ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Appraisal of clinical complications after 23,827 oocyte retrievals in a large assisted reproductive technology program

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Objective: To assess complications encountered after transvaginal oocyte retrieval procedures.
Design: Retrospective analysis.
Setting: University hospital, fertility center.
Patient(s): A total of 23,827 consecutive transvaginal oocyte retrieval procedures in 12,615 patients.
Intervention(s): Oocyte retrieval procedures performed between June 1996 and October 2016.
Main Outcome Measure(s): All oocyte retrieval complications. Those requiring hospital admission for at least 24 hours were considered severe.
Result(s): A total of 96 patients (0.76 %) suffered complications, with hospital admission necessary for 71 patients (0.56 %). When calculated per retrieval, the overall complication rate was 0.4%, whereas 0.29% was the admission rate, with an average duration of hospital stay of 2.77 ± 2.5 days. A surgical procedure was necessary for 24 patients (0.1% per retrieval and 0.19% per patient). Multivariate analysis showed a significant correlation between complications and women age, body mass index (BMI), the number oocyte retrieved, and the mean time to complete oocyte retrieval. The incidence of complications was significantly higher for physicians who had performed <250 retrievals compared with those who had completed >250 retrievals (odds ratio 0.63, 95% confidence interval 0.40–0.99).
Conclusion(s): Oocyte retrieval can be considered a safe procedure but is not without risks. The most important, identifiable, risk factors for the occurrence of complications are: [1] high number of oocytes retrieved, [2] a long duration of the procedure and mean time per oocyte retrieved, [3] inexperience of the surgeon, [4] younger patients with a lesser BMI, and [5] history of prior abdominal or pelvic surgery or pelvic inflammatory disease.
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Key Words: Oocyte retrieval, complications, vaginal and peritoneal bleeding, pelvic sepsis

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Ultrasound-guided transvaginal route (US-TV) is the most common approach used to harvest oocytes during IVF cycles. Oocyte retrieval by US-TV was first performed in 1983 (1), and as it is relatively easy to learn and much less invasive compared with the laparoscopic or transabdominal routes, it has become the gold standard for collecting oocytes (2, 3). Several observational studies evaluating the rates of complications

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associated with this procedure have shown that it is safe, with very low rates of serious adverse events. However, the risks associated with US-TV should not be underestimated because some complications, although rare, may be life-threatening (2 deaths were reported in 2010) (4). More frequent complications are vaginal and peritoneal bleeding (5–8). Dessole et al. (9) found that 230 mL was the usual estimated blood loss about 24 hours after oocyte retrieval. Rarely, ovarian bleeding may lead to severe hemoperitoneum (10) and the symptoms may appear either early or late ($\leq$28 hours) after oocyte retrieval procedures. Other complications after retrieval are pelvic sepsis or abscess (5, 6, 11). A retrospective analysis (12) suggested that particularly in patients with ovarian endometriomas, complications, such as tubo-ovarian abscess, can occur even long after the completion of the assisted reproductive technology (ART) cycle, indicating that women with endometriosis are prone to develop infectious complications. Other rarer complications, described as case reports, are ureterovaginal fistulas (13), pseudoaneurysm of the iliac artery (14, 15), ureteral injury (11, 16, 17), bladder injury with hematuria (18–20), ovarian torsion (6), and ovarian abscess (21). All of these adverse events are iatrogenic, caused by the trauma of the aspiration needle on the pelvic organs. Because most IVF centers perform oocyte retrieval procedures either under general anesthesia or with deep sedation, complications from the anesthetic agents should also be considered. In general, the rates of complications associated with oocyte retrieval procedures are not easily available unless individual programs collect these data as indicators for their own quality performance. Most ART registries focus on cycle outcomes in terms of pregnancy and live birth, but neglect to collect information about the rate of complications during oocyte retrieval procedures. In addition, as complications often occur days to weeks after the oocyte retrieval procedure, the reporting of these complications to the registry may be suboptimal. The aim of the present study was to report complication rates after oocyte retrieval in one of the largest case studies analysis conducted in a single ART program. This information is valuable for counseling and informing patients undergoing US-TV about the treatment-related complications and risks.

