




Fertility outcomes in patients with tubo-ovarian abscesses after an oocyte retrieval: a longitudinal cohort analysis

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Abstract

Purpose To determine the impact of pelvic inflammation caused by tubo-ovarian abscess (TOA) on ovarian response to stimulation.

Methods This retrospective longitudinal cohort analysis that was carried out in a tertiary university-affiliated medical center included 15 women with TOA during in vitro fertilization (IVF) cycles. The ovarian response to stimulation and the pregnancy rate were compared in two subsequent cycles, the initial IVF cycle that was complicated by TOA after oocyte retrieval (first treatment cycle) and the following IVF treatment (second treatment cycle) that occurred within a period of a year from the first cycle.

Results The mean number of retrieved oocytes was significantly higher in the first IVF cycle compared to the second cycle (8.1 ± 3.2 vs. 5.4 ± 2.5 , $P = .003$), corresponding to a 30% reduction in ovarian response to gonadotropin stimulation. Fertilization rates were significantly lower in the second cycle (4.1 ± 2.9 vs. 2.9 ± 1.7 , $P = .015$). Twelve women (80%) reached embryo transfer in the first cycle compared to 14 women (93.3%) in the second cycle. The mean number of transferred embryos was similar between the two cycles. There were no clinical pregnancies following the first cycle, and only one patient (6.6%) had a clinical pregnancy in the second treatment cycle.

Conclusions TOA following fertility treatment has a detrimental effect on ovarian function. The pregnancy rate in the immediate period following TOA is poor. Current data for recommending the deferral of fertility treatment following a TOA episode are insufficient, calling for more studies to address these issues.

Keywords Pelvic inflammatory disease · Pelvic abscess · Fertility · Endometriosis · Tuboovarian abscess

Introduction

Tubo-ovarian abscess (TOA) is a serious sequelae of pelvic inflammatory disease (PID), complicating more than 30% of the patients who are hospitalized with PID [1]. Despite adequate treatment, many patients will suffer from significant morbidity, including chronic pelvic pain, infertility and ectopic pregnancy [2, 3]. In the past, the treatment approach for TOA was surgical removal of all involved organs, i.e., total abdominal hysterectomy and bilateral adnexectomy [4]. However, this approach has been replaced by a more

conservative one as many of the patients are in their reproductive age and will desire future fertility [5]. Medical treatment with broad spectrum antibiotics is only effective in 34–87.5% of patients with TOA [6]. When clinical response is not achieved following medical treatment, additional interventions are needed by either laparoscopy, laparotomy, or imaging-guided drainage [7].

Pelvic infection is an uncommon complication following transvaginal oocyte retrieval (TVOR), with a reported incidence ranging between 0.03 and 0.24% [8]. Possible etiologies of pelvic infection following TVOR include inoculation of microorganism from the vagina into the pelvis and ovary, reinfection from preexisting chronic pelvic infection, direct contiguous bowel injury, and the presence of severe endometriosis and ovarian endometriomas [8].

We had shown that women with TOA following fertility treatments were characterized by a more severe clinical course as well as a complicated treatment outcome, as

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evidenced by higher levels of inflammatory markers, a prolonged hospitalization period, an increased surgical intervention rate, a higher conversion rate to laparotomy, and an increased perioperative complication rate [9].

The implications on ovarian response during and after an infectious episode, such as in PID, TOA, or endometrioma puncture, following fertility treatments are still inconclusive. Specifically, the deleterious effect of surgical intervention on ovarian reserve in women with TOA continues to be a matter of concern. The aim of the present study was to evaluate the ovarian response to stimulation in patients affected with TOA during in vitro fertilization (IVF) treatments and in the first cycle subsequent to the infectious episode.

Materials and methods

A longitudinal retrospective cohort study was performed in a tertiary university-affiliated medical center over 10 consecutive years. The institutional review board approved the study design, protocol, and waiver of informed consent (IRB approval number: 0533-16-TLV). The present study included 15 women who represent a subgroup of patients from our earlier study in which we evaluated the clinical course and reproductive outcomes of women with TOA following fertility treatments (IVF-associated TOA) [9]. The medical records of all patients who had undergone IVF treatments before and after TOA diagnosis between January 2007 and October 2017 were reviewed. Each woman served as her own control, with her first index cycle parameters (i.e., before TOA diagnosis) being compared with the second cycle parameters (i.e., the first one after TOA diagnosis).

