34(26.4 %)	0.05
Implantation rate	6%	10.6%	NS
Miscarriage rate	0%	25%	NS

Table 3: Hysteroscopic findings in patients who failed to conceive

Hysteroscopic Findings	Cases (n)	%
Polyps	11	64
Fibroid	1	5.8
Polypoid hyperplasia	1	5.8
Normal	4	23.5

In contrast, Isikoglu have confirmed the diagnosis of polyp in only 4 of 7 cases (57%). He reported 2 cases of thickened endometrium and a normal exam in one patient[4].

Interestingly, Lass have compared the hysteroscopy finding between women with suspected polyps on baseline ultrasound (after Agonist Gn-RH administration) or during ovarian stimulation. He reported similar findings respectively: confirmed diagnosis of polyp: 78.6% and 72.2%, polypoid hyperplasia: 14.3% and 16.7% and a normal exam: 7.1% and 11.1%[3].

In accordance with these studies, we confirmed that the intrauterine images, revealed by ultrasound during ovarian stimulation, do not correspond necessarily to polyps.

The appearance of intrauterine masses during IVF cycle is challenging situation. So far, we choose to proceed to embryo transfer as no study demonstrates a negative impact. Considering our new findings, we decided to change our strategy and we are currently evaluating freezing embryo and performing transfer after polypectomy. These have to be evaluated in a prospective study. Another strategy has been proposed by Batioglu and Madani [6-7], these authors have performed polypectomy during IVF cycle before embryo transfer. The studies reported few cases and this strategy need to be more evaluated especially the impact of an intrauterine surgery close to embryo transfer.

CONCLUSION

Intrauterine masses appearing during ovarian stimulation may correspond to an undiagnosed polyp or to polypoid hyperplasia. According our results, this situation is associated with low pregnancy rate. The adequate management of this situation is not well codified and should be evaluated.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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