MATERIALS AND METHODS

All oocyte retrieval procedures performed at the Fertility Center Humanitas Research Hospital (Rozzano, Milan, Italy) between June 1996 and October 2016 were included. All cycles consisted of controlled ovarian hyperstimulation (COH) with standard protocols (using either agonist or antagonist), with ultrasound and hormonal monitoring (17-beta-E_2 and P) beginning on day 5 of stimulation and continuing until follicles had a suitable diameter and hormone levels were acceptable. Final follicle maturation was triggered with hCG (urinary or recombinant) or, lately, with GnRH analogue to decrease the risk of ovarian hyperstimulation syndrome (OHSS). Per the protocol of the unit, routine preoperative assessment included a complete blood count with coagulation panel, fasting blood sugar, electrocardiogram, and an anesthesiologist evaluation. Specific to our unit's protocol, the day before retrieval patients were instructed to do a vaginal douching with iodopovidone 10% (Meda Pharma S.p.A), to insert a vaginal capsule of chloramphenicol (250 mg), and to do a light enema. The transvaginal ultrasound-guided oocyte retrieval procedure was performed 34–36 hours after hCG administration, in a dedicated surgical suite using either a single or double-lumen (17 G) aspiration needle (35 cm) (22), depending on the number of follicles and at a pressure of $<$150 mm Hg (23). Before retrieval, the operator scrubbed and wore powder-free sterile gloves, rinsed the vagina with isotonic saline solution, and covered the patient with sterile surgical drapes. A rotating team of gynecologists with different levels of experience performed the oocyte retrieval procedures and the times of each procedure were recorded. The oocyte retrieval procedures were performed under deep sedation using intravenous propofol (at a dose weight-related) + fentanyl (50γ), plus propofol drip (5 mg/kg/hour), IV paracetamol 1,000 mg, as well as assisted mask ventilation with oxygen. Antibiotic prophylaxis was not routinely used except in presence of risk factors, such as history of hydrosalpinx, ovarian endometrioma, pelvic inflammatory disease (PID), or when the estimated blood loss was $>$200 mL. At the end of each oocyte retrieval procedure, patients were observed for 2.5 hours and then discharged home with an emergency contact number. All data were collected using an exclusive internal web-based database. Such database allows for storage, organization, and ease in retrieving information about any patient. It also manages care processes versus time: from outpatient services to follow-up treatments, and includes tracking the details of any surgery or hospitalization. Patients' data are safeguarded by an advanced threat prevention, enterprise-class encryption, and authentication for any user with periodical need of password renewal. Patients had consented in writing that their medical records could be used for research purposes, as long as their anonymity was protected and medical record confidentiality assured. Because both conditions were met, this study had expedited review and approval (IRB number 17/17). The study protocol was registered in Clinicaltrial.com before full variable extraction and statistical analyses.

Primary outcome was the incidence of complications necessitating hospitalization or outpatient management. Cases of OHSS were not included.

Parameters considered for the statistical analyses were body mass index (BMI), patient age, duration of infertility, number of oocytes collected, time to complete the retrieval, mean time per oocyte (i.e., total time to complete the retrieval divided by the number of oocytes retrieved), and surgeon experience. Single versus double lumen needle and number of follicles at trigger were not included in the analyses for the nonindependency of the variables.

History of endometriosis, prior abdominal or pelvic surgery, PID, or hematologic disease were collected in all patients. Our internal protocol requires 50 US-TV procedures performed under supervision of a senior attending before granting privileges to junior colleagues, based on an external audit quality performance and the maintenance program was introduced in 2013. This system generates a report for all clinicians every

3 months on the number of procedures performed, the percentages of oocytes retrieved per punctured follicle, the total time of the procedure, the mean time per oocyte retrieved, and complications leading to hospital admission. These data are then compared to the mean performance of the time period and with those of previous years. This quality performance protocol has been certified during Joint Commission International Hospital renewal inspections (24).