Inclusion criteria in our study were as follows: sonographic evidence of TOA [10], diagnosis of PID according to the United States Centers for Disease Control and Prevention criteria for PID [11], diagnosis of TOA within 8 weeks following IVF treatment (first treatment cycle) and the following IVF treatment (second treatment cycle) occurred within a period of a year from the previous cycle. Patients in whom controlled ovarian hyperstimulation (COH) was not performed (frozen or egg donor cycles) were excluded.

The patients with TOA were treated according to our department protocol [9]. Briefly, those with suspected TOA were hospitalized. Intravenous (IV) antibiotics therapy consisted of the following regimen: IV ceftriaxone 1 g s.i.d, IV metronidazole 500 mg t.i.d, and doxycycline 100 mg orally b.i.d. IV antibiotic therapy was given until the patient was afebrile of at least 48 h (or a minimum of 4 days). Oral antibiotic treatment was continued for 2 weeks. Imaging-guided drainage or surgical drainage by laparoscopy was performed in patients that had positive peritoneal signs or did not improve within 72 h of antibiotic therapy. Following

TOA drainage, IV antibiotics were given for an additional 4 days, or until clinical improvement was achieved.

Demographic and clinical data were collected from medical records and the replies to a telephone questionnaire, and they included medical history, cause of infertility, COH protocol, time interval between the IVF cycles, peak serum estradiol level, number of oocytes retrieved, number of fertilized oocytes, number of embryos transferred, and pregnancy outcome. Data on abscess dimensions as measured on ultrasound findings, type of surgical intervention, conversion from laparoscopy to laparotomy, pathology results, and length of hospital stay were also collected. The effect of TOA on ovarian response was estimated by comparing the differences in the number of oocytes retrieved, fertilization rates, number of embryos available for transfer, and comparison of the pregnancy rate between the cycle before TOA and the next subsequent cycle.

The statistical analysis of the data was performed using the Statistics Package for Social Sciences (SPSS 23, Chicago, IL, USA). Data are expressed as mean \pm SD. Continuous data were analyzed with Student's *t* test or the Mann–Whitney test for non-normally distributed data, respectively. Differences were confirmed using a non-parametric Wilcoxon rank test for paired data. A *P* value < 0.05 was considered statistically significant. A linear correlation test was applied to assess the impact of time elapsed between the first and the subsequent IVF cycle on the number of aspirated follicles and fertilization rate.

Results

During the 10-year study period, 37 women were diagnosed with TOA following fertility treatment, of whom 15 patients fulfilled the inclusion criteria and comprised the study group. Demographic data and clinical characteristics of the participants at the time of TOA diagnosis are shown in Table 1. The mean time interval from fertility treatments to the onset of symptoms was 18 days following oocyte retrieval (range IQR 2–43). The mean age of the patients was 36.7 ± 5.2 years, and the mean largest diameter of the abscess was $6.0 \text{ cm} \pm 1.6$. Indications for IVF are shown in Table 2. Eight women were diagnosed with endometriosis, and antibiotic treatment during oocyte retrieval was given to two patients due to a suspected puncture of the endometrioma. Surgical intervention following antibiotic treatment failure was performed in 11 patients, with a mean time interval from admission to surgery of 2.8 ± 2.2 days. Four women underwent salpingectomy, and the remaining 11 underwent abscess drainage. In all cases of surgical drainage, endometrioma cystectomy was not performed.

Comparisons of reproductive outcome between the first and the second cycles are shown in Table 3. The mean time

Table 1 Patient demographics and clinical characteristics

	Study group (<i>n</i> = 15)
Age	36.7 ± 5.2
Largest TOA diameter (cm)	6.0 ± 1.6
Hospitalization period (days)	8.2 ± 3.9
Time interval from fertility treatments to the onset of symptoms	18 (43.2)
Admission to surgical treatment interval (days)	2.8 ± 2.2
Surgery/drainage	11 (73.3)
Surgical intervention	11 (73.3)
Transvaginal abscess drainage	1 (6.6)
Conversion to laparotomy	3 (27.23)
Pathological finding of endometrioma	3 (20)
Salpingectomy	4 (36.3)

Data are presented as mean ± SD, median (interquartile ranges) and *n* (%)