Data were described as number and percentage if categorical and 95% confidence interval (CI) were also reported. Continuous variables were described as mean and SD. Possible associations for the considered parameters and complications were explored with logistic regression analysis ($P<.05$ was considered significant). All statistical analyses were carried out with Stata 13.0 (2013, Stata Corp.).

RESULTS

During the study period, a total of 23,827 oocyte retrieval procedures (12,615 patients) were performed, of which 15,730 retrievals in women $\leq$38 years and 8,092 in women >38 years. Patient characteristics, information about their cycles, complications, and hospital admissions are shown in Table 1. A total of 96 complications related to oocyte retrieval procedures (0.40%; 95% CI 0.33%–0.49%) were encountered. A risk factor was present in 28 (29.17%) of the 96 cases experiencing complications.

The complication rate for patient was 0.76% with no recurrence of a complication in the same patient. Hospital admission was necessary for 71 of 96 (73.96%) patients suffering complications, representing 0.29% (95% CI 0.23%–0.38%) of the total retrievals and the average duration of a hospital stay was 2.77 $\pm$ 2.5 days. In 54 cases, the complication was peritoneal bleeding (0.23%, 95% CI 0.17%–0.30%). A total of 24 patients required surgery (0.1%, 95% CI 0.06%–0.15%), of which 19 for peritoneal bleeding; in 18 (33.33%) a laparoscopy could evacuate the hemoperitoneum (volume, >1,000 mL), whereas in one patient an emergent laparotomy was necessary to repair a small laceration of the iliac vein. In one patient, the pelvic bleeding occurred 2 days after the oocyte retrieval procedure; in another case, 15 days had elapsed between the oocyte retrieval procedure and the occurrence of intraperitoneal bleeding, perhaps secondary to multiple hemorrhagic corpora lutea (CL). In another two cases, a laparoscopy had to be performed for infectious complications and in one patient a laparotomy was necessary for severe sepsis. Pelvic pain was another retrieval complication and six patients required hospitalization (0.03%, 95% CI 0.009%–0.055%).

Vaginal lacerations were encountered in only two patients who required sutures (0.008%). Two cases of bladder trauma (0.008%) were noted and diagnosed by hematuria and vesical hematoma, but they did not require intervention and both patients were discharged home after 1 day of observation (Table 1).

A total of 10 cases of infectious complications (0.04%, 95% CI 0.02%–0.08%) were also documented, with six requiring hospitalization and in three a surgical intervention was necessary (2 cases had tubo-ovarian abscesses that occurred 1 week after the oocyte retrieval procedure and the purulent collections were drained by laparoscopy, whereas the third case suffered a septic shock for diffuse pelvic peritonitis 1 month after the oocyte retrieval procedure and required urgent laparotomy to drain the abscess). Hospital stay for PID in these six cases was longer than any of the other complications: 6.67 $\pm$ 5.05 days. Of the 23,827 retrievals there was only one case of right iliac vein laceration that required an urgent laparotomy.

Concerning anesthetic complications, a total of 14 patients were observed with 12 cases of circulatory shock and nausea. Two serious complications were atrial fibrillation and one case of cardiorespiratory insufficiency, agitation, and confusion.

In total 10 of 14 patients were hospitalized for complications related to anesthesia (0.04%, 95% CI 0.02%–0.08%) and all resolved. Interestingly, 28 of the 96 patients (29.17%) who suffered complications had pre-existing risk factors: history of endometriosis, history of pelvic surgery for benign reasons, previous PID. or hematologic disease (one was suffering from von Willebrand disease and one had chronic thrombocytopenia).

At univariate analysis patients with complications appear to be younger, thinner, with a longer operation time, and with a higher number of oocytes retrieved compared with patients

TABLE 1

Incidence of complications, incidence of hospitalization, and treatment in 23,827 retrievals.

Complications	No. of cases	%	No. of admissions (%)	Treatment	Hospital stay (d)
Hemoperitoneum	54	0.23	47 (87.04)	18 laparoscopy 1 laparotomy 28 observations	2.91 ± 1.91
Pelvic pain	14	0.06	8 (57.14)	Observation	1.12 ± 0.35
Vaginal wall bleeding	2	0.01	0	2 vaginal suturing	
Bladder lesions	2	0.01	0	Observation and catheter	
Infective complications	10	0.04	6 (60)	Antibiotic therapy 2 laparoscopy 1 laparotomy	6.67 ± 5.05
Anesthetic complications	14	0.06	10 (71.43)	Observation	1.1 ± 0.32
All	96	0.40	71 (73.96)	24 surgical procedures	2.77 ± 2.5

Levi-Setti. Complication rate after 23,827 oocyte retrievals. Fertil Steril 2018.

TABLE 2

Baseline characteristics of patients with and without complications.

Characteristics of patients	Oocyte retrievals without complications	Oocyte retrievals with complications	Odds ratio (95% CI)	*P*
Number	23,731	96		
Age (y)	36.4 ± 4.1	35.1 ± 3.2	0.93 (0.89–0.96)	< .001
BMI (kg/m^2)	22.2 ± 3.2	21.6 ± 2.6	0.93 (0.87–0.99)	.033
Duration of infertility (mo)	52.6 ± 31.9	51.8 ± 35.2	1.00 (0.99–1.01)	.844
Oocytes retrieved (no.)	9.6 ± 6.0	11.4 ± 6.5	1.04 (1.02–1.07)	.002
Duration of retrieval (minutes)	13.9 ± 5.4	15.5 ± 6.4	1.05 (1.02–1.08)	.004
Time for single oocyte retrieval (min)	2.11 ± 1.97	2.29 ± 3.28	1.04 (0.92–1.17)	.520
Expert surgeon (n, %)	18,555 (78.19%)	66 (68.75%)	0.61 (0.40–0.95)	.027

Note: Numbers are expressed as mean ± SD. BMI = body mass index; CI = confidence interval.

Levi-Setti. Complication rate after 23,827 oocyte retrievals. Fertil Steril 2018.

in which complications did not occur (Table 2). Duration of infertility and mean time to oocyte retrieved were not significantly correlated to oocyte retrieval procedure complication rates.

Finally, complication rates were analyzed also in relation to the experience of the operators (Table 2 and Supplemental Fig. 1). Preliminary data analyses showed <250 procedures to be significantly related to higher complication rate and this threshold was therefore introduced in the multivariate analysis. The mean incidence of complications in <250 oocyte retrieval procedures per operator was 0.61%, whereas above this threshold it was 0.36% (CI 0.40%–0.95%; *P*=.027).

At multivariate analysis, the occurrence of complications was significantly associated with the age of the patient, BMI, number of retrieved oocytes, mean time to single oocyte retrieved, and surgeon's experience (Table 3). A sensitivity and specificity odd ratio analysis for the incidence of complications showed higher specificity and an acceptable sensitivity at 250 retrievals (Table 4). Specifically, although it is sufficient to perform 50 retrievals to master the technique of oocyte retrieval, it is only after 250 procedures that the risk on the incidence of complications is significantly reduced.