TOA tubo-ovarian abscess, WBC white blood cell count, CRP C-reactive protein

interval between the first and the second IVF cycles was 26.2 weeks (SD ± 13.6). The mean number of retrieved oocytes was significantly higher in the first IVF cycle compared to the second cycle (8.1 ± 3.2 vs. 5.4 ± 2.5 , respectively, $P = 0.003$), corresponding to a 30% reduction in ovarian response to gonadotropin stimulation. Additionally, the number of fertilized oocytes (2 pronuclei 2PN) was significantly lower in the cycle subsequent to TOA compared to the one preceding it (4.1 ± 2.9 vs. 2.9 ± 1.7 , respectively, $P = 0.015$). Our reported reduction of ovarian response did not correlate in a linear regression with the time elapsed between the first and the subsequent IVF cycle. Fertilization rate is 2PN/MII. Twelve of the 15 women reached embryo transfer in the first cycle compared to 14 women in the second cycle. The mean number of transferred embryos was similar for the two cycles. No clinical pregnancies were recorded following the first cycle, and only one patient had a clinical pregnancy in the first cycle after TOA.

Discussion

The impact of pelvic inflammation caused by TOA on ovarian response to stimulation has not been conclusively determined. We had earlier observed that TOA following fertility treatment has a substantial effect on reproductive treatment outcome [9]. The findings of the present study suggest that TOAs following fertility treatment has a detrimental effect on ovarian performance during IVF treatment and on the outcome of IVF treatments, as evidenced by a 30% reduction in ovarian response to gonadotropin stimulation and a very low pregnancy rate.

TOA is a serious sequela of pelvic infection, with a potentially significant morbidity [2]. Although it is a rare complication of fertility treatments, it is the second to bleeding as being the most common complication following oocyte retrieval [8]. The association between TOA and infertility is well documented, and it is commonly attributed to distorted tubo-ovarian anatomy due to increased scarring and dense fibrous adhesions [12]. The treatment strategy in premenopausal women with TOA is to use a conservative approach to preserve fertility. Several studies, however, have shown that treatment with antibiotics alone is associated with discouraging pregnancy rates. One such study, by Landers and Sweet, reported that only 13.8% of 217 women conceived naturally following TOA treated by antibiotics alone [13]. Similar results were shown by other studies, with reported pregnancy rates that ranged between 7.8 and 14.6% [14, 15]. In contrast, the combination of antibiotics and surgery was shown to increase the pregnancy rate in these patients. Following laparoscopic surgery, Henry-Suchet et al. and Reich et al. demonstrated that natural fertility rates were 43% and 63%, respectively, after the combined treatment for TOA [16, 17]. In the present study, TOA following oocyte retrieval had a significant impact on ovarian response, as evidenced by a 30% decline in oocyte retrieval and fertilized oocytes despite the use of the same treatment protocol. The exact pathophysiology for reduced ovarian response in the setting of TOA remains unknown. One of the possible mechanisms is an association of TOA with severe inflammation which may lead to oxidative damage to the oocytes, resulting in decreased ovarian response. This is especially important in women with TOA following fertility treatment, in whom the condition was shown to be more severe [9]. Another explanation lies in the surgery itself that can be challenging or complicated due to extensive pelvic adhesions. Healthy ovarian tissue may be removed during abscess drainage and removal of necrotic tissue, especially when there is no cleavage plane between the abscess and the healthy ovary. Lastly, excessive coagulation and hemostasis may damage an ovary, thus reducing its response to stimulation.

It is possible that the presence of one healthy ovary may compensate for the affected contralateral ovary in women with TOA, but this compensation may not be applicable to women with preexisting decreased ovarian reserve. Our current study population was characterized by a high percentage of endometriosis (8/15, 53.3%) and a mean maternal age of 36.7 ± 5.2 years. These two factors taken together with the high percentage of women who underwent surgical intervention for TOA (11/15, 73.3%) indicate greater deterioration of ovarian function in those with already diminished ovarian reserve. Other factors that might have a detrimental impact on ovarian reserve are the size of the abscess and the presence of abscesses in both ovaries. Unfortunately, we were not able to determine