DISCUSSION

This retrospective analysis, performed in a large Italian ART program, showed a very low rate of serious medical and surgical complications after oocyte retrieval procedures. Of note, in the present study complications associated with hormonal stimulation, like OHSS and its consequences as ovarian torsion (25) and thromboembolic events (26), were not assessed. Likewise, complications associated with pregnancy, such as ectopic (EP) or heterotopic pregnancy, were not considered. The most common problem encountered after US-TV-guided oocyte retrieval procedure is minor vaginal bleeding, which generally stops spontaneously or can be controlled with local compression. In literature, the incidence of vaginal bleeding is reported in ≤8.6% of cases (27). This variability may be due to differences in the definition of vaginal bleeding among different centers. Conversely, peritoneal bleeding is a more serious complication. Recent studies have reported an incidence between 0.06% and 0.35% (5–8). In our study the incidence of hemoperitoneum requiring hospitalization was 0.2%. This complication is caused by damage to ovarian vessels or from bleeding of ruptured follicles or, more rarely, from direct trauma to pelvic organs (uterus, bladder, and bowels). The risk of an acute ovarian bleeding is more prevalent among lean patients with polycystic ovary syndrome (PCOS) because of the high number of oocytes generally retrieved in these patients (7). History of previous pelvic surgeries has also been correlated with an increased incidence of peritoneal bleeding. Our data support this observation as 18 of the 54 patients (33.3%) with hemoperitoneum had undergone previous laparoscopy. Per the literature, blood losses not exceeding 200 mL, as assessed by ultrasound, can be considered normal (9, 28). At times, intra-abdominal bleeding can result from coagulation disorders such as essential thrombocythemia (29), factor XI deficiency (30), or von Willebrand disease (31). In our study, of the two patients hospitalized for hemoperitoneum, one had von Willebrand disease and one had chronic thrombocytopenia. Damage to pelvic organs (bladder, ureter, bowel, large vessels, and nerves) from the aspiration needle cannot be always assessed as they may remain undetected and resolve spontaneously. Case reports in literature have described perforated appendix (32–34), damage of the ureter and ureteral obstruction or fistulas (11, 13, 17, 35). Often, however, these lesions are difficult to diagnose and may be confused with other complications such as OHSS (16). Cases of bladder injuries have also been reported (18, 19). In

TABLE 3

Multivariable analysis for complications.

	All complications	
Multivariate	**Odd ratio (95% CI)**	***P* value**
Age (y)	0.94 (0.90–0.98)	< .002
BMI (kg/m^2)	0.93 (0.87–0.99)	.032
Oocytes retrieved (no.)	1.05 (1.02–1.08)	.002
Duration of retrieval (min)	—	
Mean time to oocyte retrieved (min)	1.13 (1.03–1.24)	.011
Expert surgeon	0.63 (0.40–0.99)	.0472

Note: BMI = body mass index; CI = confidence interval.

Levi-Setti. Complication rate after 23,827 oocyte retrievals. Fertil Steril 2018.

TABLE 4

Sensitivity and specificity in relation to the incidence of oocyte retrieval complications.

Oocyte retrieval complications	Operators with less retrieval experience	Operators with more retrieval experience	*P* value	Sensitivity	Specificity
50	4 (0.92%)	92 (0.39%)	.101	0.9583	0.9908
100	16 (1.01%)	80 (0.36%)	.001	0.8333	0.9899
200	24 (0.66%)	72 (0.36%)	.023	0.7500	0.9934
250	26 (0.61%)	70 (0.36%)	.023	0.7292	0.9939
300	30 (0.58%)	66 (0.36%)	.035	0.6875	0.9942

Note: Total complications, 96.

Levi-Setti. Complication rate after 23,827 oocyte retrievals. Fertil Steril 2018.

our study we encountered bladder trauma only in 2 cases, without serious consequences. Pelvic infections or abscesses have been reported with an incidence of 0.01%–0.03% (5, 6, 36). In our study they represented the second most common complication, occurring in 0.04% of the procedures. Although infectious complications are rare, they have a very high rate of hospital admissions (60%) and the hospital stay is higher than any other complication (as reported in Table 1).

The pathogenesis mechanism may be from vaginal contamination; however, the risk increases for patients with a previous history of PID or in the presence of hydrosalpinges, severe endometriosis (37, 38). or pelvic adhesions. Pelvic pain is a common complication after an oocyte retrieval procedure and it can be easily controlled with paracetamol. Ludwig et al. (11) reported an incidence of hospitalization for pelvic pain of 0.7%. It seems to increase proportionally with the number of oocytes retrieved. In this study, only eight patients (0.03%) required hospitalization for pelvic pain; however, it is very difficult to collect objective data as it is a symptom that is experienced differently by each patient.