Table 2 Reproductive background and cycle course of each case in study group

Patient number	Causes of infertility	Protocol	Surgical drainage	Time to subsequent cycle (weeks)	OPU	Fertilized	ET	Clinical pregnancy	Patient number
A cycle with an infectious complication	Patient 1	Endometriosis	Short protocol	Yes	8	10	5	3	Negative
Subsequent cycle			Short protocol			9	4	2	Negative
A cycle with an infectious complication	Patient 2	Age-related infertility	Antagonist protocol	No	21.00	5	3	3	Negative
Subsequent cycle			Antagonist protocol			3	2	2	Negative
A cycle with an infectious complication	Patient 3	Endometriosis	Antagonist protocol	Yes	18.00	12	9	PGD	No embryo transfer
Subsequent cycle			Antagonist protocol			6	5	PGD	Negative
A cycle with an infectious complication	Patient 4	Age-related infertility	Antagonist protocol	Yes	9.00	3	3	0	No embryo transfer
Subsequent cycle			Antagonist protocol			2	2	2	Negative
A cycle with an infectious complication	Patient 5	Endometriosis	Antagonist protocol	Yes	20.00	5	3	2	Negative
Subsequent cycle			Short protocol			6	2	2	Negative
A cycle with an infectious complication	Patient 6	Unknown infertility	Short protocol	Yes	52.00	10	6	3	Negative
Subsequent cycle			Short protocol			2	1	1	Negative
A cycle with an infectious complication	Patient 7	Unknown infertility	Antagonist protocol	Yes	47.00	13	10	1	Negative
Subsequent cycle			Antagonist protocol			5	5	1	Negative
A cycle with an infectious complication	Patient 8	Mechanical factor	Antagonist protocol	No	26.00	11	8	2	Negative
Subsequent cycle			Antagonist protocol			10	7	2	Positive
A cycle with an infectious complication	Patient 9	Endometriosis	Antagonist protocol	Yes	24.00	4	2	2	Negative
Subsequent cycle			Antagonist protocol			2	1	1	Negative
A cycle with an infectious complication	Patient 10	Endometriosis	Antagonist protocol	No	8.00	5	1	1	Negative
Subsequent cycle			Antagonist protocol			6	0	0	No transfer
A cycle with an infectious complication	Patient 11	Endometriosis	Antagonist protocol	Yes	19.00	8	0	0	No transfer
Subsequent cycle			Antagonist protocol			6	2	1	Negative

Table 2 (continued)

Patient number	Causes of infertility	Protocol	Surgical drainage	Time to subsequent cycle (weeks)	OPU	Fertilized	ET	Clinical pregnancy	Patient number
A cycle with an infectious complication	Patient 12	Unknown infertility	Antagonist protocol	Yes	19.00	10	3	3	Negative
Subsequent cycle			Antagonist protocol			6	2	2	Negative
A cycle with an infectious complication	Patient 13	Endometriosis	Antagonist protocol	Yes	45.00	12	4	3	Negative
Subsequent cycle			Antagonist protocol			7	4	4	Negative
A cycle with an infectious complication	Patient 14	Endometriosis	Antagonist protocol	Yes	36.00	6	3	3	Negative
Subsequent cycle			Short protocol			3	2	2	Negative
A cycle with an infectious complication	Patient 15	Age-related infertility	Short protocol	No	42.00	8	2	2	Negative
Subsequent cycle			Short protocol			8	2	2	Negative

the impact of these two factors due to the low number of patients in our study.

None of the women in the present study had a clinical pregnancy following the first IVF cycle, and only one had a clinical pregnancy following the second IVF cycle. The detrimental effect of pelvic infection on fertility treatment outcome has been well documented. It has been suggested that altered cytokine secretion together with the presence of bacterial toxins and temperature elevation may result in impaired embryonic cell proliferation and implantation [18]. Possible explanations for the low clinical pregnancy rate in the first cycle that followed TOA can be related to a relatively advanced maternal age, a high percentage of endometriosis, and the short time interval between the TOA episode and the second cycle. In a meta-analysis by Barnhart et al., women with endometriosis-associated infertility had a pregnancy rate of $\leq 54\%$ after IVF (OR 0.56; 95%CI 0.44–0.70) compared to women with tubal infertility [19]. Furthermore, women with severe endometriosis had a 36% lower pregnancy rate compared to women with mild disease [19]. Although the exact mechanism of endometriosis-related infertility has not been fully elucidated, one possible mechanism is thought to be related to poor oocyte quality, as was proposed by Simon et al. [20].

The mean time interval from the TOA episode and the second IVF cycle was 26.2 weeks in the present study.

Interruption of the local cellular and molecular environment at the feto-maternal interface due to an inflammatory environment may have an impact on embryo quality and implantation [21]. The presence of a recent serious pelvic infection together with postsurgical inflammatory changes, such as edema, vascular injury, and ischemia, may have a prolonged effect on uterine receptivity and oocyte quality. The importance of a sufficient time interval for ovarian recovery following surgery was demonstrated by Sugita et al. in women who underwent cystectomy for ovarian endometrioma [22]. In that study, serum antimüllerian hormone levels measured 1 year following endometrioma removal were higher than those measured 1 month after the surgery, emphasizing the importance of a sufficient interval of time to ensure a good healing process and recovery of the ovary. The lack of correlation between reduction of ovarian response and time interval between the IVF cycles may be explained by the small number of patients in the study. It should be borne in mind, however, that although potential ovarian recovery and improved implantation rate may occur following TOA after a sufficient period of time, increasing age is an independent risk factor for reduced ovarian reserve. Therefore, lacking sufficient evidence to the contrary, fertility treatment following TOA should not be deferred to improve fertility treatment outcome.

Table 3 Cycle characteristics

	Mean number of cycle prior to TOA episode	Mean number of cycles subsequent to TOA	Reduction percentage (%)	Pa
OPU, <i>n</i>	8.1 ± 3.2	5.4 ± 2.5	30 ± 28	0.003
2PN	4.1 ± 2.9	2.9 ± 1.7	30.4 ± 22.3	0.015
Transferred embryos, <i>n</i>	2.2 ± 0.9	1.9 ± 0.8	34.8 ± 28.8	0.3

^aWilcoxon Rank Test

Data are presented as mean (±SD) and median (interquartile ranges)

Note: TOA, tubo-ovarian abscess; OPU, ovum pickup; 2PN, two pronuclei

To minimize the risk of pelvic infection during oocyte retrieval in women with endometrioma, preventive measures should be taken. It is advisable to avoid puncturing of endometrioma if possible. Disinfecting the vagina with betadine followed by vaginal irrigation with normal saline and prophylactic antibiotic treatment before the procedure should be considered as well [23–25]. The role of surgical intervention for reducing the risk of infection is questionable. Although surgical removal of endometriotic implant and ovarian endometrioma prior to IVF treatment potentially reduce the risk for infection, laparoscopic cystectomy for ovarian endometrioma was shown to decrease ovarian reserve and prolongs stimulation cycles [26, 27]. Treatment with Gonadotropin-releasing hormone agonist (GnRHa) for endometriosis was shown to reduce disease activity by inhibition of cell growth and inducing endometrial epithelial cell apoptosis [28, 29]. In addition, the use of GnRHa for a period of 3–6 months prior to IVF treatments in women with endometriosis was shown to improve clinical pregnancy rates [30]. Although there is no evidence that giving GnRHa treatment prior to IVF will diminish the risk for pelvic infection, choosing GnRHa long protocol for patient with known endometriosis should be considered.

Our study is limited by the relatively small number of patients in our cohort. In addition, given its retrospective design, limitations such as recall bias and incomplete medical records are also possible. The retrospective nature of our study also did not permit assessing several relevant parameters, such as possible impact of TOA on embryo quality and ovarian reserve. AMH values could not be analyzed as they are not part of the routine tests in our hospital.

Conclusion

TOA following fertility treatment has a detrimental effect on ovarian function as evidenced by a 30% reduction in ovarian response to gonadotropin stimulation. The rate of pregnancy in the immediate period following TOA is poor. Current data are too sparse to recommend the deferral of fertility treatment following a TOA episode, warranting further studies to establish evidence-based recommendations.

Author contributions YF: protocol/project development, data collection or management, manuscript writing/editing, and data analysis. YC: data management, manuscript writing/editing, and data analysis. IL: manuscript writing/editing and data analysis. AM: protocol/project development and manuscript writing/editing. FA: manuscript writing/editing. AC: protocol/project development, manuscript writing/editing, and data analysis.

Compliance with ethical standards

Conflict of interest All the authors report no conflict of interest and that this research was non-funded.

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