Complications from anesthesia (e.g., hypotension, pneumothorax, pulmonary edema, malignant hyperthermia) are more difficult to define because they are not specific to oocytes retrieval. Data from the literature and our experience indicate that after an oocyte retrieval procedure there is a low risk for postoperative nausea and vomiting. Overall 10 patients required hospital admission (0.04%) because of anesthetic complications: eight for shock, one for atrial fibrillation, and one for cardiorespiratory insufficiency with agitation and confusion.

Although most complications were treated in our institution (94/96 of the complications and 22/24 of those requiring surgery with only 2 severe late onset complications treated in other hospitals), we do not know the real number of complications as they could have been treated in another hospital or were unreported. This could reflect a possible bias with an underestimation of the incidence of complication related to the oocyte retrieval procedure.

In conclusion, the oocyte retrieval procedure can be considered a safe procedure, although patients and physicians should recognize that it is not without risks. Fortunately, severe intra-abdominal and/or vascular complications are rare, as well as injury of pelvic structures (ureter, bowel, appendix, nerves) or infection. Our data showed that the most common severe complication after the oocyte retrieval procedure is peritoneal bleeding, which occurred in 0.2% of the procedures. In general, risk factors for a complication can be identified and this information should be used to minimize the risk for occurrence. A high number of oocytes retrieved, a longer duration of operative time, a younger age, a smaller BMI, and a history of prior abdominal or pelvic surgery or PID seem to be the most important factors. In our case series, at multivariate analysis we found that only women's age, BMI, number of oocytes retrieved, the time required for the collection of each oocyte, and operator experience were statistically significant.

We outlined a learning curve regarding the correlation between surgical complications and the experience of the operator. As shown in Supplemental Figure 1, as the number of oocyte retrieval procedures increases, the percentage of surgical complication for each operator decreases.

The study by Goldman et al. (39) showed that >20 oocyte retrieval procedures as sufficient to obtain satisfactory results in terms of oocytes collected versus oocytes expected. In our data pool, we found that less experienced operators encountered a higher rate of complications after oocyte retrieval procedures. Furthermore, the threshold of proficiency appears to be higher considering rate of complications rather than the number of oocyte collected. In our dataset, oocyte retrieval procedure complications were consistently fewer when the operator had performed $\geq$250 oocyte retrieval procedures. Therefore, in the presence of identifiable risk factors, such as previous surgeries, endometriosis, PID, high responders, young patients with low BMI, more experienced surgeons should either perform the oocyte retrieval procedure or be available for supervision. Simulators for oocyte retrieval procedures could probably be a future option to decrease the learning curve and to further reduce oocyte retrieval procedure complications (40).

Finally, the data presented should be helpful for [1] counseling patients, [2] comparing center-specific rates of complications, and [3] using oocyte retrieval procedure complication rates. These are indicators of quality performance.

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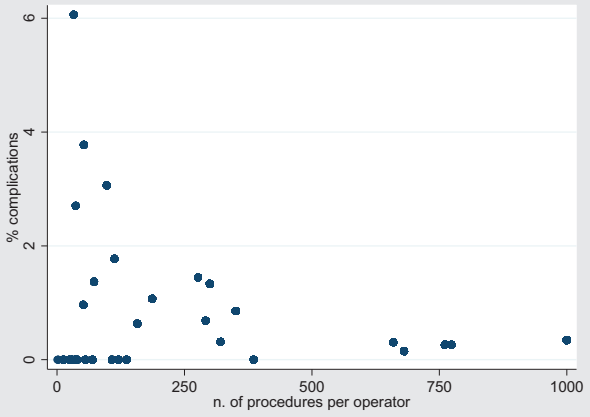
SUPPLEMENTAL FIGURE 1



Learning curve of oocyte retrieval. Rate of surgical complication for single operator (% complications) versus number (n.) of procedures made. For operators with >1,000 procedures, data in the graph were shown together.

Levi-Setti. Complication rate after 23,827 oocyte retrievals. Fertil Steril 2018.